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Are peri-operative interventions effective in preventing chronic pain after primary total knee replacement? A systematic review

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Are peri-operative interventions effective in preventing chronic pain after primary total knee replacement? A systematic review

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ABSTRACT

Objectives

For many people with advanced osteoarthritis, total knee replacement (TKR) is an effective treatment for relief of pain and improvement of function. Features of peri-operative care may be associated with chronic pain six months or longer after surgery. Effects may be direct, e.g. through nerve damage or complications, or indirect by limiting mobilisation and rehabilitation. The objective of this systematic review is to evaluate whether non-surgical peri-operative interventions prevent long-term pain after TKR.

Methods

We conducted a systematic review of peri-operative interventions for adults with osteoarthritis receiving primary TKR evaluated in a randomised controlled trial (RCT). We searched major bibliographic databases up to February 2018. After screening, two reviewers evaluated articles. Studies at low risk of bias according to the Cochrane tool were included.

Interventions

Peri-operative non-surgical interventions; control receiving no intervention or alternative.

Primary and secondary outcome measures

Pain or score with pain component assessed at six months or longer post-operative

Results

44 RCTs at low risk of bias assessed long-term pain. Intervention heterogeneity precluded meta-analysis and definitive statements on effectiveness. There was encouragement for further research into local infiltration analgesia, ketamine infusion, pregabalin, and electric muscle stimulation. In the studies we identified, tranexamic acid to prevent blood loss was not associated with long-term pain. Many extensively researched interventions including venous thromboembolism prevention have not been evaluated in relation to long-term pain.

Interpretation

Our review summarises evidence on peri-operative treatments for the prevention of long-term pain after TKR and highlights aspects of care for further evaluation in well-conducted RCTs. Long-term consequences of many widely researched treatments have not been reported.

STRENGTHS AND LIMITATIONS

For the first time, this systematic review brings together contemporary evidence on aspects of peri-operative care for people with total knee replacement and their effects on longterm pain.

Only studies assessed to be at low risk of bias were included in the narrative synthesis.

Intervention and outcome heterogeneity precluded meta-analysis.

KEYWORDS

Total knee replacement; Systematic review; Randomised controlled trial; Peri-operative care; Long-term pain

BACKGROUND

In the US about 13% of men and 19% of women will be diagnosed with knee osteoarthritis and over half will receive a total knee replacement (TKR)[1]. For people with advanced osteoarthritis unresponsive to pharmacological or conservative treatments, TKR aims to relieve pain and improve function. In the UK nearly 100,000 primary TKRs were performed in 2017[2,3] and in the USA in 2010, an estimated 4.7 million people were living with a TKR[4]. Despite good outcomes for many, some people report long-term pain and are disappointed with their surgery[5,6]. After TKR, pain levels plateau from about 6 months[7,8] after which persistent pain is considered "chronic"[9] and is reported by 10-34% of patients[10].

In the peri-operative period from hospital admission to the early stages of recovery, care focuses on acute pain management, prevention of adverse events, facilitation of early mobilisation and timely discharge. However, for people with osteoarthritis the key aim of TKR is the achievement of a long-term painless and well-functioning knee with no adverse events. All aspects of peri-operative care should work together to achieve this.

Peri-operative risk factors suggest that appropriate interventions may reduce long-term pain. For example, acute post-operative pain, which may be a direct consequence of the operation, anaesthetic protocol and subsequent analgesia, or related to particular aspects of care, is an acknowledged risk factor for chronic post-surgical pain[11]. Any treatment in the peri-operative period could potentially affect patient recovery and chronic pain, either directly or indirectly. Direct benefits may be through prevention of nerve damage[12], post-thrombotic syndrome[13], reperfusion injury[14] and articular bleeding[15]. Patients with depression and catastrophising have poor pain outcomes[16,17]. For other treatments, pathways leading to long-term pain may be indirect consequences of delayed mobilisation, rehabilitation and recovery.

Our systematic review of randomised controlled trials (RCTs) aims to evaluate the effectiveness of treatments in the peri-operative period in preventing long-term pain after TKR. By focusing on studies with low risk of bias we aim to identify interventions with robust evidence of long-term effectiveness and identify gaps in the research base.

METHODS

The systematic review protocol was registered (PROSPERO CRD42017041382) and PRISMA reporting guidelines used[18]. A checklist is included as Supplementary material.

Patient and public involvement

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As part of the STAR programme of research (NIHR RP-PG-0613-20001), this review benefited from extensive patient and public involvement. Advice was sought from patients and stakeholders at a group discussion in March 2016 with decisions made on inclusion criteria and outcomes. Our patient advisory group comprises five patients with experience of long-term pain after TKR, supported by a dedicated co-ordinator. This group will advise on dissemination of the study results to a general audience including plain language summaries.

Eligibility criteria

Participants: adults receiving unilateral primary TKR, predominantly for osteoarthritis.

Interventions: peri-operative interventions (pharmacological or non-pharmacological) were included. "Peri-operative" reflects the time from hospital admission to early stages of recovery. Interventions relating to implant designs and surgical procedures were excluded.

Comparator: usual care, placebo or alternative intervention.

Outcomes: in preference, patient-reported joint-specific pain intensity measured by tools such as the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) or Oxford Knee Score (OKS). If joint-specific measures were unavailable, pain dimensions from quality of life measures were used or pain rated on a visual analogue scale (VAS) or numerical rating scale (NRS). We also considered composite patient-reported outcome measures and surgeon scores which included a pain intensity component, such as the American Knee Society Score (KSS) and Hospital for Special Surgery (HSS) score. The occurrence of adverse events was summarised.

Setting: RCTs with follow up at \geq 6 months after surgery and a pain outcome or score including pain. Authors of studies were contacted regarding incomplete pain outcome data.

Database searches

We established an Endnote database of all RCTs in TKR. On 14th February 2018, a final search was conducted in: *The Cochrane Library*; MEDLINE, Embase and PsycINFO on Ovid; and CINAHL on EBSCOhost. The MEDLINE search strategy is included as supplementary material. Citations of key articles were tracked in Web of Science. No language restrictions were applied, and translations made. Studies reported as abstracts or unobtainable using inter-library loans and author contact were excluded.

Screening and data extraction

We imported records into Endnote X7 (Thomson Reuters). An initial screen by one reviewer excluded clearly irrelevant articles. Subsequently, abstracts and full articles were screened independently by two reviewers and reasons for exclusion recorded.

Data were extracted onto piloted forms and an Excel spreadsheet by one reviewer, specifically: country; dates; participants (indication, age, sex); inclusion and exclusion criteria; intervention and control content; setting, timing, duration and intensity of intervention; follow up intervals; losses to follow up; pain outcome data; and serious adverse events. Data was checked against source material by a second reviewer.

Authors were contacted for missing data, and data provided for previous reviews was used[10,19].

Quality assessment

Potential sources of bias were assessed by two experienced reviewers using the Cochrane risk of bias tool[20], specifically: the randomisation process; deviations from intended interventions; missing outcome data, measurement of the outcome; and selection of the reported result. Studies with serious concerns relating to risk of bias were considered high risk and those with limited reporting unclear risk. Studies with high or unclear risk of bias were excluded from the narrative synthesis but are included in supplementary summary tables with reasons for exclusion.

Data analysis

Insufficient studies with similar interventions and outcomes were identified for meta-analysis, and a narrative synthesis is presented. Results reported with p-values ≤0.001 were considered "strong" evidence of effectiveness[21], p-values 0.001-0.05 "some" evidence, and p-values 0.05-0.1 "weak" evidence. When authors reported results "statistically significant" with no p-value, this was noted. Where possible, effect sizes were compared with published minimal clinically important differences (MCID). Concerns relating to adverse events were summarised.

RESULTS

Figure 1 shows review progress and reasons for exclusion. Peri-operative interventions with follow up of \geq six months were evaluated in 130 RCTs of which 76 reported a pain outcome or score with a pain component. Detailed intervention and study characteristics and risk of bias assessments are provided as supplementary material.

Details of 44 studies assessed to be at low risk of bias are summarised in Table 1.

Table 1. Perioperative interventions with follow up for pain or score at 6 months or later and assessed to be at low risk of bias

Study Treatment common to randomised groups		Intervention	Number patients	Follow up Group difference
Pain management: nerve l	blocks			
Albrecht et al. 2014[29]	SNB	1. FNB continuous high	. FNB continuous high 99	
Canada, 2009-2011,		2. FNB continuous low		WOMAC score: no difference (p=0.68)
1 hospital		3. FNB single		(p=0.00)
Choy et al. 2011[30]	PCA	1. FNB continuous long	61	1 year
Korea, 2006-2007,		2. FNB continuous short		WOMAC pain: no difference (p=0.2)
1 surgeon				(p=0.2)
Fan et al. 2016[27]	PCA	1. FNB single	157	1 year
China, 2012-2014,		2. LIA		KSS: no difference (p=0.51)
2 surgeons				
Gao et al. 2017[23]	LIA	1. General anaesthesia	150	6 months
China, 2014-2015,		2. FNB single		HSS score: no significant
1 centre		3. FNB/ SNB single		difference
Macrinici et al. 2017[31]	LIA	1. ACB single	98	6 months
USA, Before 2017		2. FNB single		VAS pain: no difference
1 centre				
Nader et al. 2012[24]	PCA	1. FNB continuous	62	1 year
USA, 2007-2008,		2. Oral opioid		NRS pain stair: some evidenc
1 surgeon				favouring opioid (p=0.01) but not consistent. Overall NRS pain: no difference (p=1.0)
				VTE: concern opioid
Peng et al. 2014[26]		1. FNB continuous	280	6 months and 1 year
China, Before 2014,		2. PCA		NRS pain: some evidence favouring FNB at 6 months

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1 centre				(p=0.021); no difference at 1 year (p=0.273)	
Reinhardt et al. 2014[28]		1. FNB single/ epidural	94	1 year	
USA, 2010-2012,		2. LIA 48 hours		VAS pain: no difference	
2 surgeons					
Wegener et al. 2013[32]	FNB	1. SNB single	89	1 year	
The Netherlands, 2008-2010,		2. SNB continuous		WOMAC pain: no difference	
1 centre		3. PCA		(p=0.81)	
Widmer et al. 2012[22]	LIA, PCA	1. FNB single	55	1 year	
Australia, before 2012,		2. Control no FNB		WOMAC pain: no difference	
2 surgeons				(p=0.74)	
Wu and Wong 2014[25]	0	1. FNB continuous	60	6 months	
China, 2009-2011,		2. PCA	2. PCA		
1 centre					
Pain management: LIA		e e e e e e e e e e e e e e e e e e e			
McDonald et al. 2016[40]		1. LIA	222	1 year	
UK, 2010-2011		2. PCA		OKS: no difference (p=0.915)	
1 hospital					
Motififard et al. 2017[37]		1. LIA pre-emptive	120	6 months	
Iran, 2014-2015		injection		KSS: weak evidence favouring	
1 hospital		2. Control saline with	LIA (p=0.07). Difference		
		epinephrine		between groups (14.2/200) less than MCID (12.3/200).	
Niemeläinen et al. 2014[35]	PCA	1. LIA	56	1 year	
Finland, 2011-2012		2. Control saline		OKS: weak evidence from	
1 hospital				means and confidence intervals favouring LIA.	
				Difference (2.7/48) less than	
				MCID (4.0/48)	
Seah et al. 2011[41]	PCA	1. LIA with corticosteroid	100	6 months and 2 years	
Singapore, 2004-2005		2. LIA no corticosteroid		OKS: no difference	
		8			

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Williams et al. 2013[39]	LIA, PCA	1. LIA 48 hours	51	6 months and 1 year	
Canada, Before 2013		2. Control saline		VAS pain: no difference (6	
2 surgeons				months p=0.836, 1 year p=0.767)	
Wylde et al. 2015[33]	FNB, PCA	1. LIA	280	6 months and 1 year	
UK, 2009-2012		2. Control no LIA		WOMAC pain: weak evidence favouring LIA at 6 months	
1 centre				p=0.063; 1 year p=0.107.	
				Mean difference at 1 year (3.8/100) lower than MCID (8- 9/100)	
Pain management: Celecox	ib				
Meunier et al. 2007[42]	PCA	1. Celecoxib	44	1 year	
Sweden, 2004-2005		2. Control placebo	KOOS/VAS pain: no statistica difference		
1 centre					
Pain management: Ketamin	e/ Nefopam				
Aveline et al. 2014[43]	PCA	1. Ketamine infusion	75	6 months and 1 year	
France, 2005		2. Nefopam infusion		DN4/VAS pain: some evidence	
1 centre		3. Control saline		favouring ketamine (for DN4 p=0.02). Few patients had neuropathic pain at 12 months	
Pain management: Pregaba	lin				
Buvanendran et al. 2010[44]	LIA, PCA	1. Pregabalin	240	6 months	
USA, 2006-2007		2. Control placebo		S-LANSS pain: no neuropathi	
Single centre				pain reported in pregabalin group compared with 5.2% of	
				patients in control group (p=0.014)	
Tourniquet					
Ejaz et al. 2014[45]	Tranexamic	1. Tourniquet	64	6 months and 1 year	
Denmark, 2011-2012	acid	2. Tourniquet not inflated		KOOS pain: no significant	
1 centre				difference	

	Tranexamic	1. Tourniquet	100	6 months
China, 2015	acid	2. No tourniquet		VAS pain: no difference
1 centre				(p=0.728)
				Wound: concern tourniquet
Liu et al. 2014[46]		1. Tourniquet	20	6 months and 1 year
Australia, Before 2014		2. Tourniquet not inflated		OKS: no significant difference
1 surgeon				Transfusion: concern tourniquet
Mittal et al. 2012[48]		1. Tourniquet short	65	1 year
Australia, 2008-2010		duration		OKS: weak evidence from
1 centre		2. Tourniquet long duration		means and Cis on graph favouring long duration at 1 year. Mean difference (5)
				greater than MCID (4)
				Transfusions/ adverse events concern short
Zhang et al. 2017[49]		1. Tourniquet for entire	150	6 months
China, 2008-2011		operation		HSS score: no difference
1 surgeon		2. Tourniquet removed before wound closure		(p=0.839)
		3. Tourniquet from first		Transfusions: concern late tourniquet start in groups 1
		bone osteotomy until closure		and 2
Compression bandage			5,	
Brock et al. 2017[57]	Hydrocolloid	1. Compression bandage	49	6 months
UK, 2013-2014	dressing	2. Standard crepe		OKS: no difference (p=0.58)
1 hospital		bandage		
Blood conservation				
Hourlier et al. 2015[54]	Drain,	1. Continuous infusion	107	6 months
	tourniquet, electrocautery	tranexamic acid 2. Control saline		KSS: no difference (p=0.90)
France, 2009-2010	cicculocautery			

	Tourniquet	1. Intravenous and topical tranexamic acid	100	6 months
China, 2015				VAS pain: no difference
1 centre		2. No tranexamic acid		(p=0.728) HSS score: strong evidence favouring tranexamic acid
				(p<0.001). Mean difference (1.4/100) lower than MCID (8.3/100)
				Blood loss: control concern
Kim et al. 2014[51]	Tourniquet, drain,	1. Tranexamic acid	180	1 year
Korea, 2009-2011	compressive dressing	2. No tranexamic acid		WOMAC pain: no significant difference
1 hospital	diessing			Transfusion: control concern
Kusuma et al. 2013[55]	Tourniquet,	1. Thrombin infusion	80	6 months, 1 and 2 years
USA, Before 2013	Esmarch bandage,	2. No thrombin infusion		KSS: no difference (p=0.45)
1 hospital	electrocautery			
Napier et al. 2014[56]		1. Passive flexion	180	1 year
UK, 2003-2004		2. Passive extension		OKS: no difference (p=0.27)
1 hospital				Transfusion: extension concern
Sa-Ngasoongsong et al. 2011[50]	Drain and compressive	1. Tranexamic acid	48	6 months
Thailand, 2008-2009	dressing	2. Control saline		WOMAC score: no difference (p=0.282)
1 hospital				Transfusion: control concern
Sa-Ngasoongsong et al. 2013[52]	Drain and compressive	1. Tranexamic acid 500mg	135	1 year
Thailand, 2010-2011	dressing	2. Tranexamic acid		WOMAC score: no difference (p=0.42)
1 hospital		250mg 3. Control saline		Transfusions: control and 250mg group concerns
Denusomab				

Sweden, 2012-2014 2 centres		2. Placebo		KOOS pain: no significant difference
Continuous passive motio	n			
Bennett et al. 2005[61]	Physiotherapy	1. Standard CPM	147	1 year
Australia, 1997-2000		2. Early flexion CPM		KSS: no significant difference
1 hospital				
Ersözlü et al. 2009[60]	Physiotherapy	1. CPM low and	90	2 years
Turkey, 2003-2004		increasing		KSS: no difference (p=0.67)
1 hospital		2. CPM high and increasing		
		3. No CPM		
Electrical stimulation	0			
Avramidis et al. 2011[62]	Physiotherapy	1. Transcutaneous	76	1 year
Greece, 2005-2006		electric muscle stimulation		SF-36 bodily pain: strong
1 hospital		2. No treatment		evidence favouring electrical stimulation (p<0.001). Mean
				difference (12.5/100) close to MCID (16.9/100).
				OKS/ KSS: no difference
Moretti et al. 2012[64]	Rehabilitation	1. Pulsed electromagnetic	30	6 months and 1 year
Italy, 2008-2010	protocol	fields		VAS pain: some evidence
1 hospital		2. No treatment		favouring electrical stimulation (p<0.05). Mean difference
				(2.1/10) greater than MCID (16.1/100)
				Knee swelling: electrical stimulation concern
Rehabilitation				
Li et al. 2017[66]	Standard	1. Walking guidance and	86	6 months
China, 2015-2016	rehabilitation	training		VAS pain/ HSS score: some
1 hospital		2. No treatment		evidence favouring walking (both p<0.01). Mean VAS pai
		12		

				difference (2.4/100) greater than MCID (16.1/100)
Liebs et al. 2012[68]	CPM,	1. Early aquatic therapy	185	6 months, 1 and 2 years
Germany, 2003-2004	physiotherapy, post-discharge	2. Delayed aquatic therapy		WOMAC pain: no difference (p=0.22 at 12 months)
4 hospitals	aquatic therapy	шегару		(p=0.22 at 12 months)
Mahomed et al. 2008[69]	Physiotherapy	1. Multidisciplinary	234 hip	1 year
Canada, 2000-2002		supported early discharge and home physiotherapy	or knee replace	WOMAC pain: weak evidence favouring supported discharge
2 centres		2. Transfer to	ment	(p=0.08). Mean difference (4)
		rehabilitation centre		less than MCID (8-9)
Wang et al. 2014[67]		1. Wound closure in	80	6 months
China, 2009-2010		flexion		VAS pain: no difference
1 centre		2. Wound closure in		(p=0.64)
reente		extension		
Wound management				
Kong et al. 2014[58]	Skin staples and closure	1. Silicone gel	100	6 months and 1 year
South Korea, 2011	strip	0 Detrolours and		VAS pain: no difference (6 months p=0.886, 1 year
1 surgeon				p=0.201)
Anabolic steroids		4		
Hohmann et al. 2010[70]	CPM. Cold	1. Intramuscular	10	6 and 9 months, 1 year
Australia, Before 2010	compression,	nandrolone injections		KSS: some evidence favourin
1 surgeon		2. Saline injections		nandrolone (6 months p=0.04
louigoon				9 months p=0.06, 12 months p=0.03). Difference at 12
				months (10.2) close to MCID
				(12.3)
				Bone mineral density: weak evidence favouring nandrolon
ACB adductor canal blo	ock; CPM Continuou	us passive motion; DN4 Doule	eur Neurop	athique 4; FNB
Femoral nerve block; H	SS Hospital for Spe	ecial Surgery; KOOS Knee inj	ury and Os	teoarthritis Outcome
Score; KSS Knee Socie	ety Score; LIA local	infiltration analgesia; MCID m	ninimal clin	ically important
difference; NRS Numer	ical rating scale; Of	KS Oxford Knee Score; PCA	Patient con	trolled analgesia; SF-
36 Short Form 36 Healt	h Survey; S-LANSS	S Leeds assessment of Neuro	opathic Syn	nptoms and Signs Pain
		10		
		13		

Scale; SNB Sciatic nerve block; VAS Visual analogue scale; VTE Venous thromboembolism; WOMAC Western Ontario and McMaster Universities Osteoarthritis Index.

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Pain management

We identified 20 RCTs evaluating components of multi-modal pain management.

Femoral nerve block

Femoral nerve blocks (FNB) were studied in 10 RCTs.

Three RCTs compared FNB with no FNB. In one study with 55 patients, WOMAC pain scores at one year were similar in patients receiving single-shot FNB and untreated controls[22]. All patients received local anaesthetic infiltration (LIA) and patient-controlled analgesia (PCA). In another study with all participants receiving LIA, 150 were randomised to receive single-shot FNB with or without sciatic nerve block (SNB), or general anaesthesia[23]. There were no differences in HSS scores between groups at six months. Continuous FNB was compared with oral hydrocodone opioid in 62 patients receiving PCA[24]. There was some evidence for 'pain using stairs' favouring hydrocodone (p=0.01) but no difference in overall NRS-rated pain at one year and concern over venous thromboembolism in 4/31 participants treated with hydrocodone.

In two RCTs, continuous FNB was compared with PCA. In one study with 60 participants, the KSS at six months was similar between groups[25]. In another study with 280 participants, there was some evidence for higher incidence of NRS-rated pain at six months in the PCA group than the FNB group (p=0.021) but not at 12 months (p=0.273).[26]

Two RCTs compared FNB with LIA. In one study, all 157 participants also received PCA[27]. At one year, KSS values were similar in single-shot FNB and LIA groups. In the other study, 94 participants were randomised to receive single-shot FNB with continuous epidural infusion or LIA through an intra-articular catheter[28]. VAS-rated pain was similar between groups at one year.

In two RCTs, FNB procedures were compared. In one study with 99 patients randomised to two FNB concentrations, there was no difference in WOMAC score between groups at 12 months[29]. In another study with 61 participants allocated to two different durations of FNB, there was no difference in WOMAC pain scores at one year[30]. In these studies, all participants received either SNB[29] or PCA[30].

Single-shot FNB was compared with single adductor canal block in one RCT with 98 participants, all receiving LIA[31]. At six months there was no difference in VAS-rated pain. Sciatic nerve block

In one study, 89 patients were randomised to single-shot SNB, continuous SNB, or PCA[32]. All patients received FNB. At 12 months, there were no differences in pain for single-shot SNB and continuous SNB on the WOMAC pain scale or VAS-rated pain at rest or during mobilisation. Similarly, there were no differences between single-shot SNB and PCA in WOMAC pain scale or VAS-rated pain at rest or during mobilisation, or between continuous SNB and PCA.

Local anaesthetic infiltration

Four RCTs compared LIA with placebo. In one study, all 280 participants received FNB and PCA[33]. There was weak evidence that WOMAC pain scores were better in the LIA group at six (p=0.063) but not at 12 months (p=0.107) when the difference in means of 3.8/100 was lower than the MCID of 8-9/100 reported by Ehrich and colleagues[34]. In another study, 56 patients received LIA including ketorolac, or saline placebo, and all received PCA[35]. At one year, mean differences and confidence intervals provided weak evidence that OKS scores were better in the LIA group but the difference in means of 2.7/48 was less than the MCID of 4/48 reported by Beard and colleagues[36]. LIA before surgical incision was compared with placebo in one study with 120 participants[37]. None received FNB or PCA. There was weak evidence for a better KSS (function and knee score components) at six months in those receiving LIA (p=0.07) with a difference in means of 14.2/200 exceeding the MCID of 12.3/200 reported by Lee and colleagues[38]. In another study, all 51 participants received LIA intra-operatively, followed by PCA[39]. Those randomised to post-operative catheter-delivered LIA with ketorolac, or saline placebo had similar VAS-rated pain at six and 12 months.

LIA delivered as an injection and post-operative infusion was compared with epidural PCA in one study with 222 patients[40]. There was no difference between groups in OKS at 12 months.

In one study of 100 participants, LIA with or without corticosteroid were compared[41]. All patients received PCA. At two years there was no difference in OKS between groups.

Oral celecoxib

In one RCT, 44 participants received oral celecoxib or placebo[42], as well as PCA. There were no differences between groups in KOOS or VAS-rated pain at 12 months.

Ketamine or nefopam infusion

In one RCT, ketamine infusion, nefopam infusion and saline placebo were compared in 75 patients, all of whom received PCA[43]. There was weak evidence that participants receiving ketamine or nefopam had lower VAS-rated pain on movement at 12 months. For the Douleur

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Neuropathique 4 (DN4) measure of neuropathic pain, there was some evidence favouring ketamine over placebo at 6 and 12 months (p=0.02), but overall, few patients reported neuropathic pain at 12 months.

Pregabalin

Oral pregabalin was compared with placebo in one RCT with 240 participants[44]. All received LIA and PCA. At six months, no participants receiving pregabalin reported neuropathic pain when assessed using the Leeds assessment of Neuropathic Symptoms and Signs Pain Scale, compared with 5.2% of those receiving placebo (p=0.014) which represents some evidence favouring pregabalin.

Tourniquet

Five studies explored tourniquet use to provide a bloodless field.

In three RCTs, participants received TKR with or without a tourniquet. In one study with 64 patients, a difference in KOOS pain favouring tourniquet use was not significant at six or 12 months[45]. In another study with 20 patients, the OKS was not significantly different between groups at six or 12 months[46]. There were three blood transfusions in the tourniquet group, compared with none in the 'no tourniquet' group. In the third study with 100 participants, VAS-rated pain and HSS scores were similar between groups at 6 months[47]. Six cases of wound ooze occurred in the tourniquet group.

In two RCTs, short and long-duration tourniquet use were compared. In one study with 65 participants, there was weak evidence based on graphical representation of means and confidence intervals for improved OKS at 12 months in the long-duration group and the difference in means of 5/48[48] was greater than the MCID of 4/48. Adverse events were reported by 62% of participants receiving short-duration tourniquet compared with 38% in the long-duration group. The study was terminated early as 10 blood transfusions were required in the short-duration group compared with three in the long-duration group. In the second study with 150 participants, tourniquets were used in three different periods during surgery[49]. At six months, there were no differences between groups in HSS scores.

Blood conservation

Seven studies evaluated strategies to limit blood loss after TKR.

Tranexamic acid

Five RCTs evaluated tranexamic acid.

Tranexamic acid injections or infusions were compared with saline placebo or untreated control in four RCTs[47,50-52]. In all studies, control patients required more blood transfusions. In one study including 180 participants comparing intravenous tranexamic acid with untreated controls, there was no significant difference in WOMAC pain scores at one year[51]. In another study with 48 participants comparing intra-articular tranexamic acid injection with saline placebo, there was no significant difference in WOMAC scores at six months[50]. One study with 135 participants compared two intra-articular tranexamic acid doses and saline control[52]. There were no significant differences in WOMAC scores at one year. Intravenous and intra-articular tranexamic was compared with untreated controls in one study with 100 participants[47]. VAS-rated pain at six months was similar between groups, but there was strong evidence favouring tranexamic acid for HSS scores (p<0.001) although the difference in means of 1.4/100 was lower than the MCID of 8.3/100 reported by Singh and colleagues[53].

In one study, continuous tranexamic acid infusion was compared with a single bolus in 106 patients[54]. There was no difference between groups in KSS at six months or blood loss.

Thrombin infusion

In one RCT with 80 participants, thrombin infusion was compared with untreated control[55]. At one year there was no difference between groups in pain measured on the KSS.

Flexion or extension

For blood management, operated knees were kept in passive flexion or passive extension after surgery in one RCT with 180 patients[56]. At one year, OKS was similar between groups. Transfusion requirement was greater in patients with passive extension.

Compression bandage

One RCT with 49 participants compared compression bandaging to reduce post-operative knee swelling with standard bandaging. OKS was similar in randomised groups at six months[57].

Wound management

One RCT evaluated a wound care strategy to limit post-operative scar pain. Investigators compared silicone gel application to the surgical scar with placebo in 100 participants[58]. There were no significant differences in VAS-rated pain at six and 12 months.

Denusomab

BMJ Open

One RCT evaluated use of the antiresorptive monoclonal antibody Denusomab to promote bone healing. Fifty participants were randomised and at 12 and 24 months there were no significant differences between groups in KOOS pain[59].

Continuous passive motion

Two RCTs evaluated use of continuous passive motion (CPM) to minimise joint stiffness and improve range of movement. In one study, 90 participants were randomised to no CPM, CPM at low flexion from post-operative day 1–7, or CPM at high flexion from post-operative day 3–7[60]. There was no significant difference between groups in KSS at two years. In the other study, 147 participants were randomised to CPM with increasing range of movement from day 1–6, early flexion CPM from day 0–6, or no CPM[61]. There were no significant differences between groups in KSS at 12 months.

Electrical stimulation

Two RCTs evaluated electrical stimulation which is believed to have anti-inflammatory activity and limit muscle atrophy. In one study with 76 participants receiving transcutaneous electric muscle stimulation from post-operative day two for six weeks or no intervention, Short Form 36 bodily pain showed strong evidence for greater improvement at one year in the intervention group compared to control (p<0.001)[62]. The difference in means of 12.5/100 was close to the MCID of 16.9/100 reported by Escobar and colleagues[63]. There were no differences in OKS or KSS scores. In another study with 30 participants, pulsed electromagnetic fields from postoperative day 7 were compared with untreated control[64]. At 12 months, there was some evidence that VAS-rated pain was lower in intervention patients compared with controls (p<0.05). The difference in means of 2.1/10 was greater than the MCID of 16.1/100 reported by Danoff and colleagues[65]. Knee swelling was common during the intervention.

Rehabilitation

Four RCTs evaluated features of early rehabilitation focusing on regaining range of movement, functional independence and improving mobility.

Walking guidance and training

In one study, 86 participants were randomised to walking guidance and training from postoperative day two or no intervention further to standard rehabilitation[66]. At six months, there was some evidence that those receiving intervention had lower VAS-rated pain (p<0.01) and HSS score (p<0.01) than controls. The difference in mean VAS-rated pain of 2.4/10 was greater than the MCID of 16.1/100.

Flexion or extension during knee closure

Targeting improved functional recovery, wound closure performed in 90° flexion was compared with wound closure in full extension in one study with 80 participants[67]. There was no difference between groups in VAS-rated pain at six months.

Aquatic therapy

In one study with 185 participants, aquatic therapy commenced on post-operative day six or 14 were compared[68]. Patients reported similar WOMAC pain at 12 and 24 months.

Supported early discharge

In one study, early discharge supported by physiotherapist home visits and outpatient or selfdirected physiotherapy was compared with two week rehabilitation centre-based usual care[69]. The study included 234 individuals receiving TKR or total hip replacement. Compared with usual care, there was weak evidence that patients with early discharge had lower WOMAC pain scores at 12 months (p=0.08). The difference in means of 4 was less than the MCID of 8-9/100. Results were not presented separately but did not differ between patients with TKR or total hip replacement.

Anabolic steroids

Searches identified one study of anabolic steroids to improve post-operative muscle strength. Ten participants received intramuscular nandrolone injections or saline from post-operative day five for six months. KSS results indicated some evidence for improvement in the intervention group compared with controls at 12 months (p=0.03)[70]. The difference in means of 10.2/200 was close to the MCID of 12.3/200.

Interventions with no long-term outcome

Interventions with lack of RCT evidence are summarised in Figure 1.

While 148 RCTs of deep vein thrombosis (DVT) prophylaxis were identified, only five reported long-term follow up, none of which included a pain or outcome score. Among 29 RCTs of antibiotic prophylaxis, 16 reported long-term follow up, but none included a pain or outcome score. Six RCTs evaluated the use of bisphosphonates and, although all reported long-term

follow up, none reported pain or an outcome score. One study reported long-term follow up of an RCT of teriparatide but included no data on pain.

For some interventions, RCTs with long-term pain outcomes were identified, but none were at low risk of bias: cold therapy; guided imagery; platelet rich plasma; and trigger point needling.

Aspects of peri-operative care evaluated in RCTs but lacking long-term pain follow up were: adenosine triphosphate; alternative and Chinese medicine; assistive devices; brain stimulation; calcium supplements; cardiovascular drugs; colloids and crystalloids; comorbidity management; constipation treatment; creatine; delirium prevention; dexmedetomidine; glucocorticoids; glucose infusion; iron; laser therapy; methylprednisolone; music therapy; nausea prevention; nutritional supplements; physiological treatments; remote ischaemic preconditioning; sleep treatments; therapy dogs; and warming.

DISCUSSION

Peri-operative care for patients with osteoarthritis receiving TKR varies widely[71,72]. To guide decisions on appropriate care, the top level of evidence in the hierarchy of primary research is the RCT[73,74]. Bringing evidence from RCTs together in systematic reviews with thorough risk of bias assessment ensures that health professionals have the information they need to deliver a high-quality patient experience with safe, clinically-effective and cost-effective treatments[75]. Furthermore, systematic reviews can identify gaps in the evidence base and promote further research.

Much research in TKR aims to identify treatments that facilitate a speedy recovery with minimal short-term pain. However, patients choose to have joint replacement for long-term pain relief and reduction in functional limitations. Thus, changes to peri-operative care, supported by short-term RCT evidence, should be backed up with evidence about long-term effectiveness for reducing pain and reassurance that there are no long-term unfavourable consequences. To this end, we synthesised evidence from RCTs evaluating peri-operative interventions which have considered their long-term effects on pain outcomes.

A major focus of research into improving long-term pain after TKR has been through prevention of acute post-operative pain using multimodal analgesia. Our review provides some encouragement for further research on long-term benefits of intra-articular LIA injections, as previously shown in short-term studies[19,76], ketamine infusion, oral pregabalin and oral opioids. Nerve blocks are effective for managing peri-operative pain[77] but we identified no long-term benefit. In single studies, there was no benefit for nefopam infusion, oral celecoxib or LIA with additional corticosteroid. Regarding future studies, standardisation of the multi-modal regimen will allow evaluation of extra or alternative components in multiple studies in different settings. With such an approach, convincing evidence will accrue to guide multimodal pain management.

Tranexamic acid is highly effective in reducing blood transfusions during TKR[78]. We found no evidence that tranexamic acid affects long-term pain or, as observed in registry studies[79,80], adverse events. Single RCTs of thrombin infusion and maintenance of knee in flexion to prevent blood loss showed no effect on long-term pain. Tourniquets improve intraoperative visualisation of the joint, reduce blood loss and facilitate cement fixation but are associated with nerve damage, delayed recovery, acute pain and need for analgesics[81,82]. The RCTs we identified showed no effects of tourniquet use on long-term pain.

Consistent with a previous review[83], there was no suggestion that CPM affects long-term pain. Studies provided encouragement for further research into walking training, anabolic steroid injection, electrical stimulation and supported discharge.

For some interventions a direct mechanism is clear, but for others, reasons for long-term impact are less obvious. This may explain why no studies evaluated DVT prophylaxis with long-term follow up excepting a small number reporting adverse events. However, treatments to prevent symptomatic DVTs which occur in about 1% of treated patients[84] also reduce the incidence of asymptomatic DVT observed in about 28% of treated patients[85] and this may have long-term benefits. Conversely, new anticoagulants are associated with bleeding[86], which may increase the risk of wound complications[87] and joint infection[88] which are associated with long-term pain[89,90].

Our study is limited by the lack of meta-analysis which was not appropriate due to intervention and outcome heterogeneity. In the context of perioperative pain management, this was noted previously[76]. Our approach to assessing the evidence was a narrative synthesis of studies with low risk of bias. While this may seem overly restrictive, Cochrane risk of bias assessment allows us to screen out studies with important issues that may affect the validity of results. The main potential source of bias was incomplete outcome assessment. Although studies with longterm follow up are naturally at higher risk of missing data, we maintained a standard in this domain as it is recognised that research participants who do not complete follow up assessments differ in outcomes from those with follow up data and their inclusion could change the interpretation of results[91].

We summarised p-values to assess the strength of evidence but, as statistically strong evidence may not reflect clinically important results[92], where possible we also compared effect sizes with MCIDs. Our review considered a diverse range of interventions at a specific time in the TKR pathway and, as we were unable to make clinical practice recommendations, we did not adopt the GRADE system[93] for this review.

Our systematic review of peri-operative interventions brings together evidence on interventions in the peri-operative phase of the TKR pathway. Whilst not supportive of the inclusion of specific interventions in clinical practice to optimise long-term pain outcomes, there are clearly areas that merit research. High quality studies assessing long-term pain after peri-operative interventions are feasible and necessary to ensure that patients with osteoarthritis achieve good long-term outcomes after TKR.

AUTHOR CONTRIBUTIONS

All authors contributed to the conception and design of the study. ADB, JD and VW undertook the systematic review. ADB and JD carried out the risk of bias assessments. ADB drafted the article with revisions by JD and VW. All authors approved the final version for publication.

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COMPETING INTERESTS STATEMENT

The authors report no competing interests.

DATA STATEMENT

All extracted data is included in the Supplementary material.

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dentification	Articles identified in November 2016 (n=7996) Articles identified in February 2018 update (n=1701)									
				•						
Screening		Articles screened (n=9697) No relevance (n=7364)								4)
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Eligibility				Poter	ntially relev	vant (n =	2333)			
)				•						
Intervention	N	In: low risk of bias	No pain/ score outcome	High/ unclear risk of bias	No long- term follow up	Abstract only	Additional publication	Protocol	Review	Retract
Adenosine triphosphate	2	0	0	0	1	0	0	0	1	0
Alternative medicine	4	0	0	0	4	0	0	0	0	0
Anabolic steroids	2	1	0	0	0	0	0	0	1	0
Antibiotic prophylaxis	43	0	16	0	13	0	0	1	13	0
Assistive devices Bisphosphonates	2	0	0	0	2	0	0	0	0 9	0
Blood management	355	7	10	0	209	0	0	4	9 124	0
Brain stimulation	3	0	0	0	3	0	0	0	0	0
Calcium supplement	1	0	0	0	1	0	0	0	0	0
Cardiovascular drugs	4	0	0	0	2	0	0	0	2	0
Chinese medicine	2	0	0	0	2	0	0	0	0	0
Cold therapy	30	0	0	1	24	0	0	0	5	0
Colloids and crystalloids	1	0	0	0	1	0	0	0	0	0
Comorbidity management	1	0	0	0	1	0	0	0	0	0
Compression Constipation treatment	8	1	0	0	6	0	0	1	0	0
Continuous passive motion	56	2	8	0	2	1	0	1	14	0
Creatine monohydrate	1	0	0	0	1	0	0	0	0	0
Delirium prevention	4	0	0	0	3	0	0	0	1	0
Denusomab	1	1	0	0	0	0	0	0	0	0
Dexmedetomidine	1	0	0	0	1	0	0	0	0	0
Deep vein thrombosis prophylaxis	474	0	5	0	143	0	4	8	314	0
Electrical stimulation	37	2	0	3	20	0	2	0	10	0
Glucocorticoid	2	0	0	0	0	0	0	0	2	0
Glucose infusion Guided imagery	1 5	0	0	0	4	0	0	0	0	0
Iron	7	0	0	0	6	0	0	0	1	0
Laser therapy	1	0	0	0	1	0	0	0	0	0
Methylprednisolone	3	0	0	0	3	0	0	0	0	0
Music therapy	9	0	0	0	9	0	0	0	0	0
Nausea prevention	11	0	0	0	9	0	2	0	0	0
Nutritional supplements	4	0	0	0	4	0	0	0	0	0
Pain management	987 26	20 0	5	12 0	711 23	1	20 0	9	207 2	2
Physiological Platelet rich plasma	12	0	0	1	<u>23</u> 6	0	0	0	5	0
Rehabilitation	67	4	0	2	43	0	0	1	17	0
Remote ischaemic pre-conditioning	5	0	0	0	5	0	0	0	0	0
Sleep treatment	3	0	0	0	2	0	1	0	0	0
Teriparatide	1	0	1	0	0	0	0	0	0	0
Therapy dogs	1	0	0	0	1	0	0	0	0	0
Tourniquet use	100	5	3	3	67	0	2	1	19	0
Trigger point needling	1	0	0	1	0	0	0	0	0	0
Warming	19	0	0	0	16	0	0	0	3	0
Wound management	17	1	0	0	12	0	0	1	3	0

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Supplementary material. Search strategy as applied in MEDLINE on Ovid

- 1 randomized controlled trial/ or randomized controlled trial.pt.
- 2 controlled clinical trial.pt.
- 3 randomized.ab.
- 4 placebo.ab.
- 5 randomly.ab
- 6 trial.ab
- 7 randomised.tw
- 8 1 or 2 or 3 or 4 or 5 or 6 or 7

9 review/

- 10 'systematic review\$'.mp
- 11 9 or 10
- 12 8 or 11
- 13 Arthroplasty, Replacement, Knee/
- 14 Knee Prosthesis/

15 (arthoplast\$ adj3 knee\$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

16 (knee\$ adj3 replac\$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

17 (knee adj3 implant\$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

18 13 or 14 or 15 or 16 or 17

19 12 and 18

Supplementary material. All peri-operative interventions with long-term pain or score follow up

1. Pain management

Author	Indication	Common anaesth	esia			Follow up
Country Recruitment dates Setting	Number randomised intervention; control Age % female	Group 1 (intervention)	Group 2 (intervent	ion)	Group C (control)	Losses to follow up intervention; control Risk of bias issues Key results
FNB single vs No F	NB	6				
Widmer et al. 2012[22] Australia Before 2012 2 surgeons	Elective unilateral TKR 27; 28 Median 72.1 (IQR 64.4, 76.5); 69.4 (63.4, 75.5) 44.4%; 44.4%	Premedication 1-3mg i.v. midazolam. Propofol induction and sevoflurane general anaesthetic.LIA with 200mg ropivacaine and 0.5mg adrenaline in 100ml saline.PCA 20µg fentanyl at 5-minute intervals on demand until morning POD2. Then, oral oxycodone SR 10mg every 12 hours. Daily COX II inhibitor and paracetamol 1g every 6 hours as tolerated. For breakthrough pain, 5-10mg oxycodone immediate release every 3 hours as needed.Ultrasound guided FNB with 100mg ropivacaine in 30ml salineSham setup for FNB. No identification or injection of femoral sheath			1 year No losses to follow up reported Low risk of bias WOMAC pain (high score favourable) at 1 year: FNB and LIA median 2.0 (IQR 0, 2.8); LIA no FNB 1.0 (0, 2.0). p=0.74 No adverse events occurred in either group	
FNB single vs ONB		1				
Bergeron et al. 2009[94] Canada 2005-2006 1 centre	Primary unilateral TKR 19; 20; 20 Mean 65.1 (SE 2.0); 72 (1.8); 67 (1.3) 79%; 80%; 75%	Intraoperative sedation with iv propofol at discretion of anaesthesiologist. Lumbar spinal anaesthesia with 12mg 0.5% bupivacaine. Postoperative i.v. PCA with fentanyl 50µg/ml set to deliver 25µg every 5 min as needed. Celecoxib 100mg and acetaminophen 650mg on arrival in recovery room and every 12 and 6 hrs respectively. Breakthrough medication with intramuscular ketorolac 10 mg every 4 hrs.				1 year Overall 32 lost to follow up High risk of bias: only 27/59 patients followed up due to resource limitations. No difference in HSS pain at rest or during activity at 1 year between the study groups.

2009[95] Singapore Before 2009 1 hospitalosteoarthritis 20 (17 received treatment); 20 (18 received treatment); 20bupivacaine. Intraoperative sedation with midazolam in increments of 0.5mg. Intravenous PCA morphine (1mg/ml, on-demand bolus doses of 1 mg with 5 minute lockout, maximum dose 816.4% of patients who received intervention lost to follow up Unclear risk of bias due to differences in OKS and weight at baseline, and limited methodologics details.1 hospitalWean 66.7 (SD 8.4); 65.4 (8.4); 67.8 (5.5)Low dose continuous FNB at conclusion of TKR with ropivacaine 0.15% (10 ml/hr in the first 24 hours, followed by 5ml/hr in the next 24 hours)No FNBNo FNBSNB injection vs SNB continuous vs controlLorazepam 1mg 2 hours and acetaminophen 2g 1 hour before surgery. FNB with stimulating catheter: loading dose 20 ml levobupivacaine 0.375% and after 45 minutes a continuous infusion of levobupivacaine 0.125% 10 ml/hr. General anaesthesia induced with 3-5 µg/ml propofol minutes a continuous infusion of levobupivacaine 0.125% 10 ml/hr. General anaesthesia induced with 3-5 µg/kg/min and maintained with 3-3 µg/ml at 0.1-0.25 µg/kg/min. Postoperatively, FNB dot patient controlled FNB singlection s0 (range 25- 100, SNB continuous 90 (55-100) and PCA only 90 (35-100), p=0.81.			FNB with stimulator. 20ml 0.5% bupivacaine with 1/200,000 epinephrine.	ONB with stimulator. 20ml 0.5% bupivacaine with 1/200,000 epinephrine.	No injection but inguinal area prepared, and sham block performed behind drapes.	No long-term complications attributable to anaesthetic regimen
2009[95] osteoarthritis 20 (17 received Before 2009 1 hospital 20 (17 received 1 hospital 20 (17 received 1 hospital 20 (17 received 20 (17 received Intravenous PCA morphine (1mg/ml, on-demand bolus 20 (17 received Intravenous PCA morphine (1mg/ml, on-demand bolus 20 (17 received Intravenous PCA morphine (1mg/ml, on-demand bolus 20 (17 received Intravenous PCA morphine (1mg/ml, on-demand bolus 20 (17 received Intravenous PCA morphine (1mg/ml, on-demand bolus 20 (17 received Intravenous PCA morphine (1mg/ml, on-demand bolus 20 (17 received Intravenous PCA morphine (1mg/ml, on-demand bolus 20 (17 received Intravenous PCA morphine (1mg/ml, on-demand bolus 40 (18 (11 mg/ml, on-demand bolus Intravenous PCA morphine (1mg/ml, on-demand bolus 20 (17 received Intravenous PCA morphine (1mg/ml, on-demand bolus 30 (17 (11 mg/ml, on-demand bolus Intravenous PCA morphine (1mg/ml, on-demand bolus 40 (10 ml/hr in the pirst 24 hours, followed by 5ml/hr Intravenous PCA morphine (1mg/ml, on-demand bolus 31 (1 ments 29; 30; 30 (90 Trandmised 12 (2 morths 29; 30; 30 (90 Trandmised			uous high dose vs N	o FNB		
Wegener et al. 2013[32]TKR 29; 30; 30 (90 randomised)Lorazepam 1mg 2 hours and acetaminophen 2g 1 hour before surgery. FNB with stimulating catheter: loading dose 20 ml levobupivacaine 0.375% and after 45 minutes a continuous infusion of levobupivacaine 0.125% 10 ml/hr. General anaesthesia induced with 3-5 µg/ml propofol infusion and remifentanil 0.5 µg/kg/min and maintained with 2-3 µg/ml at 0.1-0.25 µg/kg/min. Postoperatively, FNB changed to patient controlled FNB, 5ml bolus, 30-minute lockout; basal rate 6 ml/hr. i.v. morphine administered if needed. Postoperative analgesia with acetaminophen 1g 4 times daily. Diclofenac 50mg or tramadol 50mg 3 times daily. Tramadol 100mg before removal of nerve catheters.12 months 2;7;5 lost to follow up Low risk of bias Median WOMAC pain scores at 12 months: SNB injection 80 (range 25- 100), SNB continuous 90 (55-100) and PCA only 90 (35-100), p=0.81. No difference between groups in VA pain at rest (p=0.90) or during mobilisation (p=0.43).	Shum et al. 2009[95] Singapore Before 2009 1 hospital	osteoarthritis 20 (17 received treatment); 20 (18 received treatment); 20 Mean 66.7 (SD 8.4); 65.4 (8.4); 67.8 (5.5) 88%; 72%; 80%	bupivacaine. Intraop increments of 0.5mg Intravenous PCA mo doses of 1 mg with 5 mg/hr) Low dose continuous FNB at conclusion of TKR with ropivacaine 0.15% (10 ml/hr in the first 24 hours, followed by 5ml/hr in the next 24 hours)	High dose continuous FNB at conclusion of TKR with ropivacaine 0.2% (10 ml/hr in the first 24 hours, followed by 5 ml/hr in the next	midazolam in demand bolus timum dose 8	 16.4% of patients who received intervention lost to follow up Unclear risk of bias due to differences in OKS and weight at baseline, and limited methodologica details. No separate pain outcome but mean OKS slightly more favourable in group with no FNB, 18.2 (SD 3.7) compared with combined FNB groups, 19.8 (5.4) but this was not significant. No complications attributable to use
 2013[32] The Netherlands 2008-2010 1 centre 29; 30; 30 (90 randomised) Median 65 (range 43-81); 66 (43-83); 62 (50-79) 62%; 70%; 73% before surgery. FNB with stimulating catheter: loading dose 20 ml levobupivacaine 0.375% and after 45 minutes a continuous infusion of levobupivacaine 0.125% 10 ml/hr. General anaesthesia induced with 3-5 µg/ml propofol infusion and remifentanil 0.5 µg/kg/min and maintained with 2-3 µg/ml at 0.1-0.25 µg/kg/min. Postoperatively, FNB changed to patient controlled FNB, 5ml bolus, 30-minute lockout; basal rate 6 ml/hr. i.v. morphine administered if needed. Postoperative analgesia with acetaminophen 1g 4 times daily. Diclofenac 50mg or tramadol 50mg 3 times daily. Tramadol 100mg before removal of nerve catheters. 29; 30; 30 (90 randomised) 20; 75 lost to follow up Low risk of bias Median WOMAC pain scores at 12 months: SNB injection 80 (range 25- 100), SNB continuous 90 (55-100) and PCA only 90 (35-100), p=0.81. No difference between groups in VA pain at rest (p=0.90) or during mobilisation (p=0.43). No information on adverse events. 	-					
	Wegener et al. 2013[32] The Netherlands 2008-2010 1 centre	29; 30; 30 (90 randomised) Median 65 (range 43-81); 66 (43-83); 62 (50-79)	before surgery. FNB dose 20 ml levobupiv a continuous infusion General anaesthesia infusion and remifent with 2-3 µg/ml at 0.1- changed to patient co lockout; basal rate 6 needed. Postoperativ times daily. Diclofena daily. Tramadol 100m	with stimulating cathe vacaine 0.375% and a n of levobupivacaine (induced with 3-5 µg/ tanil 0.5 µg/kg/min an -0.25 µg/kg/min. Post ontrolled FNB, 5ml bo ml/hr. i.v. morphine a ve analgesia with ace ac 50mg or tramadol so ng before removal of	eter: loading after 45 minutes 0.125% 10 ml/hr. ml propofol d maintained operatively, FNB olus, 30-minute dministered if taminophen 1g 4 50mg 3 times	2;7;5 lost to follow up Low risk of bias Median WOMAC pain scores at 12 months: SNB injection 80 (range 25- 100), SNB continuous 90 (55-100) and PCA only 90 (35-100), p=0.81. No difference between groups in VA pain at rest (p=0.90) or during mobilisation (p=0.43).

General anaesthesi	a vs FNB single vs FN	Group Fs: SNB single injection. SNB loading dose of 20 ml levobupivacaine 0.375%.	Group FCS: SNB continuous infusion. SNB loading dose of 20 ml levobupivacaine 0.375%. Continuous infusion of levobupivacaine 0.125% 10 ml/hr started 45 mins after catheter placement. SNB maintained for 36 hours postoperatively (10 ml/hr).	Group F: No SNB. PCA via femoral nerve catheter	
Gao et al. 2017[23] Primary unilateral China 2014-2015 1 centre 50; 50; 50 Mean 65.8 (SD 6.7); 66.4 (7.4); 67.6 (6.3) 81%; 80%; 76%	Primary unilateral TKR for osteoarthritis 50; 50; 50	Pre-operative and post-operative celecoxib 0.2g twice daily. 100ml intra-operative LIA with ropivacaine 200mg and epinephrine 0.25 mg.			6 months 2; 1; 0 Low risk of bias Mean HSS at 6 months: 87.1 (SD
	General anaesthesia	Ultrasound guided FNB 5g/l ropivacaine 20ml plus 0.1mg epinephrine	Ultrasound guided FNB 5g/l ropivacaine 20 ml plus 0.1mg epinephrine and SNB 5g/l ropivacaine 20ml plus 0.1mg epinephrine	6.9); 87.4 (7.3); 88.5 (6.7). No significant difference. Nausea and vomiting: 4; 2; 1, urinary retention: 3; 1; 2.	
	id vs No LIA/ placebo				
Wylde et al. 2015 [33]	Primary unilateral TKR for		nulator and/ or ultraso (caine). Spinal or gen		6 and 12 months
UK	osteoarthritis	Intra-operative anal	gesia provided by titr morphine if necessa	24;19 at 12 months (including those who did not receive treatment)	

2009-2012 1 centre	157; 159 (143; 137 received treatment)	paracetamol 30 minutes before the end of operation. Immediately post-operative 400mg oral ibuprofen.	Low risk of bias	
i centre	Mean 69.5 (SD 9.4); 68.7 (7.9) 52%; 54%	PCA with morphine 1mg/ml, 1 mg bolus dose and a 5- minute lock-out. If necessary morphine bolus up to 0.2mg/kg as rescue analgesia. During hospital stay, visit from pain specialist nurse. Oral or i.v. paracetamol every 6 hours and ibuprofen 400mg every 8 hours. When PCA no longer needed, oral codeine phosphate 30-60mg every 6 hours, tramadol 50-100mg every 6 hours and oramorph 10-20mg as rescue analgesia.60ml intra-operative LIA with 0.25% bupivacaine and 1/200,000 adrenaline injected into the posterior capsule, medial and lateral capsule, fascia and muscle, and subcutaneous tissues.No treatment other than standard care	At 12 months WOMAC pain score (0 100) in LIA group median 90 (IQR 30), Control 85 (35); ITT-CC linear regression coefficient 3.83 (95%CI - 0.83, 8.49), p=0.107. At 6 months WOMAC pain score ITT-CC linear regression coefficient 4.10 (95%CI - 0.22, 8.43), p=0.063. Mean differences lower than MCID of 8- 9[34]. Superficial and deep wound infection rate in LIA group 3.2% and 1.9% in control group, p=0.500. No differences in serious adverse event between groups	
Williams et al. 2013[39] Canada Before 2013 1 centre, 2 surgeons	Primary unilateral TKR for osteoarthritis 35; 32 (26; 25 received treatment) Mean 66 (SD 9.7); 67 (12.5) 58%; 60%	Sedation with i.v. midazolam and propofol. Intraoperative LIA loading dose of 20ml 0.25% bupivacaine/ epinephrine injection, 10ml into medial and lateral subcutaneous tissue around the incision and 10ml intra-articular after closure. Infiltrate delivered by pain pump into lateral recess of intra- articular space. Spinal anaesthetic with 10-15 mg of 0.75% or 0.5% plain bupivacaine and 20µg fentanyl. Postoperative morphine PCA. 7.5mg i.v ketorolac preoperatively plus 15mg every 6 hours postoperatively for 48 hours, then oral ketorolac 10mg every 6 hours for 2 days. Gabapentin 600mg given preoperatively plus 300mg twice daily for 48 hours postoperatively. Oxycodone 10mg twice daily for 48 hours postoperative. Oral paracetamol 650mg every 4 hours for 72 hours. Infusion of 0.5% bupivacaine at 2ml/hr for 48 hrs	6 and 12 months 3;1 of those who received treatment Low risk of bias Mean VAS pain score at 6 months 1.2 (SD 1.3); 1.2 (1.2). p=0.836. At 12 months 0.9 (1.2); 1.0 (1.1). p=0.767 No short-term differences in adverse events except control patients more likely to be drowsy at 48 hrs. Long- term adverse events not reported.	
Niemeläinen et al. 2014[35] Finland 2011-2012	Primary unilateral TKR for osteoarthritis 30; 30 (27; 29 received treatment)	Oral paracetamol 1g given 1 hour before surgery. Spinal anaesthesia with 15mg bupivacaine in 3ml. After surgery oral paracetamol 1g every 6 hours and oral meloxicam (15mg) every 24 hours. PCA with oxycodone 2mg, lock-out time 8 min.	12 months 1; 4 Low risk of bias No pain measure separate from OKS Weak evidence of more favourable	

1 hospital	Mean 65 (SD 4.9); 64 (6.7)	Rescue levobupivacaine medic epidural catheter	ation through a lumbar	OKS (0-48) in the LIA group at 12 months, mean difference -2.7 (95%		
	56%; 48%	Intra-operative periarticular LIA of 100ml saline with levobupivacaine (150mg) mixed with ketorolac (30mg) and adrenaline (0.5mg).	Intra-operative periarticular LIA of 100ml saline	CI -5.48, 0.07). Difference lower than MCID of 4.0[36]. Infection: 0; 0. Severe pain treated with epidural analgesia: 0; 3. Nausea 1; 1		
Motififard et al. 2017[37]Primary unilateral TKR for osteoarthritis 60; 601 hospitalMean 66.4 (6.4); 64.5 (6.0) 86.0%; 94.3%		Spinal anaesthesia. No FNB or SNB. Pain medication provided as re meloxicam (15 mg daily), celec acetaminophen (1g every 8 hou 8 hours), ketorolac (30 mg slow dose max), and morphine (5–1)	6 months 3; 7 Low risk of bias No separate pain measure. Weak evidence for improved KSS (0-200) in LIA group at 6 months, mean 115.55 (SD 15.506); 101.40 (16.117).			
		Peri-articular injection, 15 minutes before incision, of 100ml saline containing 50 mg bupivacaine hydrochloride 0.5%, 1 ml morphine sulphate 10 mg/ml, 300 µg epinephrine (1:1000) and 30 mg ketorolac	100ml saline containing 300 µg epinephrine (1:1000)	P=0.07. Difference of 14.15 greater than MCID of 12.3[38]. Difference was significant at 6 weeks, p<0.001 No complications related to TKR or LIA. Low back pain (1; 2), stroke (0; 1), CHF (1; 0)		
McDonald et al. 2016[40] UK 2010-2011 1 hospital	Primary unilateral TKR for osteoarthritis 113; 109 received common spinal anaesthesia (121; 121 randomised) Median 68 (IQR 62, 72); 67 (62, 73) 59%; 55%	Oral premedication with 10-20r ranatidine, 10mg dexamethaso paracetamol. Spinal anaesthesia Intra-articular and subcutaneous infiltration during surgery of 200 ml of 2mg/ml ropivacaine without adrenalin or additives. Catheter inserted, and 20 ml infiltrate injected following wound closure. Further boluses of 40 ml 2 mg/ml ropivacaine via infusion pump 4 hours after leaving theatre and morning of POD1. Two		12 months 9; 11 of those receiving treatments Low risk of bias No separate pain outcome. Mean OKS at 12 months: median 41 (IQR 35, 44); 41 (34;44). P=0.915 Suspected infection 2; 1. MI 0; 1. GI bleed 1; 0. renal failure 1; 0. Died 2; 0)		

		additional top ups of 40 ml 2mg/ml ropivacaine were prescribed if required.		
Celecoxib vs placeb	0			
Meunier et al. 2007[42] Sweden 2004-2005 1 centre	Elective primary unilateral TKR for osteoarthritis 25; 25 (24; 20 received treatment) Mean 68 (SD 6.3); 69 (7.7)	midazolam or propofol sedation if needed. Paracetamol 1 g preoperatively and then with tramadol 50-100 mg 4 times a day during hospital stay. Ketobemidone (2.5-5mg i.v. or subcutaneous) on demand. Paracetamol and tramadol used as required after discharge.		12 months No losses to follow up after surgery reported Low risk of bias No effect of celecoxib on VAS or KOOS pain at 1 year.
	71%; 40%	preoperatively and twice daily for 3 weeks	hour preoperatively and twice daily for 3 weeks	DVT: 0; 1. Deep infection: 0; 0.
Ketamine vs placebo)	NO		
Purcell2009 [96]TKRAustralia16 (5; 7 complet study per protocBefore 2009study per protoc1 centre (pilot study)Mean 65.6 (SD	16 (5; 7 completed study per protocol) Mean 65.6 (SD 10.2); 60.3 (11.9)	Intrathecal injection of 15mg bupivacaine and 100µg morphine. General anaesthesia. After surgery 1.5g paracetamol and then 750mg every 4 hours; PCA with morphine 2mg boluses with 10-minute lockout; morphine rescue 2.5mg intravenously as required; and rescue oral ibuprofen 800mg.Ketamine 0.5mg/kg bolusSaline infusion.		6 months 3 protocol breaches and 1 patient with uncontrolled pain. High risk of bias due to non-ITT reporting and recruitment difficulties 2/5 ketamine group had mild/moderate pain on the WOMAC pain scale at 26 weeks or failed to
		followed by 4µg/kg/min infusion. Commenced before surgical incision and continued until wound bandaged or syringe empty.	Commenced before surgical incision and continued until wound bandaged or syringe empty.	improve compared with 5/7 controls 1 adverse psycho-mimetic effect no attributed to intervention or control treatment
Ketamine vs Nefopa	m vs placebo			
Aveline et al. 2014[43] France 2005 1 centre	Elective unilateral TKR for osteoarthritis 25; 25; 25 Mean 73 (SD 9); 72 (9); 70 (7) 67%; 60%; 63%	General anaesthesia induced with 1.5-2mg/kg propofol, 1µ/kg remifentanil and a single bolus of cisatracurium 0.15mg/kg. Remifentanil infusion at 0.15µg/k/min until skin closure. Anaesthesia maintained with sevoflurane 0.9- 1.2% with 50% nitrogen in oxygen. 20 mins before skin closure, 0.15mg/kg i.v. morphine bolus and 0.625mg droperidol. PCA with morphine hydrochloride 1 mg i.v. bolus with 7-min lockout. On arrival in recovery room, 3 mg i.v. morphine boluses at 5 minute intervals.		6 and 12 months 3; 1; 2 Low risk of bias Median DN4 at 12 months: 1 (IQR 1 2); 1 (0, 1); 2 (1, 3). p=0.02 for difference between ketamine and placebo groups. Number of patients with VAS pain on movement score

	Ĩ,	nefopam I administered a over 20 min 2 before incision; i 2mg/mI I nefopam c continuous i infusion at 2 120µg/kg/hr e until end of a	0.2mg/kg ketamine administered over 20 min before incision; 2mg/ml ketamine continuous infusion at 120µg/kg/hr until end of surgery and 60µg/kg/hr for 48 hours	Saline administered over 20 minutes before incision; saline continuous infusion until second post- operative day	 ≥40mm at 12 months by group: nefopam (3/22, 13.7%), ketamine (3/24, 12.5%), and placebo group (6/23, 26.1%). Ketamine reduced DN4 pain (P=0.02) compared with placebo. At 12 months only 7/69 patients had DN4≥4 indicative of neuropathic pain. Infection: 0; 0; 0. Revision: 0; 0; 0.
Pregabalin vs place Buvanendran et al. 2010[44] USA 2006-2007 Single centre	Primary unilateral TKR for osteoarthritis. 120; 120 (9; 2 did not receive post- operative treatment but ITT analysis) Mean 64.0 (SD 8.3); 63.3 (8.9) 76%; 70%	Sedation with midazolam and i.v. propofol. Combined spinal-epidural anaesthetic. 1.5ml 0.75% hyperbaric bupivacaine with 25µg injected intrathecally. Catheter inserted for epidural drug administration. LIA 60 ml 0.25% bupivacaine with epinephrine infiltrated into the wound at capsule closure. From completion of surgery until 32-42 hours post-operative, epidural infusion of fentanyl (5µg/ml) and bupivacaine (1mg/ml) initiated using continuous basal infusion of 6ml/hr with epidural PCA bolus doses (maximum 10ml/hr). Patients transitioned to oral opioid (morphine, oxycodone, and hydromorphone) as required. All patients received preoperative oral celecoxib 400mg 1–2 hours before surgery and 200mg twice daily for 3 days in hospital.			6 months 7; 5 Low risk of bias In the pregabalin group the incidence of neuropathic pain measured using S-LANSS was 0% (0/113) and 5.2% (6/115) in the placebo group (p=0.014). No clinically significant adverse events up to 6 months and no falls. Sedation, confusion and dry mouth more frequent in pregabalin than placebo group on day of surgery and first postoperative day.
	/s FNB short duration	Oral pregabalin 300 h before surgery, 15 twice daily for the fin postoperative days, twice daily on days 12, and 50mg twice days 13 and 14	50mgsurgeryrst 10first 10, 75mgtwice d11 and12, and	acebo 1–2 h before /, twice daily for the postoperative days, aily on days 11 and twice daily on days 14	

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Ilfeld et al. 2009[97] USA 2005-2007 2 centres	Primary unilateral TKR for osteoarthritis 25; 25 Median 66 (IQR 60, 70); 64 (60, 69) 56%; 60%	Femoral catheter inserted usin 0.2% ropivacaine infusion (8ml controlled bolus; 30-minute loc POD1. 1 week oral acetaminophen (9 sustained release oral opioid (0 hours), and either oral aspirin ((200mg every 12 hours). Oral o or i.v. morphine sulfate 2-4 mg	 6 and 12 months 4; 1 lost to follow up High risk of bias: uneven loss to follow up between groups; muscle weakness resulted in lower dose of infusion on POD1 (10 continuous; 3 saline) Groups had similar WOMAC pain scores at 6 and 12 months 		
	0	At 6 a.m. POD1, infusion pump replaced with infusion pump with 0.2% ropivacaine. At 6 p.m. POD2 pump replaced with portable infusion pump (400ml 0.2% ropivacaine). Catheter removed evening of POD4.	At 6 a.m. POD1, infusion pump replaced but saline substituted. At 6 p.m. POD2 pump replaced with portable infusion pump (saline). Catheter removed evening of POD4	(p>0.05). MI: 1; 0. PE: 1; 0. Fall: 1; 0. Catheter leak, dislodged: 1; 2	
Ilfeld et al. 2011[98] USA 2007-2009 2 centres	Primary cemented TKR for osteoarthritis 40; 40 (39; 38 included in RCT) Median 61 (IQR 58, 67); 66 (60, 70) 67%; 66%	Femoral catheter inserted using nerve stimulator. FNB with 0.2% ropivacaine infusion (6ml/hr basal; 4ml patient-controlled bolus; 30-min lockout) from surgery until POD1. 1 week oral acetaminophen (975mg every 6 hours), sustained release oral opioid (Oxycontin, 10mg every 12 hours), and either oral aspirin (650mg daily) or celecoxib (200mg every 12 hours). Oral (oxycodone 5mg or 10mg tablets) and/ or i.v. opioids (morphine sulfate 2-4mg) for breakthrough pain.		12 months 11; 12 incomplete follow up High risk of bias: 11;12 did not hav 4 measures out of 6 up to 12 months; graph suggests WOMAC pain lower pre-intervention in continuous infusion group. No difference in WOMAC pain scores between randomised group	
		At 6 a.m. POD2, infusion pump replaced and 0.2% ropivacaine continued. At 6 p.m. POD2 pump replaced with portable infusion pump (400ml 0.2% ropivacaine). Catheter	At 6 a.m. POD2, infusion pump replaced but saline substituted. At 6 p.m. POD2 pump replaced with portable infusion pump (saline). Catheter removed evening of POD4	(p>0.05). Falls: 4; 0	
Choy et al. 2011[30] Korea 2006-2007	Primary unilateral TKR for osteoarthritis	removed evening of POD4 Spinal anaesthesia. Continuou POD3. Catheter inserted with u Analgesia induced with 20ml o 2% lidocaine with 1:200,000 ep	2 years 4; 3 lost to follow up		

1 surgeon	33; 30 (2 patients received GA and excluded) Mean 66.7 (SD 10); 67.5 (11)	infusion with 0.125% butorphanol 4mg, keto programmed to deliver maximum dose 6mg/hr oral ibuprofen 600mg 3	rolac 150mg, salir 1 mg bolus (locko . i.v. paracetamol :	Low risk of bias for 2 year outcome measures. At 2 years, intervention WOMAC pain mean 7.2 (SD 2), control 6.3 (SD 1); p=0.2	
	97%; 93%	Continuous femoral nerve block via catheter continued from POD3 to POD7Continuous femoral nerve block discontinued on POD3			Superficial infection: 1; 1
FNB continuous	high concentration vs F	NB low concentration v	s FNB single		
Albrecht et al. 2014[29] Canada 2009-2011 1 hospital	Primary unilateral TKR 32; 32; 35 Mean 61 (CI 57, 64); 63 (60, 67);63 (60, 66) 46%; 44%; 52%	B low concentration vs FNB singleStimulating catheter inserted with ultrasound guidance.Immediately after catheter placement, 10ml mepivacaine 2%was injected through the catheter. SNB using 30 mlropivacaine 0.2%. Spinal anaesthesia with 2.5 to 3.0 mlisobaric bupivacaine 0.5% and 0.1mg intrathecal morphine.Bolus of 20mlropivacaine 0.2% withepinephrine1:400,000 into thefemoral catheterfollowed byropivacaine 0.2% at arate of 5 ml/hr withpatient-controlledboluses of 5mlavailable every30minutes.		12 months 4;0;2 lost to follow up Low risk of bias. No separate pain outcome. Mean WOMAC score at 12 months: high concentration FNB 17 (95% CI 7, 27); 22 (14, 30); 18 (8, 27). P=0.68 Falls: 0; 0; 1	
	vs Psoas compartment		•	•	
Morin et al. 2005[99] Germany Before 2005 1 centre	Elective TKR 30; 30; 30 Median 68 (IQR 62, 74); 71 (63, 74); 65 (53, 73)	Oral pre-medication with 20mg chlorazepate. General anaesthesia with intravenous propofol and 4–8µg/kg i.v. fentanyl and desflurane in N2O. 100mg diclofenac suppository after anaesthesia induction and 2.5g intravenous metamizole before end of surgery. Post- operative 3 daily doses of oral diclofenac 50mg. i.v. PCA			9–12 months7; 6; 5High risk of bias due to large losse to follow up, non-blinded outcome collection, and differences between

	50%; 70%; 59%	with piritramide bo 10 mins for 48 hou	olus 2mg as needed wit urs.	h lockout interval of	groups in BMI and anaesthetist's opinion of difficulty of catheter placement. No difference between groups in level of pain at the knee joint during past 4 weeks: FNB median 2.5 (IQR 1, 4), FNB and SNB 2 (1, 4), Psoas block 2 (IQR 1, 4), p=0.44 No early complications but longer term adverse events not reported.
		Continuous FNB Stimulating catheter used. Initial bolus of prilocaine 1% and ropivacaine 0.75%. 300mg prilocaine 1% (30ml) and 150mg ropivacaine 0.75% (20ml). During first 48hrs post- operative ropivacaine 0.2% infusion 14ml/hr.	Continuous FNB and continuous SNB Stimulating catheter used. Initial bolus of prilocaine 1% and ropivacaine 0.75%. In each catheter: 200mg prilocaine 1% (20ml) and 75mg ropivacaine 0.75% (10ml). During first 48hrs post-operative infusion through each catheter of 0.2% ropivacaine 7ml/hr.	Continuous psoas compartment block Stimulating catheter used. Initial bolus of prilocaine 1% and ropivacaine 0.75%. 300mg prilocaine 1% (30ml) and 150mg ropivacaine 0.75% (20ml). During first 48hrs post- operative ropivacaine 0.2% infusion 14ml/hr.	
ACB continuous vs I				0	
Davidson et al. 2016[100] USA 2013-2014 2 studies combined from 1 centre	Primary, unilateral TKR or unicompartmental 54 (39 TKR, 16 UKR); 56 (41 TKR, 15 UKR) TKR mean 67 (SD 8); 66 (7). UKR 70 (10); 68 (12)	hydromorphone, a LIA with 30 ml rop epinephrine (5 µg Post-operative: or celecoxib (200 mg oxycodone (10 mg infusion pump bol titrated to pain sev	vivacaine (0.5%), ketoro	blac (30 mg), and mg every 6 hr), tained release akthrough pain, ut). Rescue opioid 2%) bolus was	12 months 31; 29 High risk of bias due to partial follow up TKR and UKR combined. Pain score (0-10) at 12 months median 0.0 (IQR 0.0, 3.0); 0.5 (0.0, 2.0). P=0.80). Pain score >0: 35%; 32%. P=0.65. No difference at 4 months when follow up more complete (51;
	For peer	review only - http://	11 ′bmjopen.bmj.com/site/a	about/guidelines.xhtm	Ι

	TKR 59%; 66%. UKR 47%; 47%	Ultrasound guided ACB. Ropivacaine 0.2% at basal rate of 6 ml/hr, a 4-ml bolus, and a lockout of 30 minutes	Ultrasound guided continuous FNB. Ropivacaine 0.2% at basal rate of 6 ml/hr, a 4-ml bolus, and a lockout of 30 minutes	52) in pain score (p=0.80) or pain score >0 (p=0.48). Falls in hospital: 2; 5	
ACB single vs FN	IB single				
Macrinici et al. 2017[31] USA Before 2017 1 centre	Primary unilateral TKR 49; 49 Mean 67 (SD 8); 67 (8) 61%; 63%	Multimodal regimen including N analgesics, opioids. LIA 40ml N All patients received an ultrasc into ACB and FNB sites. Immediately after surgery, 30ml solution with 100ml Marcaine into ACB site. 30 ml saline into FNB site	Marcaine 0.25%.	6 months 3; 4 lost to follow up. 6; 3 complications Low risk of bias VAS pain similar between groups a 6 months. No difference in functional outcomes Medical complications: 3; 0. Surgical complication: 0; 1. Temporary foot drop: 3; 2.	
FNB continuous	vs oral opioid				
FNB continuous vs oral opioid Nader et al. Elective TKR 2012[24] 31; 31 USA Median (IQR) 65 2007-2008 (60, 76); 64 (60, 71) 1 surgeon 58%; 77%		Before surgery, patients receiv needed. Epidural with 10mg 0. injected intrathecally. Intraoper infusion of 25-75mcg/kg/minute area, PCA epidural with basal bupivacaine and 10 mg/ml hyd activated boluses of 3 ml with a minutes and per hour maximur discontinued and epidural cath POD 1. All subjects received 5 surgery and 40 mg enoxaparin	6 and 12 months 1; 1 lost to follow up at 12 months Low risk of bias No difference in overall median NRS pain score at 6 months and 1 months: 0 (IQR 0, 1); 0 (0, 1). p=1.0. At 12 months, some evidence favouring hydrocodone f pain ascending/ descending stairs 1 (0, 2); 0 (0, 0). p=0.01. Also, suggestion of reduced pain in		
		Continuous FNB inserted with use of stimulator. After discontinuation of epidural anaesthesia on the morning of POD1 10mL bolus of ropivacaine 0.25% followed by 5ml/h infusion of 0.1% ropivacaine. On morning of POD 2, ropivacaine infusion	10 mg oral hydrocodone plus 325mg acetaminophen every 4-6 hours administered for pain as needed. Sustained release oxycodone 10mg for 12 hours with oral hydromorphone 2 mg over	 suggestion of reduced pain in hydrocodone group at night in bec (p=0.06) and sitting/ lying (p=0.07) standing upright (p=0.10). No difference walking on flat surface (p=0.41). Falls in month after surgery: 1;0. Positive joint aspirate: 3; 0. VTE: 0 4. 	

		discontinued. Femoral catheter removed 24 hours after previous dose of enoxaparin.	4 hours for breakthrough pain	
<i>FNB continuous vs i</i> Wang et al. 2015[101] China 2012-2013 3 centres	Elective TKR 82; 86 No significant differences in age or sex	General anaesthesia with mida fentanyl (1µg/kg), propofol (1-2 (0.15mg/kg). Anaesthesia mair during surgery. Intramuscular in metoclopramide and 2.5mg dro surgery. Post-surgery, celocoxi patients with severe pain, and in Continuous FNB with ultrasound stimulator. After surgery, 0.2% ropivacaine (20ml) injected through catheter. Then an analgesia pump was attached delivering 0.2% ropivacaine 8ml/hr.	mg/kg) and cisatracurium ntained with sevoflurane njection with 10mg operidol 30 minutes before b and parecoxib 40mg for .v. morphine if needed. Epidural PCA 0.2% ropivacaine was injected a rate of 5 ml/hr in a 2ml pulse dose	
Peng et al. 2014[26] China Before 2014 1 centre (2 surgical teams with 4 surgeons and 2 anaesthesiologists)	Unilateral TKR 140;140 Mean: 66.8 (SD 9.4); 68.0 (SD 11.2) 73%; 65%	General intravenous and inhala midazolam 0.1-0.15mg/kg (eto patients >65 years), propofol 2 0.3-1.0µg/kg, and vecuronium of anaesthesia. Maintenance w sevoflurane and continuous int remifentanil 7-8µg/kg/hr and pr wound closure, 5-10µg intraver dose of PCA injected. i.v. inject FNB with ultrasound guidance. Initial dose of 10ml 2% lidocaine and 10ml 1% ropivacaine. 30 minutes before end of operation, catheter connected to PCA pump; patients received loading dose of 5ml of 0.15% ropivacaine followed by infusion of 0.15% ropivacaine at 5ml/hr, with bolus of 5mL	midate 0.15-0.2mg/kg for .0-2.5mg/kg, sufentanil citr 0.08-0.12mg/kg for induction ith inhalation of 1%-3% ravenous infusion of opofol 25-75µg/kg/min. Aft nous sufentanil and loading	Chronic post-operative pain (NRS 1+) in 38.5% of PCA group at 6 months compared with 25.7% in FNB group (p=0.021). No difference at 12 months (p=0.273). Authors only reported short term adverse events associated with use of PCA.

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		and lock time of 30 min. Preoperatively, a loading dose of 30ml was injected for intraoperative analgesia.		
Nu and Wong 2014[25]Unilateral elective TKRChina 2009-201140; 39 (30; 30 afte post randomisation exclusions)I centreMean 68.8 (SD 6.4); 68.9 (7.5) 73%; 73%		Paracetamol, sustained release diclofenate, opioids (codeine or morphine). Spinal anaesthesia Catheter inserted under nerve stimulation and ultrasound guidance. Standardised bolus of 15 mL 0.5% levobupivacaine. Continuous infusion of 8 to 12 mL/h 0.08% levobupivacaine postoperatively until POD 3 Intravenous PCA morphine after the operation		6 months 2; 2 not pre- and peri-operative exclusions Low risk of bias No separate pain outcome but improvement of KSS from pre- operative was FNB 48.73 and PCA 44.7 (p=0.513) Including patients not followed up. Deaths: 0; 0. Infection: 1;1. DVT: 2; 3. Shock: 3;2. Transfusion: 2;3. Also from excluded cases. Atrial fibrillation and confusion: 0; 1. PE: 0; 1. Sepsis: 1;0. ICU admission for shock: 1; 0.
FNB and SNB continuous vs epidural PC Anastase et al. Primary TKR 2014[102] 55; 50 Germany Mean 68.2 (SD 2010-2011 9.2); 69.7 (SD 8.7) 1 centre 65%; 69%	Premedication with 10 mg ora anaesthesia with light sedatio Supplemental postoperative a piritramid After spinal anaesthesia installed, SNB and FNB catheters inserted with ultrasound guidance. 5 ml	6 and 12 months 15; 14 High risk of bias due to large loss t follow up Pain during previous 4 weeks: 1 nd pain, 2 very little, 3 little, 4 moderate, 5 loud, 6 very loud (translation from German). No		
		bolus 0.2% ropivacaine. FNB with an hourly rate of 5 ml, bolus administration of 5 ml by the patient and the lock-out interval of 20 mins. SNB 5 ml/h to a maximum of 8 ml/h, 5 ml bolus administered by the patient	performed through the epidural catheter. Hourly rate 3 ml, bolus administration of 5 ml, and lock-out period of 30 minutes.	difference at 6 months p=0.37. At 12 months, FNB/SNB median 2.00 (1.00, 2.00), PCA 2.00 (2.00, 2.00) p=0.004 favouring FNB/SNB. No falls associated with quadriceps weakness. 6 and 12 month adverse events not reported.

		and lock-out interval of 20 minutes.		
FNB single vs LIA		1		
Fan et al. 2016[27] Primary TKR China 80; 80 (78; 79 in analysis) 2012-2014 Mean 68.4 (SD 8.8); 67.6 (6.3) 79%; 86% 79%; 86%		General anaesthesia in all but surgery, i.v. morphine, PCA ar FNB performed pre- operatively with 20ml ropivacaine 0.5%. After cementing prostheses, 50ml of saline injected into periarticular soft tissue.	1 year 3 protocol violations Low risk of bias No separate pain outcome. Mean KSS at 1 year similar between groups: 94.2 (SD 2.6); LIA 93.9 (3.1). p=0.51 Infection: 0; 0. DVT: 1; 1. Femoral nerve injury: 1; 0.	
FNB single and epid Reinhardt et al. 2014[28] USA 2010-2012 2 surgeons	Elective unilateral TKR for osteoarthritis 51; 51 (49; 45 received allocated intervention) Mean 67.9 (SD 10.9); 66.6 (10.1) 59.2%; 57.8%	Spinal anaesthetic (2.5ml 0.5% daily. Oral Perocet or Vicodin a Dilaudid for severe breakthrou Combined spinal-epidural (500ml hydromorphone 10µg/ml and bupivacaine HCl 0.06%). Single intra-operative FNB injection (30ml 0.25% bupivacaine). Continuous 48-hour epidural infusion (4ml/hr with 4ml per demand dose, locked out every 10 minutes with an hourly limit of 20ml). Epidural infusion weaned to 2ml/hr on POD1 and to 0 ml/hr at 5 p.m. on POD1. Demand dose with	as required. Subcutaneous	1 year 0: 0 of patients who received allocated intervention Low risk of bias VAS pain at 1 year similar betwee groups (noted in text and shown graphically) No wound-related complications o infections. 1 DVT and 1 DVT plus PE in epidural group. Arthrofibrosit 2; 1

LIA with corticostere	Did vs LIA with no co	lockout parameters continued for 48 hours. Placebo intraarticular knee catheter placed intra- operatively with continuous saline 7ml/hr infusion until POD2. orticosteroid		
Seah et al. 2011[41] Singapore 2004-2005 1 hospital	50; 50 Mean 65.4; 67.9 Sex not stated	General or spinal anaesthesia. and PCA (with morphine bolus minutes, and maximum dose 8 Intraoperative periarticular injection of 0.5ml/kg 1:200,000 epinephrine and 0.5% bupivacaine diluted with 30ml of normal saline. 40mg of corticosteroid (triamcinolone acetonide) was added to half the mixture. The solution with the corticosteroid was injected into the deep tissues. The remaining solution was injected into the skin incision before closure.	of 1mg, lock-out time 5	6 months and 2 years No losses to follow up reported Low risk of bias No separate pain outcome but no statistically significant difference in OKS between groups at 2 years Deep infection: 1; 1
Yue et al. 2013[103] China 2011-2012 1 hospital	for osteoarthritis 36; 36 Mean 70.2 (SD 6.4); 69.3 (5.7) 89%; 89%	General anaesthesia. PCA (25 bolus, 6 minutes lock-out, and 5 hours after surgery. 5-10mg intr rescue. Celecoxib pre- and pos Injections with local anaesthetic agent and adrenaline (0.75% ropivacaine 30ml, 1:1000 adrenaline 0.5ml, and isotonic sodium chloride solution 70ml) plus corticosteroid (1ml betamethasone).	img/hr maximum) for 72	6 and 12 months No loss to follow up reported Unclear risk of bias. No separate pain outcome. No difference in mean KSS between groups at 6 or 12 months No incision infection or tendon rupture complications

		Another 50ml syring without corticosteroi infiltrated into the sk	d was withou	er 50ml syringes fluid t corticosteroid was ed into the skin	
LIA including ketoro Spreng et al. 2012[104], Spreng et al. 2010[105] Norway 2007–2009 1 hospital	Spreng 105] cemented TKR with no patella resurfacing	Premedication with oral paracetamol (1-2g). Spinal anaesthesia with 13-15mg bupivacaine 5mg/ml with 20µg fentanyl. If indicated, up to 10ml/hr 10mg/ml propofol for sedation. Acetaminophen 1g every 6 hours. i.v. PCA morphine for 48 hours after surgery (2mg bolus with 10 minutes lockout time). When PCA stopped, 10mg slow release oxycodone twice daily. 5mg oxycodone as rescue analgesia.i.v. injection of ketorolac 1ml (30mg/ml) and morphine 5mli.v. injection of 6ml saline. Infiltration with repivaceine			12 months 13 did not provide complete data Unclear risk of bias due to limited reporting (long-term outcome only reported as conference abstract). Perioperative analgesic treatment did not have any significant influence on any KOOS outcomes. Infection: 0; 0; 1. No long-term advers events reported
		morphine 5ml (1mg/ml). Infiltration with ropivacaine 150mg, epinephrine 0.5mg, ketorolac 30mg and morphine 5mg in 150ml saline. After closure, catheter placed into knee joint and 10ml infiltrate injected. 22-24 hours after surgery, 20ml injection through catheter of ropivacaine 19ml (7.5mg/ml) and ketorolac 1ml (30mg/ml). i.v. injection of	ropivacaine 150mg, epinephrine 0.5mg, ketorolac 30mg and morphine 5mg in 150ml saline. After closure, catheter placed into knee joint and 10 ml infiltrate injected. 22-24 hours after surgery, 20ml injection through catheter of ropivacaine 19ml (7.5mg/ml) and saline 1ml. i.v. injection of saline 1ml. Sham epidural catheter.	before spinal anaesthesia. When spinal anaesthesia started to wear off, epidural infusion for 48 hrs with 6-10 ml/hr fentanyl 2µg/ml, epinephrine 1µg/ml, bupivacaine 1mg/ml. No knee infiltrations. Sham knee catheter with no injections	

		ketorolac 1ml (30mg/ml). Sham epidural catheter.			
Spinal with added sulphate	I high dose morphine	sulphate vs spinal	with added low dos	e morphine sulpha	te vs spinal with no morphine
Foadi et al.	TKR or THR for	3ml spinal anaesthe	sia with 0.5% bupiva	caine	6 months
2017[106]	osteoarthritis	Post-operative 1 g r	metamizole (orally or	"only a few dropouts". >70%	
Germany	16; 16; 17		morphine (intraveno	questionnaire return rate.	
Before 2017	Mean 67.63 (SE	subcutaneous) as re	escue		Unclear risk of bias due to limited reporting of pilot RCT.
1 centre	2.45); 67.33	medication			
	(2.87); 63.71 (3.14) 56%; 44%; 65%	0.2mg morphine sulphate added to spinal anaesthesia	0.1mg morphine sulphate added to spinal anaesthesia	No morphine sulphate added to spinal anaesthesia	No difference in WOMAC pain between groups at 6 months. No adverse events noted
2. Myofascial	trigger point dry nee	dling	ro.		

Myofascial trigger point dry needling 2.

Author	Indication	Common pain managemen	nt	Follow up
Country Recruitment dates Setting	Number randomised intervention; control Age % female	Group 1 (intervention)	Group C (control)	Losses to follow up intervention; control Risk of bias issues Key results
Mayoral et al. 2013[107] Spain 2007-2008 Single centre	TKR for osteoarthritis 20; 20 Mean 71.7 (SD 6.1); 72.9 (7.9) 72.5%	General or spinal anaesthes After anaesthesia and surgery started, dry needling applied 20 times to all myofascial trigger points by a trained and experienced physical therapist.	ia If spinal anaesthesia used, dry needling simulated behind screen	6 months 4; 5 High risk of bias due to large losses to follow up WOMAC pain at 6 months: mean 3.24 (SD 3.03); 3.13 (2.72). Difference not statistically significant No difference between groups in VA pain (p=0.725) or proportion of patients reporting significant VAS pain at 6 months.

				No complications related to the dry needling intervention. Other adverse events not collected.
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3. Tourniquet

Author	Indication	Common blood conservation	on strategies	Follow up Losses to follow up intervention; control Risk of bias issues Key results
Country Recruitment dates Setting	Number randomised intervention; control Age % female	Group 1 (intervention)	Group C (control)	
Ejaz et al. 2014[45] Denmark 2011-2012 1 centre	Primary TKR 35; 35 (33; 31 received intervention) Mean 68 (SD 8.0); 68 (7.8) 45.5%; 45.2%	Before surgery, oral tranexan (0.5g) 3 hours after surgery a postoperatively. Appropriately sized thigh tourniquet applied. Limb exsanguination by elevation for 2 minutes and cuff inflated to 250mm Hg.	nic acid (1g). Tranexamic acid and 6 and 12 hours Appropriately sized thigh tourniquet applied but not inflated. Served as safety device in case of uncontrollable bleeding.	 6 and 12 months 0; 0 of those who received intervention Low risk of bias Statistically significant difference in KOOS pain intensity at 2 months favouring TKR without a tourniquet (p < 0.001). Small difference between groups not statistically significant at 6 and 12 months. Small number of adverse events did not suggest extra risk in the group with no tourniquet.
Liu et al. 2014[46] Australia Before 2014 1 surgeon	TKR for osteoarthritis 10; 10 Mean 67.0; 70.0 30%; 10%	PCA. No CPM Tourniquet inflated to 300 mmHg before skin incision. Tourniquet deflated after wound closure and dressing.	Tourniquet placed but not inflated	6 and 12 months 0; 0 Low risk of bias No separate pain measure. Total OKS not significantly different at 6 and 12 months Blood transfusions: 3; 0.
Mittal et al. 2012[48] Australia 2008-2010	Primary unilateral TKR 31; 34	Autologous blood re-infused Short duration. Tourniquet set at 300mm Hg inflated	if required Long-duration. Tourniquet set at 300mm Hg inflated before	1 year 5; 2

1 centre	Mean 67.5 (SD 8.9); 66.6 (8.4) 81%:74%	prior to cement application and deflated when cement hardened		skin incision and deflated when cement hardened		Low risk of bias. However, RCT terminated early due to increased need for blood transfusion in short duration tourniquet group.
	A					No separate pain outcome. Total OKS (0-48) at 52 weeks higher in long-duration group reflecting better recovery than short duration group but not significantly (p=0.12). Mean difference approximately 5 which is greater than MCID of 4[36].
	6				Transfusions: 10; 2. Patient reported adverse event: 26; 12	
Abdel-Salam and Eyres 1995[108] UK Date not stated 1 surgeon	Primary TKR 40; 40 Mean 72 (range 65-80); 74 (64- 82) 57.5%; 62.5%	Tourniquet placed around thigh Limb exsanguinated for 2 minutes and tourniquet inflated to twice systolic blood pressure Tourniquet not inflated		1 and 2 years 0; 0 Unclear risk of bias due to limited reporting of methods. No pain measure or PROM Surgeon recorded HSS score at 1 year 90 (78-97); 91 (80-97). Not significantly different at 1 or 2 years.		
				4		Blood loss similar between groups. Wound infections: 5;0. DVT: 4;0
Şükür et al.2016[109]	Primary TKR, women	Pneumatic tou blood pressure	urniquet inflated e	6 months 0;0;0;0		
Turkey 2015 1 surgeon	30; 30; 30; 30 Mean 67.0 (SD 7.0); 66.9 (8.5);	Knee in 90° flexion and tourniquet	Knee in 90° flexion and tourniquet	Knee in full extension and	Knee in full extension and	High risk of bias. KSS outcome noted in methods but not presented in results.
	68.4 (6.9); 68.4 (6.8) 100%	deflated during wound closure	inflated during wound closure	tourniquet deflated during wound closure	tourniquet inflated during wound closure	KSS results not reported at 6 months but no significant differences betweer groups at 3 months. Surgical and wound complications similar between groups. No infections, fractures or instability requiring revision within 6 months
		Blood transfus	sion if required	·	•	3-22 months, mean 12;13 months

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Zhang et al.2016	Primary TKR for	Tourniquet		No tourni	quet	Not clear
[110]	osteoarthritis					High risk of bias. Variable follow up
China	84; 82					HSS outcome noted in methods bu
2014-2015	Not reported					not presented in results.
1 hospital	Not reported					HSS not reported.
	A.	6				Transfusion rates similar between groups. At mean follow up of 12 -1 months, patients operated on witho a tourniquet had a lower rate of DV (2.4%) compared with those with a tourniquet (10.7%).
Zhang et al.	Unilateral	Tourniquet inflated t	o 300-337	mm Hg. Tr	anexamic acid not	6 months
2017[49]	cemented KR for osteoarthritis	generally used	r		1	0; 0; 0
China		Tourniquet for	Tourniqu		Tourniquet from	Low risk of bias
2008-2011	50; 50; 50 Maan 70 2 (SD	entire operation	removed before wound closure		first bone osteotomy until	No separate pain outcome. HSS
1 surgeon	Mean 70.3 (SD 6.6); 71 (10.2);			wound closure	similar between groups at 6 month (p=0.839).	
	68.2 (6.8)					At 2 weeks DVT: 0; 0; 1.
	54%; 60%; 50%					Intramuscular vein thrombosis: 4; 3 3. Transfusions: 30%; 26%; 10%
Huang et al.	Primary unilateral	Tranexamic acid				6 months
2017[47]	TKR for osteoarthritis	Tourniquet		No tourni	quet	0; 0
China	50; 50					Low risk of bias
2015 1 centre	50, 50 Mean 66.2 (SD 8.3); 65.1 (6.8)					VAS pain similar between groups a months (p=0.728). Mean HSS scor 90.3 (SD 3.2); 91.2 (2.5). P=0.151
	64%; 68%					DVT: 0; 0. PE: 0; 0. Intramuscular
						venous thrombosis: 6; 4. Superficia
						infection: 1; 0. Wound secretion: 6; No significant difference in blood lo
						between groups.

4. Compression bandage

Author	Indication	Common treatments	Follow up

Country Recruitment dates Setting	Number randomised intervention; control Age % female	Intervention	Control	Losses to follow up intervention; control Risk of bias issues Key results
Brock et al. 2017[57] UK 2013-2014 1 hospital 6. Blood conser	Primary TKR for osteoarthritis 25; 25 (24 received intervention) Mean 67.3 (SD 8.2); 69.5 (6.8) 66.7%; 64.0%	Hydrocolloid dressing left in p 10-14 Soft inner layer with compressive outer layer bandage. Removed after 24 hours.	lace until clips removed on day Standard bandaging with soft inner layer and crepe bandage outer layer. Removed after 24 hours and cryocuff used.	6 months 0; 0 of patients receiving intervention Low risk of bias No separate pain outcome. Mean OKS similar between groups at 6 months: 35.8 (SD 7.7); 34.3 (10.6). P=0.58 No infections or thromboembolic events in either group
Author	Indication	Common blood conservatio	on strategies	Follow up
Country Recruitment dates Setting	Number randomised intervention; control	Intervention	Control	Losses to follow up intervention control Risk of bias issues
	Age % female		06	Key results
Tranexamic acid		I		
Sa-Ngasoongsong et al. 2011[50] Thailand 2008-2009 1 hospital	Primary knee osteoarthritis with unilateral primary cemented computer assisted TKR 24; 24 69.0 (SD 8.2); 69.2 (7.6)	Drain and compressive dressi 25ml saline solution containing 250mg tranexamic acid injected into knee joint after fascial closure	ing 25ml saline solution injected into knee joint after fascial closure	6 months 0; 0 Low risk of bias No separate pain score reported but WOMAC overall score mean 18.6 (SD 7.6); 20.8 (6.4). P=0.282 Lower peri-operative blood loss in tranexamic acid group and need for blood transfusion, 1/24 compared

						wound complications or infection reported in either group
Kim et al. 2014[51] Korea 2009-2011 1 hospital Sa-Ngasoongsong et al. 2013[52] Thailand 2010-2011 1 hospital	Primary unilateral TKR 90; 90 Mean 73.5 (SD 5.5); 71.9 (SD 5.9) 88%; 87% Primary unilateral cemented TKR for osteoarthritis 45; 45; 45 Mean 68.1 (SD 6.2); 67.6 (8.7); 66.2 (7.3) 88.9%; 93.3%; 95.6%	Tourniquet, drain, con transfusion and intrav required 10 mg/kg body weigh tranexamic acid in 10 normal saline given a intravenous injection before tourniquet defl and the same amoun hours later. Drain and compressiv 25ml saline solution containing 500mg tranexamic acid injected into knee joint after fascial closure via drain tube.	t 0 mL of s slow 30 min ation, t 3 /e dressir 25ml sa solution containi tranexar injected joint afte	No tranexa placebo ng line ng 250mg		 1 year 0; 0 Low risk of bias WOMAC pain mean 3.2 (2.6); 2.8 (2.3). Difference not statistically significant Lower blood loss and need for allogenic transfusion in tranexamic acid group. No DVT. 1 PE in control group. 1 year 0; 0; 0 Low risk of bias No separate pain outcome but WOMAC mean 14.5 (7.1); 15.1 (6.2) 15.5 (6.6). P=0.42 Total blood and Hb loss lower in intervention groups than control. Fewer transfusions in 500mg (0) that 250mg tranexamic acid group (6) and control group (10). 2 DVT in 500mg group. 1 DVT in 250mg group. 1 PE and 3 DVT in control group. No infections.
Hourlier et al. 2015[54]	Primary unilateral TKR	Tourniquet, electrocautery, routine haemostasis, superficial drain. No blood salvage system.		6 months 0: 0		
France	52; 54	10 mg/kg intra-operat			is of 30 mg/kg	Low risk of bias.
2009-2010	74 (SD 6); 72 (7)	tranexamic infusion.			c acid as an	No separate pain score but KSS
1 hospital	62%; 63%	hours, continuous infu tranexamic acid 2 mg for 20 hours via elect syringe	/kg/hr	2 hours, p	tive infusion. After lacebo saline s infusion via ringe	 clinical score mean 90 (SD 6); 90 (13). P=0.90 No difference between groups in tota blood loss. 1 MUA in single treatment

				group. No deep infections or revisions.
Huang et al. 2017[47] China 2015 1 centre	Primary unilateral TKR for osteoarthritis 50; 50 Mean 66.2 (SD 8.3); 65.8 (6.3) 64%; 70%	Tourniquet inflated to 100mm and deflated after wound closu Intravenous tranexamic acid 20mg/kg before incision and tranexamic acid 10mg/kg at 3, 6, 12 and 24 hours. 1g tranexamic acid in 50ml saline irrigated into wound during operation		6 months 0; 0 Low risk of bias VAS pain similar between groups at 6 months (p=0.728). Mean HSS score (0-100) better in tranexamic acid group than controls: 90.3 (SD 3.2); 88.9 (3.0). P<0.001. Mean difference 1.4 lower than MCID of 8.29[53] Greater blood loss in control group than tranexamic group (p<0.001). DVT: 0; 0. PE: 0; 0. Intramuscular venous thrombosis: 6; 3. Superficial infection: 1; 3. Wound secretion: 6; 9
Thrombin infusio				· · · · · · · · · · · · · · · · · · ·
Kusuma et al. 2013[55] USA Not stated 1 hospital	Primary TKR 40; 40 Mean 64.6 (SD 10.2); 64.5 (7.3) 82.5%; 67.5%	Tourniquet, drain, Esmarch ba 20,000 IU thrombin infusion (1,000 IU/mL) through fascial defect	Indage, electrocautery Closure and drain placement protocol without the thrombin infusion.	1 year (6 months and 2 years also reported) 0; 0 Low risk of bias No separate pain outcome. KSS mean 95.5; 96.0. p=0.45 Lower drop in Hb in thrombin group. Blood transfusion in 4 intervention and 7 control patients. 1 control patient had haematoma. No hospital readmissions
Flexion vs extens				
Napier et al. 2014[56] UK 2003-2004 1 hospital	Primary TKR 90; 90 Mean 70.4 (SD 9.9) 71.0 (7.6) 74%; 64%	No drains or tranexamic acid Flexion. Operated knee kept in passive flexion (120°) post-operatively for 6 hours using a jig. Wound redressed and placed in flexion over a	Extension. Operated knee kept in full passive extension	1 year 5; 1 (12 did not attend follow up) Low risk of bias. No separate pain outcome. OKS mean 20.5 (SD9.0); 22.1 (9.7). P=0.27

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		single pillow until POD1 morning.		1 MI and 1 DVT in each group. 1 haematoma in flexion group. 1 deep infection and 1 extensor muscle weakness in extension group. More transfusions in extension group (p=0.002)
Auto-transfusion				
Thomas et al.	TKR	Allogenic transfusion if Hb fell	-	6 months
2001[111]	115; 116	Auto-transfusion of wound	Wound drainage discarded	Losses to follow up not reported
UK	Mean 69.3	drainage if volume >125ml		Unclear risk of bias due to limited
Not stated	(range 32-95); 🔪	post-operative. Blood washed and re-suspended before re-infusion using a		details of methods and follow up.
1 hospital	70.0 (40-88)			No separate pain outcome. No
	62%; 53%	centrifugal cell washing machine		significant difference in EQ-5D between groups.
		machine		7% of auto-transfusion group require
				allogenic transfusion compared with
				28% in control group. Fewer
				infections, readmissions and GP
				visits in auto-transfusion group. No significant differences in other seriou
				adverse events or mortality between
				groups.

6. Platelet rich plasma

Author	Indication	Common blood conservation strategies		Follow up
Country Recruitment dates Setting	Number randomised intervention; control Age % female	Group 1 (intervention)	Group C (control)	Losses to follow up intervention; control Risk of bias issues Key results
Aggarwal et al. 2014[112]	Primary unilateral surgery or first surgery of staged	Tourniquet. No tranexamic acid or suction drain. Blood transfusion if necessary due to intraoperative blood loss or postoperative haemoglobin <8g/dl.		6 months No losses to follow up reported

Author	Indication	Common treatment		Follow up
Cryotherapy	Č			
	Mean 56.43 (SD 7.59); 53.79 (9.75) Sex not stated	ratio. PRP and calcium chloride injected into the posterior recess, gutters and capsule, and repaired extensor mechanism and prepatellar fat.		total at 6 months PRP mean 7.14 (S 0.69), controls 7.86 (1.23), p=0.173 PRP group had lower fall in haemoglobin and need for blood transfusion
1 surgeon	7; 14	chloride for activation given in a separate syringe in 4:1		randomised groups. No separate pain outcome. WOMAC
2010-2011	osteoarthritis	patient's blood. Calcium		differences in numbers of patients in
India	bilateral TKR for	8 ml PRP, prepared from	No treatment	High risk of bias due to unexplained

Author	Indication	Common treatment		Follow up
Country Recruitment dates Setting	Number randomised intervention; control Age % female	Group 1 (intervention)	Group 1 (intervention)	Losses to follow up intervention; control Risk of bias issues Key results
Wang 2017[113] China 2013-2015	Unilateral TKR for osteoarthritis 53; 53 Mean 65.23 (SD 5.41); 64.97(5.36) 62.3%; 58.5%	CPM for 2 weeks Compression cold therapy for 48 hours	No compression cold therapy	6 months 0; 0 Unclear risk of bias due to limited reporting No separate pain outcome. At 6 months 87% of cryotherapy patients had excellent or good knee function compared with 69% of controls (p=0.032). No adverse events reported in either group during functional training

8. Denusomab

Author Indication		Common treatment		Follow up
Country Recruitment dates Setting Number randomised intervention; control Age % female	Group 1 (intervention)	Group 1 (intervention)	Losses to follow up intervention; control Risk of bias issues Key results	
Ledin et al. 2017[59] Sweden 2012-2014 2 centres	Elective cemented primary TKR for osteoarthritis 25; 25 Mean 66 (SD 6.3); 64 (5.5) 60%; 60%	Injection of 60mg denusomab 1 day after surgery and after 6 months	Injection of placebo 1 day after surgery and after 6 months	 12, 24 months 0; 2 Low risk of bias No significant differences in KOOS pain or other KOOS domains between groups 12 12 o 24 months No suspected unexpected adverse reactions in either group
). Continuous p	bassive motion	Common treatment		Follow up
-				•

Continuous passive motion 9.

Author	Indication	Common treatment		C	1	Follow up
Country Recruitment dates Setting	Number randomised intervention; control Age % female	Group 1 (intervention)	Group 2 (intervent	ion)	Group C (control)	Losses to follow up intervention; control Risk of bias issues Key results
Leach et al. 2006[114] UK	Cruciate retaining rotating platform TKR for	Physiotherapy protoc exercises to improve exercises.			6 and 12 months 25 patients lost to follow up High risk of bias due to large loss	
Before 2005 1 hospital	osteoarthritis 85 overall Mean 71.2 (range 53-84); 72.9 (52- 89)	CPM commenced on postoperative day set range 0–30 and used hour twice per day. E	t at a for 1	No CPM		to follow up and use of date of birth randomisation No difference in mean VAS pain at 1 year, CPM 0.6; control 0.9. p=0.49

	50%; 54%	range was increased with discharge at POE				Adverse events not reported
Sahin et al. 2006[115] Turkey Before 2006 1 hospital	Primary unilateral TKR for osteoarthritis 15; 16 Mean 61 (SD 6.0); 61.6 (7.5) 86%; 86%	Standard physiothera From POD 1, CPM 2. 2x/day. Initially 0-40° 1 and increased by 10° until POD 7	5 hours No C flexion	CPM		6 months 3 lost to follow up Unclear risk of bias as patients were followed up by treating physician. Mean difference in VAS pain 0.1/10 slightly favouring no CPM group (95% CI -0.8, 0.9; P=0.87) Adverse events not known
Pope et al. 1997[116] Australia 1988-1999 1 hospital	Primary TKR 62 (70 knees). Authors excluded those not followed up so groups were 18; 20; 19 Mean 72.5 (95% Cl 64.4, 74.98); 72.7 (70.4, 75.0); 69.4 (64.4, 74.98) 64.7%; 50%; 72.2%	0-40° increased by 10° twice, on day after surgery and day 2, so that 0-60°	enced on postope Patients had an initial CPM range 0-70° increased 10° twice, on dat after surgery and day 2, so that 0- flexion achieved before removal of machine at 48 hours	le of e by t ly d -90°	day 1 Knee placed in an extension splint in the recovery room	 6 and 12 months 8 patients (12 knees) excluding 1 death High risk of bias due to losses to follow up and limited reporting of methods No separate pain outcome. However, "pain disability" contributed up to 50 points out of a total of 70-point functional score (70 best outcome). No difference between groups in functional score: CPM 0-40 median 56 (range 20, 70); CPM 0-70 52 (10, 70); no CPM 52 (25, 70). p=0.80 CPM groups had greater blood loss than controls, p=0.008). 1 manipulation under anaesthesia in no CPM group, 2 revisions due to patellar dislocation in the 0-40 CPM group.
Beaupré etal. 2001[117]	Primary TKR	Standardised exercise a slider board session	• •	admiss	ion which included	6 months

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Canada	40; 40; 40	3 sessions (2		of two 10-	No intervention	6; 8; 6
1997-1998 1 hospital	Mean 68 (SD 9); 68 (9); 69 (8) 52.5%; 50%; 30%	hours) with CPM machine per day from POD2. Range increased from starting range 0-30 degrees as tolerated.	minute sli therapy s per day ir to one in standardi exercise. knee flexi extension and lying performed independ tolerated.	a addition the sed Active on and i in sitting positions d ently as	further than standardised exercise.	Unclear risk of bias due to loss to follow up Mean WOMAC pain at 6 month 76 (15); 85 (15); 79 (16). No difference over time between groups, p=0.62. Long-term adverse events. New for MUA: 1; 1; 0. DVT: 0; 1; 0. Cellulitis: 0; 0; 1. Infection 0; 0;
Kumar et al.	Primary TKR for	Standard physiothera				6 months
1996[118] USA Before 1996 1 hospital	osteoarthritis 40 (46 knees); 33 (37) Mean 69 (range 52-86); 68 (42-88) 58%; 67%	CPM from POD 0. In hours/ day 0-90° unt discharge	itially 10	movemen to 90° 2x/	Passive range of t ("drop and dangle") day initially for 20 ater 30-45 minutes.	15; 13 lost to follow up High risk of bias due to large losses to follow up No separate pain outcome. KS CPM 82.7; Drop and dangle 80 p=0.78 Haematoma 3;1. Closed
						manipulation 1;3. DVT 0;0. PE
Worland et al.	TKR for	CPM and physiother				6 months
1998[119] USA 1996 1 hospital	osteoarthritis. 91 patients (114 knees randomised. After post- randomisation	At home after discha machine 3 hours per replaced knee for 10	day on		herapist home visit 1 times per week for	11 patients (11 knees) Unclear risk of bias due to post operative exclusions not report separately for groups and limite reporting of methods.
	exclusions: 37 (49 knees); 43 (54 knees) Mean 70.2 (range					No separate pain outcome. At 6 months, mean HSS score CPM 95.3 (SD 2.8); physiotherapy 95 (3.0). P=0.49.
	44-84)					Adverse events not reported.
MacDonald et al. 2000[120]	66.25% TKR for osteoarthritis	Active ROM, passive using walker or crute		cises, mobil	lised as tolerated	6 and 12 months

Canada	40; 40; 40	CPM commenced	CPM commenced	No CPM	Not reported
Before 2000 1 hospital	Age and sex not reported	POD 0. Initially 0- 50 degrees. Provided for 18-24 hour/ day. Increased by 10 degrees/ hour as tolerated. Continued until POD 1	POD 0. Initially 70- 110 degrees. Provided for 18-24 hr/ day. Not increased. Continued until POD 1		Unclear risk of bias due to limited and selective reporting. No separate pain outcome. No statistical differences between groups for KSS at 6 and 12 months. Adverse events not reported
Bennett et al.	Primary unilateral	Standard in hospital	physiotherapy program	ime	12 months
2005[61] Australia	TKR for osteoarthritis	Standard CPM from 0° to 40° for 2x3	commenced in	No CPM	1 patient excluded due to inability to achieve 90° flexion
1997-2000	47; 48; 52	hours on POD 1 increased by 10° per day until POD 6. Extension splint	recovery room from 90° to 50° knee flexion. Increased gradually to CPM		Low risk of bias
1 hospital	hospital 70.7; 71.4; 71.7 72.3%; 64.6%; 67.3%				No separate pain outcome. No significant difference in KSS between groups at 1 year.
		applied overnight	90° to 0° for 2x3 hours in day 4-6.		No difference in wound healing between groups
Ersözlü et al.	TKR for	Conventional physica	al therapy		2 years
2009[60]	osteoarthritis	CPM set at 30-40°	CPM set at 60-70°	No CPM	1; 1; 2
Turkey	30; 30; 30	from POD1. Increased as	from POD3. Increased by 10°/ day to POD7. 1 hour CPM 3x/day.	1.	Low risk of bias
5 8	Mean 65 (range 54-73); 61 (49- 80); 62 (52-78)	tolerated to POD7. 54-73); 61 (49- 80); 62 (52-78) 1 hour CPM 3x/day.		0,	No separate pain outcome. KSS scores 98; 95; 92. No significant difference between groups
	66%; 55%; 57%				p=0.67.
				J	Infection 0; 0; 1. Arrhythmia 0; 1; 0. No difference in complications between groups

10. Electrical stimulation

Author	Indication	Common rehabilitation strategies		Common rehabilitation
Country Recruitment dates Setting	Number randomised intervention; control	Intervention	Intervention	strategies

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	Age % female			
Avramidis et al.	Unilateral TKR for	Standard physiotherapy for 6 we	eks. No CPM	1 year
2011[62] Greece 2005-2006 1 hospital	osteoarthritis 38; 38 Mean 70.54 (SD 4.68); 70.66 (3.73) 80%; 82.9%	Transcutaneous electric muscle stimulation of the vastus medialis muscle from POD2 2x/ day for 2 hours for 6 weeks.	No intervention	3 (intervention intolerance); 3 Low risk of bias Improved SF-36 bodily pain at 1 year in intervention group compared with control, mean 92 (SD 10.57); 79.48 (12.72). P<0.001. Difference of 12.52 close to MCID of 16.86[63]. No difference in OKS or American KSS Adverse events not reported
Stevens-Lapsley et al. 2012[121] USA 2006-2010 1 hospital	Primary unilateral TKR 35; 31 Mean 66.2 (SD 9.1); 64.8 (7.7) 57.1%; 51.6%	Standard inpatient rehabilitation, therapy Neuromuscular electrical stimulation commenced on POD2 for 6 weeks 2x/ day.	, home and outpatient physical	 6 months and 1 year 5; 6 Unclear risk of bias due to baseline differences in WOMAC No difference in resting pain (points) at 1 year intervention mean 0.6 (SD 1.4); control 0.4 (1.5). Also similar at 6 months. Mean WOMAC total score better at 1 year in intervention group compared with control, 5.7 (5.9); 10.0 (12.2) and at 6 months. However, probably explained by baseline differences. Authors state no differences for change i WOMAC. DVT 1; 0. Unspecified complication 1; 0. Infection 0; 2. Revision 0; 1
		2 sessions of ROM exercise		6 months

Levine et al.	Elective TKR for	Neuromuscular electrical	Formal physical therapy	5; 9
2013[122] USA	osteoarthritis 35; 35	stimulation commenced 14 days pre-operatively until 1	programme with progressive resistive exercises and	Unclear risk of bias due to large uneven losses to follow up
Before 2013 1 surgeon	Mean 68.1; 65.1 76%; 62%	day before surgery. Recommenced at POD1 for 60 days. After hospital discharge no direct contact with a physical therapist	strengthening in hospital and after discharge supervised by physical therapist.	KSS pain favoured intervention a 6 months but not significantly 79.08 (SD 10.97); 75.5 (14.77); 95%CI for difference -3.78, 10.93 Similar for WOMAC total score, 95%CI for difference -3.19, 14.81 Confusion 2; 0
Moretti et al.	TKR for	Rehabilitation protocol including	СРМ	6 and 12 months
2012[64]	osteoarthritis	Pulsed electromagnetic fields	No intervention	No losses to follow up
Italy	15; 15	(I-ONE therapy) from POD7, 4		Low risk of bias
2008-2010 1 hospital		hours/ day for 60 days	ien	Mean VAS pain (10-point scale) lower at 12 months in intervention group compared with control, 0.5 (SD 1.3); 3.6 (3.9). p< 0.05. Meal difference of 2.1 (10-point scale) greater than MCID of 16.1 (100- point scale)[65]
				Difference also at 6 months.
			NOD.	More swelling of the knee in intervention patients than controls, statistically significant a 1 and 2 months
Adravanti et al.	Primary TKR for	Standard rehabilitation protocol:	active and passive mobilisation	6 months
2014[123] Italy 1 hospital	osteoarthrosis 16; 17 Mean 66 (SD 13); 73 (5)	Pulsed electromagnetic fields (I-ONE therapy) by POD7 for 4 hours/ day for 60 days	No intervention	4; 3 High risk of bias: small study, proportionately high losses to follow up
	62.5%; 52.9%			At 6 months, mean VAS pain in intervention group lower than in controls (p<0.05). At 3 years, 1/1 intervention patients and 4/12 controls reported severe pain

			No difference between groups in swelling at 6 months.
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11. Rehabilitation

Author	Indication	Common rehabilitation stra	ategies	Follow up
Country Recruitment dates Setting Number randomised intervention; control Age % female		Intervention Control		Losses to follow up intervention; control Risk of bias issues Key results
Walking guidance a	nd training	No	•	
Li et al. 2017[66] China 2015-2016 1 hospital	Unilateral TKR 43; 43 Mean 76.33 (SD 5.28); 78.47 (5.50) 55.8%; 51.2%	muscle strength, use of aids, methods and precautions. Knee passive flexion and ext muscle strength training com straight leg raising exercises increased joint activities and	ce on joint activities, quadriceps diet guidance, correct walking tension to 90° and quadriceps menced on POD 1. POD 3-7, . 2 weeks after replacement, muscle strength training, centre nb weight training, and walking No additional rehabilitation	6 months 0; 0 Low risk of bias Mean VAS pain at 6 months: 0.51 (SD 0.74); 2.83 (0.88) favouring walking intervention group, p<0.01. Difference of 2.42 (10 point scale) greater than the MCID of 16.1 (100- point scale)[65]. HSS scores at 6 months favoured intervention, p<0.01. No infection, allergic reaction or immune reaction in either group. Intervention not associated with swelling, pain, prosthesis loosening, thrombosis, or delayed wound healing
Aquatic therapy				
Liebs et al. 2012[68] Germany 2003-2004 4 hospitals	Elective unilateral TKR for osteoarthritis 87;98	suction drains. Programme of motion activities; exercises for	nce, coordination and gait; and	6, 12 and 24 months 13.8%; 19.4% excluding deaths and unexplained reasons Low risk of bias

	Mean 68.5 (SD 8.6); 70.9 (7.5) 70.1%;73.5%		Aquatic therapy for 30 minutes 3 times a week up to postoperative week 5. Pool exercises aimed at training of proprioception, coordination and strengthening with aid of float cuffs, training kickboards and bar floats.			WOMAC pain at 12 months: early aquatic mean 13.2 (SD 15.0); late aquatic 17.4 (22.4) p=0.22. No difference at 6 and 24 months.
	K	Aquatic therapy beg on the 6th postopera day with the wound covered with a wate adhesive dressing.	ative	exercise a	erapy as pool fter the completion healing on the 14th ive day	5 early aquatic therapy patients and 1 late aquatic therapy patient readmitted to hospital within 3 months. 2 early aquatic patients and 1 late aquatic patient readmission directly or indirectly related to the intervention.
Rahmann et al. 2009[124] Australia	Primary TKR or THR for osteoarthritis	Standard ward-based physiotherapy until day 3. 1 ward physiotherapy treatment per day. Surgical wounds covered with an occlusive, waterproof dressing. 40 mins/ day.			6 months 4;2;0 for combined THR and TKR Unclear risk of bias as TKR patients	
2003-2005 1 hospital with 2 surgeons	(50% TKR) 18;19;17 (11 had been excluded post- randomisation due to complications in hospital Mean 69.4 (SD 6.5); 69.0 (8.9); 70.4 (9.2) 44.4%; 63.2%; 70.6%	From day 4, 1 to 1 individual physiotherapy. Aquatic physiotherapy programme to maximize function and strength. 40 mins/ day. Fast pace metronome 80-88 bpm	individua physioth Water ex program general e not targe specific f retraining aquatic	erapy. kercise me with exercises eted at functional g in the hent. Slow tronome	From day 4, 1 to 1 individual ward- based physiotherapy. 40 mins/ day	more likely to receive ward-based control intervention. THR and TKR analysed together No difference in overall WOMAC outcome at 6 months in THR and TKR patients combined between aquatic at fast pace and ward-based (p=0.929) and aquatic at 2 paces (p=0.872). No adverse events reported after intervention commenced.
Supported early di						
Mahomed et al. 2008[69] Canada 2000-2002 2 centres	Unilateral TKR or THR for osteoarthritis (approximately 50% TKR) 119;115 68	Inpatient physiothera Discharged home w to independently transupine to sitting and standing, walk 30 m climb stairs if necess Physiotherapist hom within 48 hours and subsequent manage	hen able nsfer sitting to etres and sary. ne visit		to independent tion centre for 14	12 months No losses to follow up Low risk of bias (analysis by actual treatment received showed similar results) WOMAC pain at 12 months marginally favoured home-based rehabilitation mean 87 (SD 16); 83

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	About 67% women	along a multidisciplinary clinical pathway (4-16 visits). Then outpatient physiotherapy or self- directed programme.		SD (20), p=0.08 but this was not statistically significant. Mean difference of 4 less than MCID of 8- 9[34]. Results did not differ between TKR and THR patients.
				Similar rates of dislocation, DVT and readmissions between groups. 2% inpatient group developed infections compared with 0 in home group
UK primary 1997-1998 diagnos 1 centre concorr disease 70 rand with 32	Unilateral, primary TKR, irrespective of	Care pathway for medical, nursing and physiotherapy care from admission until day 5		1 year No losses to follow up reported after commencement of intervention
	diagnosis or concomitant	Outreach team domiciliary visit prior to admission with assessment of home	Inpatient care until removal of skin clips and wound healing.	Unclear risk of bias due to limited reporting of methods.
	70 randomised, with 32;28 eligible for trial at	environment. At days 5–7, patients assessed to ensure discharge safe. Outreach team visit on day of discharge with further visits as required. 1+		No pain outcome or patient reported outcome. Control group had better mean KSS scores, but this did not reach statistical significance at 1 yea or earlier.
		physiotherapist visit linked with nurses to monitor knee performance. Discharge when skin clips removed, wound healed and specialist orthopaedic assistance not required, usually day 10–12	ien op	1;1 serious infection, other wound infections 1;6, painful joints 9;4, othe minor complications similar between groups
Flexion or extension	1	1		
Wang et al. 2014[67]	Primary TKR for osteoarthritis	No patellar replacement or late Articular capsule, soft tissue	eral retinacular release Wound closure performed in	6 months No losses to follow up
China	40; 40	and skin enclosed in 90° flexion which was maintained for 1-2 min after wound closure.	full extension	Low risk of bias
2009-2010 1 centre	Mean 68.34 (SD 7.09), 67.87 (6.47)			Mean VAS pain in flexion group 1.15 (SD 0.73); extension group 1.12 (0.68), p=0.64
	17.5%; 22.5%			No wound complications, patella fracture or infection requiring surger in either group

Wound management 12.

Author Indication		Common wound manageme	Follow up	
Country Recruitment dates Setting	Number randomised intervention; control Age % female	Intervention	Control	Losses to follow up intervention; control Risk of bias issues Key results
Kong et al. 2014[58] South Korea 2011 1 surgeon	Primary cemented unilateral TKR for osteoarthritis 50; 50 Mean 69.0 (SD 7.7); 68.0 (4.8) 89.6%; 87.5%	Skin staples removed on day applied for 5 days After removal of wound closure strip, patients managed operation scars with application of silicone gel for 1 month after stitches removed	10 and wound closure strip After removal of wound closure strip, patients managed operation scars with application of petroleum gel for 1 month after stitches removed	6 and 12 months 2; 2 lost to follow up Low risk of bias At 12 months, VAS pain in silicone gel group mean 2.50 (SD 1.16); control 2.92 (1.90). P=0.201. No difference at 6 months, p=0.886. No wound dehiscence or infection associated with application of silicone gel or petroleum
3. Anabolic ster	oids Indication	Common rehabilitation strat	egies	Follow up

Anabolic steroids 13.

Author Indication		Common rehabilitation strategies		Follow up
Country Recruitment dates Setting	Number randomised intervention; control Age % female	Intervention	Control	Losses to follow up intervention; control Risk of bias issues Key results
Hohmann et al.	TKR for	Cold compression and CPM	-	6, 9 and 12 months
2010[70] Australia Before 2010	osteoarthritis 5; 5	On day 5, intramuscular injection of 50 mg Nandrolone decanoate solution. Patients visited	On day 5, intramuscular injection of saline. Patients visited every 2 weeks and	0; 0 lost to follow up Low risk of bias (but small feasibility study)

1 surgeon	Mean 66.2 (range 58, 72);	every 2 weeks and injections continued for 6 months.	injections continued for 6 months.	No separate pain outcome. KSS at 12 months in intervention group mean
	65.2 (59, 72)	continued for o months.	monuis.	91.4 (SD 3.5); control 81.2 (SD 7.1).
	20%; 40%			p=0.03. Difference also at 6 months
				(p=0.04), marginal at 9 months (p=0.06). Difference in means at 12 months of 10.2 close to MCID of 12.3[38].
		4		Intervention group had smaller decrease in bone mineral density at 6 months than controls but not significant

14. **Guided imagery**

Author Indication		Common rehabilitation strategies		Follow up
Country Recruitment dates Setting	Number randomised intervention; control Age % female	Intervention	Control	Losses to follow up intervention; control Risk of bias issues Key results
Jacobson et al. 2016[126] USA 2011-2012 1 surgeon	Unilateral TKR 42; 40 (41; 39 received treatment) Mean 65.0 SD 8.6) 62.2%	Participants listened to a 19- 21-minute CD each day for 2 weeks before and 3 weeks after surgery. Content covered concerns and hopes about TKR with aim to facilitate mind–body connections to promote optimal TKR outcomes.	Participants listened to a 17- 21-minute CD each day for 2 weeks before and 3 weeks after surgery. Content comprised poetry, short stories and essays	6 months 12; 10 of patients receiving treatments High risk of bias due to large losses to follow up Mean WOMAC pain 2.7 (SD 3.1); 3.5 (SD 3.3). P<0.001 Adverse events not reported

CD compact disc; CPM Continuous passive motion; DN4 Douleur Neuropathique 4; FNB Femoral nerve block; HSS Hospital for Special Surgery; i.v. intravenous; KOOS Knee injury and Osteoarthritis Outcome Score; KSS Knee Society Score; LIA local infiltration analgesia; NRS Numerical rating scale; OKS Oxford Knee Score; ONB obturator nerve block; PCA Patient controlled analgesia; PNB psoas nerve block; SF-36 Short Form

36 Health Survey; S-LANSS Leeds assessment of Neuropathic Symptoms and Signs Pain Scale; SNB Sciatic nerve block; TKR Total knee replacement; VAS Visual analogue scale; VTE Venous thromboembolism; WOMAC Western Ontario and McMaster Universities Osteoarthritis Index.

ITT, ITT CC, POD, MI, PE For beer review only

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Supplementary material. Risk of bias assessment

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blind outcome assessment	Incomplete outcome data	Selective reporting	Other bias	Summary
Pain manageme	ent	•		•			•	
Albrecht et al. 2014[29]	Computer generated	Anaesthetist blind to allocation	Physiotherapists, surgeons, research assistants collecting data, and members of the Acute Pain Service were kept blinded to group allocation.	Physiotherapists, surgeons, research assistants collecting data, and members of the Acute Pain Service were kept blinded to group allocation.	ITT analysis low losses to follow up	No but not checked protocol	Study was terminated early with 61% of planned recruitment completed due to change in standard anaesthesia at hospital	Low
Anastase et al. 2014[102]	Method of the Ulm Institute of Statistics	Method of the Ulm Institute of Statistics	No	No	15:14 lost to follow up	No but not checked protocol	ASA comorbidities differed between groups	High
Aveline et al. 2014[43]	Computer generated	opaque sealed envelopes	Blinded syringes prepared by nurse not involved in study	Yes	Low losses to follow up	Consistent with short term follow up paper	No	Low
Bergeron et al. 2009[94]	Blocks of different sizes according to list preprepared by study epidemiologist	Not described	Anaesthetist not blind. Patients blind	Nurse observers collecting data blind to allocation	32/59 lost to follow up	No but not checked protocol	No	High
Buvanendran et al. 2010[44]	computer generated	Yes, physicians and nurses blind	Yes	Yes	ITT	No but not checked protocol	No	Low

Choy et al. 2011[30]	Computer generated	sealed envelope	No, the catheter was removed at either day 3 or 7	Patient reported outcome. Other outcomes by blinded independent physician	Low losses to follow up	Protocol not checked but reasonable range of outcomes	No	Low
Davidson et al. 2016[100]	Computer generated	Sealed opaque envelopes	Subjects and investigators were not masked to treatment group	Subjects and investigators were not masked to treatment group. PROM	31; 29 lost to follow up	None apparent but protocol not checked	Combined data from 2 RCTs	High
Fan et al. 2016[27]	No details	sealed opaque envelopes	Patients and assessors blind to randomisation	Patients and assessors blind to randomisation	2% protocol violation	No but not checked protocol	No	Low
Foadi et al. 2017[106]	Computer generated	Not described	Not described	Patient reported outcome	>70% questionnaire return	None apparent but protocol not checked	Described as pilot study	Unclea
Gao et al. 2017[23]	Random number table	Not described	Blind to patients	Blind to observers	2; 1; 0	None apparent but protocol not checked	Groups similar at baseline	Low
llfeld et al. 2009[97]	Computer generated	Investigators, patients, and all clinical staff were unaware of treatment group assignments	Investigators, patients, and all clinical staff were unaware of treatment group assignments	Investigators, patients, and all clinical staff were unaware of treatment group assignments	4:1 lost to follow up	No but not checked protocol	Basal infusion halved on POD1 in 10 intervention patients compared with 3 controls	High
llfeld et al. 2011[98]	Computer generated tables	Solutions prepared by investigational pharmacist	Yes. Intervention and control solutions indistinguishable	Patient reported outcomes. Staff masked to treatment group	11;12 did not have 4 measures out	Protocol not checked	WOMAC and WOMAC domain scores	High

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Nader et al. 2012[24]	Computer generated	Opaque envelope	No	Patient reported outcome	1:1 lost to follow up	Protocol not checked but reasonable range of outcomes	FNB group somewhat higher BMI	Low
Niemeläinen et al. 2014[35]	No details	Opaque sealed envelopes	Only research nurse preparing infiltrate aware of randomisation. All other personnel unaware until after 1 year follow up	Only research nurse preparing infiltrate aware of randomisation. All other personnel unaware until after 1 year follow up	All patients who received intervention completed follow up	No but not checked protocol	No	Low
Peng et al. 2014[26]	Computer generated	Not possible	Not possible	Patient reported outcome	31:38 lost at 12 months but ITT and per- protocol analysis	No but not checked protocol	No	Low
Perrin and Purcell 2009[96]	No details	Sealed syringe code stored in pharmacy department	yes	Yes	4 failed to complete protocol	No but not checked protocol	Pilot investigation. High risk of bias due to recruitment difficulties leading to small trial	High
Reinhardt et al. 2014[28]	Computer generated	Maintained by pharmacy department for blinding	Patients blind to intervention	Blinded research assistant and partially physical therapist	0 reported lost to follow up of those who received interventions	No but not checked protocol	No	Low
Seah et al. 2011[41]	Randomisation tables	Sealed envelopes. Anaesthetist and surgeon blind before opening of	Blinding of patients not stated	Blind outcome assessors and PROMs	No losses to follow up reported	No but not checked protocol	No	Low

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		sealed envelope						
Shum et al. 2009[95]	No details	No details	Anaesthetist performing the blocks was not involved in the postoperative follow-up and data collection	Patient reported	14% and 20%	No but not checked protocol	Mean patient weight lower in no FNB group. More favourable mean OKS in no FNB group. Two groups combined for 2 year outcome but not for earlier	High
Spreng et al. 2012[104], Spreng et al. 2010[105]	Hospital pharmacy	Epidural catheter or sham set-up taped along the back of the patient and connected to an infusion pump covered in an opaque bag. Also sham knee catheter	Patients blind	Blind outcome assessment	13%	Limited reporting in conference abstract	Conference abstract only so limited information additional to early follow up paper	Unclea
Wang et al. 2015[101]	No details	No details	Not stated	Not stated	2:4 lost to follow up	No but not checked protocol	No	Unclea
Wegener et al. 2013[32]	No details	Opaque envelope	Patients, surgeons and researchers not blind to intervention	Patients not blinded	2:7:5 lost to follow up	No. Protocol checked	no	Low
Widmer et al. 2012[22]	Coded envelope	Coded envelope	Except for anaesthetist and surgeon	Both the investigators and patients were blinded	None reported as incomplete	No but protocol not checked	No	Low

Page	76	of	94
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Williams et al. 2013[39]	Computer generated	Not stated	Patients and assessors blind	Patients and assessors blind	3:1 of those who received treatment	No but not checked protocol	No
Wu and Wong 2014[25]	Computer	Sealed envelopes	No	No	Available cases	No but not checked protocol	No
Wylde et al. 2015[33]	Trials unit	Trials unit	Surgeon and anaesthetist not blind to allocation, Patients blind	Patients and research nurses blind to allocation	ITT with imputed data	No as per protocol	No
Yue et al. 2013[103]	No details	No details	Surgeons and patients were double-blinded to the injection administered	surgeons and patients were double-blinded to the injection administered	Losses to follow up not reported	Limited reporting	No
	ger point dry ne		•		-		
Mayoral et al. 2013[107]	Computerised	Not described	Patient and other researchers apart from physical therapist blind	Patient outcomes	4: 5 loss to follow up	None apparent but protocol not checked	No
Tourniquet		4	•			•	
Abdel-Salam and Eyres 1995[108]	Card system	Not described	No	No	No losses to follow up	None apparent but protocol not checked	No
Ejaz et al. 2014[45]	Block randomised	Sealed envelopes	Patients unaware	PROM	No losses to follow up of those who received treatments	None apparent but protocol not checked	No
Huang et al. 2017[47]	Computer generated	Sealed opaque envelopes	Surgeons not blind. Patients blind to allocation	Data collector blind to allocation	No losses to follow up reported	None apparent but protocol	Group simila basel

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						not checked		
Liu et al. 2014[46]	Excel	Not described	Patients blind	PROM	No losses	None apparent but protocol not checked.	No	Low
Mittal et al. 2012[48]	Computer generated	Sealed opaque envelopes	Patient blind	Outcome assessors blind. PROM	5:2	None apparent but protocol not checked	Study stopped because of high risk of transfusion in short tourniquet duration group	Low
Şükür et al.2016[109]	Computer generated	Not described	Possibly patients	Outcome assessors blind	No losses to follow up	KSS outcome noted in methods but not presented in results	No	Higl
Zhang et al. 2017[49]	Excel	Randomisation by blinded researcher.	Patients and nurses on ward blind	Not clear	No losses reported	None apparent but protocol not checked	Groups similar at baseline	Low
Zhang et al.2016[110]	Randomly allocated	Not clear	Not clear	Not clear	Not clear	HSS outcome noted in methods but not presented in results	No	Higl

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Brock et al. 2017[57]	Web-based	Not specified	Not possible	No but PROMs	4; 2 of those receiving intervention	None apparent but protocol not checked	Groups similar at baseline	Low
Blood conserva	ation	ł	I		•	-		
Hourlier et al. 2015[54]	Computer generated	Opaque envelopes	Anaethsetist, surgeon and patient blind to treatment allocation	Assessors blind	No missing data	None apparent but protocol not checked	No	Low
	Computer generated	Sealed opaque envelopes	Surgeons not blind. Patients blind to allocation	Data collector blind to allocation	No losses to follow up reported	None apparent but protocol not checked	Groups similar at baseline	Low
Kim et al. 2014[51]	Computer generated	Not stated	patients blind to allocation	Clinical investigator blind to allocation	No missing data	None apparent but protocol not checked	No	Low
Kusuma et al. 2013[55]	Computer generated	Sealed envelopes	Surgeon and patient blind	Outcome assessor blind	No missing data	None apparent but protocol not checked	No	Low
Napier et al. 2014[56]	Computer generated	Sealed envelopes	Unlikely	Not stated but PROM	low losses to follow up	None apparent but protocol not checked	No	Low
Sa- Ngasoongsong et al. 2011[50]	Computer generated	Sealed envelopes	Surgeon and patient blind	Outcome assessor blind	No missing data	None apparent but	No	Low

						protocol not checked	
Sa- Ngasoongsong et al. 2013[52]	Computer generated	Sealed envelopes	Surgeon and patient blind	Outcome assessor blind	No missing data	None apparent but protocol not checked	Some differen betwee groups operativ
Thomas et al. 2001[111]	Not described	not stated	Not reported	Not reported but PROM	Not reported but ITT	None apparent but protocol not checked	No
Platelet rich pla		1	1			1	
Aggarwal et al. 2014[112]	Not described	Opaque envelopes	Patients blind	Patients and examiners blind	No losses to follow up reported	None apparent but protocol not checked	Odd nu in group from random
Cryotherapy			1	-		1	
Wang 2017[113]	No details	No details	No details	No details	No losses to follow up	None apparent but protocol not checked	Groups similar baselin
Denusomab				•			
Ledin et al. 2017[59]	Randomisation list produced by the study monitor	Syringes prepared independently	Investigators and patients blind	Unblinding was done after all the data had been locked	0; 2	None apparent but protocol not checked	No
Continuous pas			1			1	
Beaupré etal. 2001[117]	Computer generated	Sealed envelopes	No	Researcher unaware and PROMs	6:8:6. Results carried	No	4 contro SB
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					forward for missing data		reassigned to CPM	
Bennett et al. 2005[61]	Block	Not stated	Operating surgeon blind. Patient not	Independent assessor blind	1 not included in analyses as not able to achieve 90 degree flexion	No	No	Low
Ersözlü et al. 2009[60]	Divided into groups by random selection	Not described	No	Surgeon score	A diabetic patient from the control group was excluded because of a superficial wound infection, a patient with a cardiac problem in group II due to dysrhythmia, and two patients due to insufficient follow-up.	Not apparent	No differences baseline	Unclear
Kumar et al. 1996[118]	Random number generator	Not stated	No	Not described	Large loss to follow up	Not all data clearly reported	No	High
Leach et al. 2006[114]	Allocation by date of birth	No	No	Blinded evaluation	Large loss to follow up	No	No	High
MacDonald et al. 2000[120]	Computer generated	Allocation concealed	No	Not described	Not reported	Yes, not all outcomes reported in full	No	Unclea
Pope et al. 1997[116]	Not described	Not described	Not described	Not described	No separate reporting. 8 patients (12 knees)	None apparent but protocol	No	High

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45 46 47 No

No

No

Baseline

similar

No

No

WOMAC, BMI

unequal at baseline

Unclear

Unclear

High

Low

Unclear

Low

Unclear

					excluding 1 death	not chec
Sahin et al. 2006[115]	Not described	Not stated	No	Followed up by treating physician	Low loss to follow up	No
Worland et al. 1998[119]	Not described	Not described	No	Researcher blind	Not reported separately	Non appa but prot not chee
Electrical stimu	ilation					
Adravanti et al. 2014[123]	Computer generated	Not described	Research assistant not involved in patient assessment	Principal investigator and all physicians in charge of clinical controls were blinded to patient allocation	78% retained at 6 months	Not appa but prote not chee
Avramidis et al. 2011[62]	Computer generated	Not described	No	Independent assessors blind	3 (intolerance of intervention); 3	Not app
Levine et al. 2013[122]	Drawing papers from hat	Not described	No	Not described. WOMAC PROM	5:9 for KSS pain and WOMAC	Not app but prot not
Moretti et al. 2012[64]	Computer generated	Not described	Physicians, as well as medical assessors, were blinded to the allocation of patients in the study groups	Physicians, as well as medical assessors, were blinded to the allocation of patients in the study groups	No losses reported	Not appa but prot not chee
Stevens- Lapsley et al. 2012[121]	Stratified	Concealed	No	no but standardised scripts used	5; 6	Not app but prot

						not checked		
Rehabilitation						0		
Hill et al. 2000[125]	Not described	Not stated	Not possible	Not described	No losses to follow up after initial 23222	No but protocol not checked	No	Unclea
Li et al. 2017[66]	Random number table	Not stated	Not possible	Not described but PROM	No losses to follow up	No but protocol not checked	Groups similar at baseline	Low
Liebs et al. 2012[68]	Computer generated	Allocation concealed	Not possible	No but PROM	Low losses to follow up (<20% if deaths and other explained reasons not counted)	No but protocol not checked	No	Low
Mahomed et al. 2008[69]	Block randomisation	Not stated	Not possible	PROM	No loss	No but protocol not checked	ITT gave similar results to analysis according to actual discharge destination (20 inpatient group received home based)	Low
Rahmann et al. 2009[124]	Not described	Sealed numbered envelopes	Not possible	Assessor blind to intervention. Patient reported outcome	Low losses to follow up	No but protocol not checked	TKR patients more likely to receive ward- based control intervention. THR and TKR analysed together	Unclea
Wang et al. 2014[67]	Computer generated	Surgeons did not participate	Surgery was performed by the	Postoperative evaluation was	No loss to follow up	None apparent	No baseline differences	Low

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Wound manage	ament	in pre- operative grouping	physicians who did not participate in the preoperative grouping and postoperative evaluation	conducted by the physicians who were unaware of the grouping.		but protocol not checked		
Kong et al. 2014[58] Anabolic stero	Not described	Not described	Placebo used	Patient outcome	Low loss to follow up	None apparent but protocol not checked	Similar at baseline	Low
Hohmann et al. 2010[70]	Internet based	Not reported	Placebo trial	Double-blind design minimized systemic error and eliminated observer and experimenter's bias	0 loss to follow up	None apparent	None apparent but small study	Low
Guided imager Jacobson et al.	y Permuted	Opaque CD	Personnel yes,	Yes	12; 10 of	None	No	High
2016[126]	blocks	holders	participants no		patients receiving treatment	apparent but protocol not checked		

References to all RCTs of peri-operative interventions with long-term pain or score follow up, irrespective of risk of bias assessment (numbering consistent with main article, also includes studies reporting minimal clinically important differences)

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Page

Reporting checklist for systematic review and meta-analysis.

Based on the PRISMA guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the PRISMA reporting guidelines, and cite them as:

Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for

Systematic Reviews and Meta-Analyses: The PRISMA Statement

			i ugo
		Reporting Item	Number
	#1	Identify the report as a systematic review, meta-analysis, or	1
		both.	
Structured	#2	Provide a structured summary including, as applicable:	2
summary		background; objectives; data sources; study eligibility criteria,	
		participants, and interventions; study appraisal and synthesis	
	For	peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	

1 2			methods; results; limitations; conclusions and implications of	
3 4			key findings; systematic review registration number	
5 6 7	Rationale	#3	Describe the rationale for the review in the context of what is	4
8 9			already known.	
10 11 12	Objectives	#4	Provide an explicit statement of questions being addressed	4
13 14			with reference to participants, interventions, comparisons,	
15 16 17			outcomes, and study design (PICOS).	
17 18 19	Protocol and	#5	Indicate if a review protocol exists, if and where it can be	4
20 21	registration		accessed (e.g., Web address) and, if available, provide	-
22 23			registration information including the registration number.	
24 25 26				
20 27 28	Eligibility criteria	#6	Specify study characteristics (e.g., PICOS, length of follow-up)	5
29 30			and report characteristics (e.g., years considered, language,	
31 32			publication status) used as criteria for eligibility, giving rational	
33 34	Information	#7	Describe all information sources in the search (e.g., databases	5
35 36 37	sources		with dates of coverage, contact with study authors to identify	
38 39			additional studies) and date last searched.	
40 41	Q. a such		Descent full shows in a cash short and for still set and	
42 43	Search	#8	Present full electronic search strategy for at least one	See note
44 45 46			database, including any limits used, such that it could be	1
40 47 48			repeated.	
49 50	Study selection	#9	State the process for selecting studies (i.e., for screening, for	5,6
51 52			determining eligibility, for inclusion in the systematic review,	
53 54 55			and, if applicable, for inclusion in the meta-analysis).	
56 57				
58 59				
60		For p	eer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	

1 2	Data collection	#10	Describe the method of data extraction from reports (e.g.,	6
3 4	process		piloted forms, independently by two reviewers) and any	
5 6 7			processes for obtaining and confirming data from investigators.	
8 9	Data items	#11	List and define all variables for which data were sought (e.g.,	6
10 11			PICOS, funding sources), and any assumptions and	
12 13			simplifications made.	
14 15				
16 17	Risk of bias in	#12	Describe methods used for assessing risk of bias in individual	6
18 19 20	individual studies		studies (including specification of whether this was done at the	
21 22			study or outcome level, or both), and how this information is to	
23 24 25			be used in any data synthesis.	
26 27	Summary	#13	State the principal summary measures (e.g., risk ratio,	6
28 29 30	measures		difference in means).	
31 32 33	Planned	#14	Describe the methods of handling data and combining results	6
34 35	methods of		of studies, if done, including measures of consistency (e.g., I2)	
36 37 38	analyis		for each meta-analysis.	
39 40	Risk of bias	#15	Specify any assessment of risk of bias that may affect the	6
41 42 43	across studies		cumulative evidence (e.g., publication bias, selective reporting	
43 44 45			within studies).	
46 47	Additional	#16	Describe methods of additional analyses (e.g., sensitivity or	6
48 49		#10		0
50 51	analyses		subgroup analyses, meta-regression), if done, indicating which	
52 53			were pre-specified.	
54 55				
56 57				
58 59				
60		For p	eer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	

1 2	Study selection	#17	Give numbers of studies screened, assessed for eligibility, and	See note
3 4			included in the review, with reasons for exclusions at each	2
5 6 7			stage, ideally with a flow diagram.	
8 9 10	Study	#18	For each study, present characteristics for which data were	See note
11 12	characteristics		extracted (e.g., study size, PICOS, follow-up period) and	3
13 14 15			provide the citation.	
16 17	Risk of bias	#19	Present data on risk of bias of each study and, if available, any	See note
18 19 20	within studies		outcome-level assessment (see Item 12).	4
20 21 22 23	Results of	#20	For all outcomes considered (benefits and harms), present, for	See note
24 25	individual studies		each study: (a) simple summary data for each intervention	5
26 27			group and (b) effect estimates and confidence intervals, ideally	
28 29 30			with a forest plot.	
31 32 33	Synthesis of	#21	Present the main results of the review. If meta-analyses are	15-21
34 35	results		done, include for each, confidence intervals and measures of	
36 37 38			consistency.	
39 40	Risk of bias	#22	Present results of any assessment of risk of bias across	See note
41 42 43	across studies		studies (see Item 15).	6
44 45	Additional	#23	Give results of additional analyses, if done (e.g., sensitivity or	15-21
46 47 48 49	analysis		subgroup analyses, meta-regression [see Item 16]).	
50 51	Summary of	#24	Summarize the main findings, including the strength of	21-23
52 53	Evidence		evidence for each main outcome; consider their relevance to	
54 55			key groups (e.g., health care providers, users, and policy	
56 57 58			makers	
59 60		For p	eer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	

1 2	Limitations	#25	Discuss limitations at study and outcome level (e.g., risk of	21-23
3 4			bias), and at review level (e.g., incomplete retrieval of identified	
5 6 7			research, reporting bias).	
8 9 10	Conclusions	#26	Provide a general interpretation of the results in the context of	21-23
11 12			other evidence, and implications for future research.	
13 14 15	Funding	#27	Describe sources of funding or other support (e.g., supply of	23
16 17			data) for the systematic review; role of funders for the	
18 19 20			systematic review.	
21 22 23	Author notes			
24 25 26 27	1. 5, Suppleme	tary mat	erial	
28 29 30	2. 6, Figure 1			
31 32 33	3. 15-21, Table	1, Suppl	lementary material	
34 35 36	4. 6, Suppleme	ntary ma	aterial	
37 38 39	5. 15-21, Table	1, Suppl	lementary material	
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46 47	CC-BY. This chec	cklist wa	s completed on 21. November 2018 using <u>http://www.goodreports.c</u>	<u>org/</u> , a
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Are peri-operative interventions effective in preventing chronic pain after primary total knee replacement? A systematic review

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Are peri-operative interventions effective in preventing chronic pain after primary total knee replacement? A systematic review

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ABSTRACT

Objectives

For many people with advanced osteoarthritis, total knee replacement (TKR) is an effective treatment for relief of pain and improvement of function. Features of peri-operative care may be associated with the adverse event of chronic pain six months or longer after surgery; effects may be direct, e.g. through nerve damage or surgical complications, or indirect through increasing risks of adverse events. The objective of this systematic review is to evaluate whether non-surgical peri-operative interventions prevent long-term pain after TKR.

Methods

We conducted a systematic review of peri-operative interventions for adults with osteoarthritis receiving primary TKR evaluated in a randomised controlled trial (RCT). We searched *The Cochrane Library*, MEDLINE, Embase, PsycINFO and CINAHL from inception to February 2018. After screening, two reviewers evaluated articles. Studies at low risk of bias according to the Cochrane tool were included.

Interventions

Peri-operative non-surgical interventions; control receiving no intervention or alternative treatment.

Primary and secondary outcome measures

Pain or score with pain component assessed at six months or longer post-operative.

Results

44 RCTs at low risk of bias assessed long-term pain. Intervention heterogeneity precluded meta-analysis and definitive statements on effectiveness. There was encouragement for further research into local infiltration analgesia, ketamine infusion, pregabalin, and electric muscle stimulation. In the studies we identified, tranexamic acid to prevent blood loss was not associated with long-term pain. Many extensively researched interventions including venous thromboembolism prevention have not been evaluated in relation to long-term pain.

Conclusions

To prevent chronic pain after TKR, peri-operative interventions including components of multimodal analgesia, early rehabilitation and supported discharge, electrical stimulation and anabolic steroids show promise that merits further research. Tranexamic use is not associated

with chronic pain but the long-term consequences of many widely researched treatments have not been reported.

STRENGTHS AND LIMITATIONS

• For the first time, this systematic review brings together contemporary evidence on aspects of peri-operative care for people with total knee replacement and their effects on long-term pain.

- Only studies assessed to be at low risk of bias were included in the narrative synthesis.
- Intervention and outcome heterogeneity precluded meta-analysis.

KEYWORDS

Total knee replacement; Systematic review; Randomised controlled trial; Peri-operative care; Long-term pain

BACKGROUND

In the US about 13% of men and 19% of women will be diagnosed with knee osteoarthritis and over half will receive a total knee replacement (TKR)[1]. For people with advanced osteoarthritis unresponsive to pharmacological or conservative treatments, TKR aims to relieve pain and improve function. In the UK nearly 100,000 primary TKRs were performed in 2017[2,3] and in the USA in 2010, an estimated 4.7 million people were living with a TKR[4]. Despite good outcomes for many, some people report long-term pain and are disappointed with their surgery[5,6]. After TKR, pain levels plateau from about 6 months[7,8] after which persistent pain is considered "chronic"[9] and is reported by 10-34% of patients[10].

The mechanisms that influence the development of chronic pain after total knee replacement may be biological, mechanical and psychosocial. Biological causes include the sensitising impact of long-term pain from osteoarthritis[11,12], inflammation, infection and localised nerve injury[13]. Mechanical causes include altered gait, prosthesis loosening, and effects on ligaments[14,15]. Psychological factors including depression and catastrophizing may also influence outcomes[16-19]. Much research has focused on pre-operative predictors of outcomes and these include pain intensity, presence of widespread pain, anxiety, depression and catastrophizing.[10,20] However, attempts to target or modify pre-operative care have, as yet, shown no benefit regarding chronic pain or other long-term patient outcomes[10,21-23].

Peri-operative risk factors suggest that appropriate interventions may reduce long-term pain. For example, acute post-operative pain, which may be a direct consequence of the operation, anaesthetic protocol and subsequent analgesia, or related to particular aspects of care, is an acknowledged risk factor for chronic post-surgical pain[24].

In the peri-operative period from hospital admission to the early stages of recovery, care focuses on acute pain management, prevention of adverse events, facilitation of early mobilisation and timely discharge. However, for people with osteoarthritis the key aim of TKR is the achievement of a long-term painless and well-functioning knee with no adverse events. All aspects of peri-operative care should work together to achieve this.

Any treatment in the peri-operative period including pain management, blood conservation, deep vein thrombosis (DVT) and infection prevention, and inpatient rehabilitation could potentially affect patient recovery and chronic pain, either directly or indirectly. Direct mechanisms may be through prevention of nerve damage[25], post-thrombotic syndrome[26], reperfusion injury[27] and articular bleeding[28]. For other treatments, pathways leading to long-

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term pain may be indirect, possibly being mediated through increased risks of adverse events[29]. Irrespective of mechanism, chronic pain is a highly prevalent adverse event after TKR and should be considered along with infection, DVT and other complications in the safety profile of interventions.

Our systematic review of randomised controlled trials (RCTs) aims to evaluate the effectiveness of treatments in the peri-operative period in preventing long-term pain after TKR. By focusing on studies with low risk of bias we aim to identify interventions with robust evidence of long-term effectiveness and identify gaps in the research base.

METHODS

The systematic review protocol was registered (PROSPERO CRD42017041382) and PRISMA reporting guidelines used[30]. A checklist is included as Supplementary material.

Patient and public involvement

As part of the STAR programme of research (NIHR RP-PG-0613-20001), this review benefited from extensive patient and public involvement. Advice was sought from patients and stakeholders at a group discussion in March 2016 with decisions made on inclusion criteria and outcomes. Our patient advisory group comprises five patients with experience of long-term pain after TKR, supported by a dedicated co-ordinator. This group will advise on dissemination of the study results to a general audience including plain language summaries.

Eligibility criteria

Studies were eligible if they satisfied PICOS criteria defined in the protocol. Participants were adults receiving unilateral primary TKR with osteoarthritis in at least 75% of patients. Pharmacological or non-pharmacological interventions commenced in the peri-operative setting with "peri-operative" reflecting the time from hospital admission to immediately post-discharge. Interventions relating to implant designs and surgical procedures were excluded. The comparator was usual care, placebo or an alternative intervention. Outcomes were, in preference, patient-reported joint-specific pain intensity measured by tools such as the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) or Oxford Knee Score (OKS). If joint-specific measures were unavailable, pain dimensions from quality of life measures were used or pain rated on a visual analogue scale (VAS) or numerical rating scale (NRS). We also considered composite patient-reported outcome measures and surgeon scores which included a pain intensity component, such as the American Knee Society Score (KSS) and Hospital for Special Surgery (HSS) score. Measures specifically of neuropathic pain were also used. The occurrence of adverse events was summarised. The studies included were RCTs with follow up at ≥6 months after surgery and a pain outcome or score including pain. Authors of studies were contacted regarding incomplete pain outcome data.

Database searches

We established an Endnote database of all RCTs in TKR. On 14th February 2018, a final search from database inception was conducted in: *The Cochrane Library*; MEDLINE, Embase and PsycINFO on Ovid; and CINAHL on EBSCOhost. The MEDLINE search strategy is included as supplementary material. Citations of key articles were tracked in Web of Science. No language restrictions were applied, and translations made. Studies reported as abstracts or unobtainable using inter-library loans and author contact were excluded.

Screening and data extraction

We imported records into Endnote X7 (Thomson Reuters). An initial screen by one reviewer excluded clearly irrelevant articles. Subsequently, abstracts and full articles were screened independently by two reviewers and reasons for exclusion recorded.

Data were extracted onto piloted forms and an Excel spreadsheet by one reviewer, specifically: country; dates; participants (indication, age, sex); inclusion and exclusion criteria; intervention and control content; setting, timing, duration and intensity of intervention; follow up intervals; losses to follow up; pain outcome data; and serious adverse events. Data was checked against source material by a second reviewer.

Authors were contacted for missing data, and data provided for previous reviews was used[10,31].

Quality assessment

Potential sources of bias were assessed by two experienced reviewers using the Cochrane risk of bias tool[32], specifically: the randomisation process; deviations from intended interventions; missing outcome data (>20%), measurement of the outcome; and selection of the reported result. Studies with serious concerns relating to risk of bias were considered high risk and those with limited reporting unclear risk. Studies with high or unclear risk of bias were excluded from the narrative synthesis but are included in supplementary summary tables with reasons for exclusion.

Data analysis

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Insufficient studies with similar interventions and outcomes were identified for meta-analysis, and a narrative synthesis is presented. Results reported with p-values ≤0.001 were considered "strong" evidence of effectiveness[33], p-values 0.001-0.05 "some" evidence, and p-values 0.05-0.1 "weak" evidence. When authors reported results "statistically significant" with no p-value, this was noted. Where possible, effect sizes were compared with published minimal clinically important differences (MCID). Concerns relating to adverse events were summarised.

RESULTS

Figure 1 shows review progress and reasons for exclusion. Of 1515 RCTs of interventions in the peri-operative setting, 1385 had no long-term follow up. Peri-operative interventions with follow up of \geq six months were evaluated in 130 RCTs of which 76 reported a pain outcome or score with a pain component. Detailed intervention and study characteristics and risk of bias assessments are provided as supplementary material. Studies excluded had concerns for risk of bias pertaining to at least one of: large baseline differences in group characteristics or numbers in groups (n=4); incomplete outcome data (n=15); limited or selective reporting (n=12); or unblinded surgeon follow up (n=1).

Details of 44 studies assessed to be at low risk of bias are summarised in Table 1. In 34 studies, patients received TKR exclusively for osteoarthritis and in three, 75% or more patients. In seven studies there was no information on reason for surgery but there was no suggestion that patients had an indication other than osteoarthritis. Interventions focused on pain management (n=20), tourniquets (n=5), compression bandages (n=1), blood conservation (n=7), denusomab (n=1), continuous passive motion (n=2), electrical stimulation (n=2), rehabilitation (n=4), wound management (n=1) and anabolic steroids (n=1). Primary pain outcome measures reported were VAS or NRS pain (n=12), WOMAC pain (n=7), KOOS pain (n=3), Leeds assessment of Neuropathic Symptoms and Signs Pain Scale (S-LANSS) (n=1), SF-36 bodily pain (n=1), or composite scores including a pain measure, OKS or WOMAC (n=10), KSS or HSS (n=10). Latest outcomes were recorded at 6 months (n=12), 12 months (n=26) and 24 months (n=6). Reporting of adverse events covered the entire follow up period in 27 studies, short-term after surgery in 15 studies, but were not reported in two studies.

Table 1. Perioperative interventions with follow up for pain or score at6 months or later and assessed to be at low risk of bias

Study	Treatment common to randomised groups	Intervention	Number patients	Follow up Group difference
Pain management: nerve	blocks			
Albrecht et al. 2014[34]	SNB	1. FNB continuous high	99	1 year
Canada, 2009-2011,		2. FNB continuous low		WOMAC score: no difference
1 hospital		3. FNB single		(p=0.68)
Choy et al. 2011[35]	PCA	1. FNB continuous long	61	1 year
Korea, 2006-2007,		2. FNB continuous short		WOMAC pain: no difference
1 surgeon				(p=0.2)
Fan et al. 2016[36]	PCA	1. FNB single	157	1 year
China, 2012-2014,		2. LIA		KSS: no difference (p=0.51)
2 surgeons				
Gao et al. 2017[37]	LIA	1. General anaesthesia	150	6 months
China, 2014-2015,		2. FNB single		HSS score: no significant
1 centre		3. FNB/ SNB single		difference (p> 0.05)
Macrinici et al. 2017[38]	LIA	1. ACB single	98	6 months
USA, Before 2017		2. FNB single		VAS pain: no difference
1 centre				
Nader et al. 2012[39]	PCA	1. FNB continuous	62	1 year
USA, 2007-2008,		2. Oral opioid		NRS pain stair: some evidence
1 surgeon				favouring opioid (p=0.01) but not consistent. Overall NRS pain: no difference (p=1.0)
				VTE: concern opioid
Peng et al. 2014[40]		1. FNB continuous	280	6 months and 1 year
China, Before 2014,		2. PCA		NRS pain: some evidence favouring FNB at 6 months
		8		

1 centre				(p=0.021); no difference at 1 year (p=0.273)
Reinhardt et al. 2014[41]		1. FNB single/ epidural	94	1 year
USA, 2010-2012,		2. LIA 48 hours		VAS pain: no difference
2 surgeons				
Wegener et al. 2013[42]	FNB	1. SNB single	89	1 year
The Netherlands, 2008-2010,		2. SNB continuous		WOMAC pain: no difference
1 centre		3. PCA		(p=0.81)
Widmer et al. 2012[43]	LIA, PCA	1. FNB single	55	1 year
Australia, before 2012,		2. Control no FNB		WOMAC pain: no difference (p=0.74)
2 surgeons				0
Wu and Wong 2014[44]		1. FNB continuous	60	6 months
China, 2009-2011,		2. PCA		KSS: no difference (p=0.513)
1 centre				
Pain management: LIA				
McDonald et al. 2016[45]		1. LIA	222	1 year
UK, 2010-2011		2. PCA		OKS: no difference (p=0.915)
1 hospital				
Motififard et al. 2017[46]		1. LIA pre-emptive	120	6 months
Iran, 2014-2015		-		KSS: weak evidence favouring
1 hospital		2. Control saline with epinephrine		LIA (p=0.07). Difference between groups (14.2/200) less than MCID (12.3/200).
Niemeläinen et al. 2014[47]	PCA	1. LIA	56	1 year
Finland, 2011-2012		2. Control saline		OKS: weak evidence from
1 hospital				means and confidence intervals favouring LIA. Difference (2.7/48) less than MCID (4.0/48)
Seah et al. 2011[48]	PCA	1. LIA with corticosteroid	100	6 months and 2 years
Singapore, 2004-2005		2. LIA no corticosteroid		OKS: no difference

1 hospital				
Williams et al. 2013[49]	LIA, PCA	1. LIA 48 hours	51	6 months and 1 year
Canada, Before 2013		2. Control saline		VAS pain: no difference (6
2 surgeons				months p=0.836, 1 year p=0.767)
Wylde et al. 2015[50]	FNB, PCA	1. LIA	280	6 months and 1 year
UK, 2009-2012		2. Control no LIA		WOMAC pain: weak evidence favouring LIA at 6 months
1 centre				p=0.063; 1 year p=0.107.
				Mean difference at 1 year
				(3.8/100) lower than MCID (8- 9/100)
Pain management: Celeco	xib			
Meunier et al. 2007[51]	PCA	1. Celecoxib	44	1 year
Sweden, 2004-2005		2. Control placebo		KOOS/VAS pain: no difference
1 centre				
Pain management: Ketami	ine/ Nefopam	0,		
Aveline et al. 2014[52]	PCA	1. Ketamine infusion	75	6 months and 1 year
France, 2005		2. Nefopam infusion		DN4/VAS pain: some evidence
1 centre		3. Control saline		favouring ketamine (for DN4 p=0.02). Few patients had
				neuropathic pain at 12 months
Pain management: Pregab	alin	C	5.	
Buvanendran et al. 2010[53]	LIA, PCA	1. Pregabalin	240	6 months
USA, 2006-2007		2. Control placebo		NRS pain: some evidence
Single centre				favouring pregabalin at 6 months (p=0.0176)
				S-LANSS pain: no neuropathio
				pain reported in pregabalin group compared with 5.2% of
				patients in control group
				(p=0.014)
				Sedation and confusion day 0
				and day 1: concern pregabalir
		10		

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Tourniquet				
Ejaz et al. 2014[54]	Tranexamic	1. Tourniquet	64	6 months and 1 year
Denmark, 2011-2012	acid	2. Tourniquet not inflated		KOOS pain: no significant
1 centre				difference
Huang et al. 2017[55]	Tranexamic	1. Tourniquet	100	6 months
China, 2015	acid	2. No tourniquet		VAS pain: no difference (p=0.728)
1 centre				Wound: concern tourniquet
Liu et al. 2014[56]	0,	1. Tourniquet	20	6 months and 1 year
Australia, Before 2014		2. Tourniquet not inflated		OKS: no significant differenc
1 surgeon				Transfusion: concern tourniquet
Mittal et al. 2012[57]	(1. Tourniquet short duration	65	1 year
Australia, 2008-2010 1 centre		2. Tourniquet long duration		OKS: weak evidence from means and Cis on graph favouring long duration at 1 year. Mean difference (5)
				greater than MCID (4) Transfusions/ adverse event concern short
Zhang et al. 2017[58]		1. Tourniquet for entire	150	6 months
China, 2008-2011		operation 2. Tourniquet removed		HSS score: no difference (p=0.839)
1 surgeon		before wound closure		 Transfusions: concern late
		3. Tourniquet from first bone osteotomy until closure		tourniquet start in groups 1 and 2
Compression bandage				
Brock et al. 2017[59]	Hydrocolloid	1. Compression bandage	49	6 months
UK, 2013-2014	dressing	2. Standard crepe		OKS: no difference (p=0.58)
1 hospital		bandage		
Blood conservation				
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Hourlier et al. 2015[60]	Drain,	1. Continuous infusion	106	6 months
France, 2009-2010	tourniquet,	tranexamic acid		KSS: no difference (p=0.90)
	electrocautery	2. Control saline		
1 hospital				
Huang et al. 2017[55]	Tourniquet	1. Intravenous and topical	100	6 months
China, 2015		tranexamic acid		VAS pain: no difference
		2. No tranexamic acid		(p=0.728)
1 centre				HSS score: strong evidence favouring tranexamic acid (p<0.001). Mean difference (1.4/100) lower than MCID (8.3/100)
				Blood loss: control concern
Kim et al. 2014[61]	Tourniquet,	1. Tranexamic acid	180	1 year
Korea, 2009-2011	drain, compressive	2. No tranexamic acid		WOMAC pain: no significant
1 hospital	dressing			difference
Thoopiai				Transfusion: control concern
Kusuma et al. 2013[62]	Tourniquet,	1. Thrombin infusion	80	6 months, 1 and 2 years
USA, Before 2013	Esmarch bandage,	2. No thrombin infusion		KSS: no difference (p=0.45)
1 hospital	electrocautery			ч <i>У</i>
Napier et al. 2014[63]		1. Passive flexion	180	1 year
UK, 2003-2004		2. Passive extension		OKS: no difference (p=0.27)
1 hospital				Transfusion: extension concern
Sa-Ngasoongsong et al.	Drain and	1. Tranexamic acid	48	6 months
2011[64]	compressive dressing	2. Control saline		WOMAC score: no difference
Thailand, 2008-2009	ucssing			(p=0.282)
1 hospital				Transfusion: control concern
Sa-Ngasoongsong et al.	Drain and	1. Tranexamic acid	135	1 year
2013[65]	compressive	500mg		WOMAC score: no difference
Thailand, 2010-2011	dressing	2. Tranexamic acid		(p=0.42)
1 hospital		250mg		Transfusions: control and
		3. Control saline		250mg group concerns

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Denusomab				
Ledin et al. 2017[66]		1. Denusomab	50	1 and 2 years
Sweden, 2012-2014		2. Placebo		KOOS pain: no significant
2 centres				difference
Continuous passive motio	n			
Bennett et al. 2005[67]	Physiotherapy	1. Standard CPM	147	1 year
Australia, 1997-2000		2. Early flexion CPM		KSS: no significant difference
1 hospital		3. No CPM		
Ersözlü et al. 2009[68]	Physiotherapy	1. CPM low and	90	2 years
Turkey, 2003-2004		increasing		KSS: no difference (p=0.67)
1 hospital		2. CPM high and increasing		
		3. No CPM		
Electrical stimulation	Dhysisthereny		76	1.voor
Avramidis et al. 2011[69]	Physiotherapy	1. Transcutaneous electric muscle	70	1 year
Greece, 2005-2006		stimulation		SF-36 bodily pain: strong evidence favouring electrical
1 hospital		2. No treatment		stimulation (p<0.001). Mean
				difference (12.5/100) close to MCID (16.9/100).
				OKS/ KSS: no difference
Moretti et al. 2012[70]	Rehabilitation	1. Pulsed electromagnetic	30	6 months and 1 year
Italy, 2008-2010	protocol	fields		VAS pain: some evidence
1 hospital		2. No treatment		favouring electrical stimulation (p<0.05). Mean difference
				(2.1/10) greater than MCID
				(16.1/100)
				Knee swelling: electrical stimulation concern
Rehabilitation				
Li et al. 2017[71]	Standard	1. Walking guidance and	86	6 months
China, 2015-2016	rehabilitation	training		
		13		

1 hospital		2. No treatment		VAS pain/ HSS score: some evidence favouring walking (both p<0.01). Mean VAS pain difference (2.4/100) greater than MCID (16.1/100)
Liebs et al. 2012[72]	CPM,	1. Early aquatic therapy	185	6 months, 1 and 2 years
Germany, 2003-2004	physiotherapy, post-discharge	2. Delayed aquatic therapy		WOMAC pain: no difference (p=0.22 at 12 months)
4 hospitals	aquatic therapy	liolopy		(p 0.22 at 12 monalo)
Mahomed et al. 2008[73]	Physiotherapy	1. Multidisciplinary supported early discharge	234 hip or knee	1 year
Canada, 2000-2002		and home physiotherapy	replace ment	WOMAC pain: weak evidence favouring supported discharge
2 centres		2. Transfer to rehabilitation centre	ment	(p=0.08). Mean difference (4) less than MCID (8-9)
Wang et al. 2014[74]	0	1. Wound closure in	80	6 months
China, 2009-2010		flexion 2. Wound closure in		VAS pain: no difference (p=0.64)
1 centre		extension		(p=0.04)
Wound management		C.		
Kong et al. 2014[75]	Skin staples and closure	1. Silicone gel	100	6 months and 1 year
South Korea, 2011	strip	2. Petroleum gel		VAS pain: no difference (6 months p=0.886, 1 year
1 surgeon				p=0.201)
Anabolic steroids		C		
Hohmann et al. 2010[76]	CPM. Cold compression,	1. Intramuscular nandrolone injections	10	6 and 9 months, 1 year
Australia, Before 2010		2. Saline injections		KSS: some evidence favourin nandrolone (6 months p=0.04
1 surgeon		,		9 months p=0.06, 12 months p=0.03). Difference at 12 months (10.2) close to MCID (12.3)
				Bone mineral density: weak evidence favouring nandrolon
ACB adductor canal blo	ock; CPM Continuou	is passive motion; DN4 Doule	eur Neurop	athique 4; FNB
Femoral nerve block; H	SS Hospital for Spe	cial Surgery; KOOS Knee inj	ury and Os	teoarthritis Outcome
		afiltantian analysis MOID a	المرابعة المرابعة	colly important
Score; KSS Knee Socie	ety Score; LIA local	Inflitration analgesia; MCID r	iinimai ciini	cally important

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difference; NRS Numerical rating scale; OKS Oxford Knee Score; PCA Patient controlled analgesia; SF-36 Short Form 36 Health Survey; S-LANSS Leeds assessment of Neuropathic Symptoms and Signs Pain Scale; SNB Sciatic nerve block; VAS Visual analogue scale; VTE Venous thromboembolism; WOMAC Western Ontario and McMaster Universities Osteoarthritis Index.

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Pain management

We identified 20 RCTs with 2393 participants evaluating components of multi-modal pain management. Four studies each were from China and the USA, two each from Canada and the UK and one each from Australia, Finland, France, Iran, Singapore, South Korea, Sweden and The Netherlands. All were conducted at a single centre and, in those with dates, participants were recruited between 2004 and 2015. Sample sizes ranged from 44 to 280 participants, with a median of 96. Four studies had three trial arms and 16 had two. The range of mean or median ages of participants in randomised groups was 61 to 73 years and, in 17/19 studies with data, a majority of participants were women.

Femoral nerve block

Femoral nerve blocks (FNB) were studied in 10 RCTs.

Three RCTs compared FNB with no FNB. In one study with 55 patients, WOMAC pain scores at one year were similar in patients receiving single-shot FNB and untreated controls[43]. All patients received local anaesthetic infiltration (LIA) and patient-controlled analgesia (PCA). In another study with all participants receiving LIA, 150 were randomised to receive single-shot FNB with or without sciatic nerve block (SNB), or general anaesthesia[37]. There were no differences in HSS scores between groups at six months. Continuous FNB was compared with oral hydrocodone opioid in 62 patients receiving PCA[39]. There was some evidence for 'pain using stairs' favouring hydrocodone (p=0.01) but no difference in overall NRS-rated pain at one year and concern over venous thromboembolism in 4/31 participants treated with hydrocodone.

In two RCTs, continuous FNB was compared with PCA. In one study with 60 participants, the KSS at six months was similar between groups[44]. In another study with 280 participants, there was some evidence for higher incidence of NRS-rated pain at six months in the PCA group than the FNB group (p=0.021) but not at 12 months (p=0.273).[40]

Two RCTs compared FNB with LIA. In one study, all 157 participants also received PCA[36]. At one year, KSS values were similar in single-shot FNB and LIA groups. In the other study, 94 participants were randomised to receive single-shot FNB with continuous epidural infusion or LIA through an intra-articular catheter[41]. VAS-rated pain was similar between groups at one year.

In two RCTs, FNB procedures were compared. In one study with 99 patients randomised to two FNB concentrations, there was no difference in WOMAC score between groups at 12 months[34]. In another study with 61 participants allocated to two different durations of FNB,

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there was no difference in WOMAC pain scores at one year[35]. In these studies, all participants received either SNB[34] or PCA[35].

Single-shot FNB was compared with single adductor canal block in one RCT with 98 participants, all receiving LIA[38]. At six months there was no difference in VAS-rated pain.

Sciatic nerve block

In one study, 89 patients were randomised to single-shot SNB, continuous SNB, or PCA[42]. All patients received FNB. At 12 months, there were no differences in pain for single-shot SNB and continuous SNB on the WOMAC pain scale or VAS-rated pain at rest or during mobilisation. Similarly, there were no differences between single-shot SNB and PCA in WOMAC pain scale or VAS-rated pain at rest or during mobilisation, or between continuous SNB and PCA.

Local anaesthetic infiltration

Four RCTs compared LIA with placebo. In one study, all 280 participants received FNB and PCA[50]. There was weak evidence that WOMAC pain scores were better in the LIA group at six (p=0.063) but not at 12 months (p=0.107) when the difference in means of 3.8/100 was lower than the MCID of 8-9/100 reported by Ehrich and colleagues[77]. In another study, 56 patients received LIA including ketorolac, or saline placebo, and all received PCA[47]. At one year, mean differences and confidence intervals provided weak evidence that OKS scores were better in the LIA group but the difference in means of 2.7/48 was less than the MCID of 4/48 reported by Beard and colleagues[78]. LIA before surgical incision was compared with placebo in one study with 120 participants[46]. None received FNB or PCA. There was weak evidence for a better KSS (function and knee score components) at six months in those receiving LIA (p=0.07) with a difference in means of 14.2/200 exceeding the MCID of 12.3/200 reported by Lee and colleagues[79]. In another study, all 51 participants received LIA intra-operatively, followed by PCA[49]. Those randomised to post-operative catheter-delivered LIA with ketorolac, or saline placebo had similar VAS-rated pain at six and 12 months.

LIA delivered as an injection and post-operative infusion was compared with epidural PCA in one study with 222 patients[45]. There was no difference between groups in OKS at 12 months. In one study of 100 participants, LIA with or without corticosteroid were compared[48]. All

patients received PCA. At two years there was no difference in OKS between groups.

Oral celecoxib

In one RCT, 44 participants received oral celecoxib or placebo[51], as well as PCA. There were no differences between groups in KOOS or VAS-rated pain at 12 months.

Ketamine or nefopam infusion

In one RCT, ketamine infusion, nefopam infusion and saline placebo were compared in 75 patients, all of whom received PCA[52]. VAS-rated pain on movement did not differ between groups at 12 months. For the Douleur Neuropathique 4 (DN4) measure of neuropathic pain, there was some evidence favouring ketamine over placebo at six and 12 months (p=0.02), but overall, few patients reported neuropathic pain at 12 months.

Pregabalin

Oral pregabalin was compared with placebo in one RCT with 240 participants[53]. All received LIA and PCA. At six months, there was some evidence for better NRS pain in patients receiving pregabalin compared with placebo (p=0.0176) but the difference in means of 0.54/10 was less than the MCID of 1/10 reported by Salaffi and colleagues[80]. No participants receiving pregabalin reported neuropathic pain when assessed using the S-LANSS, compared with 5.2% of those receiving placebo (p=0.014). Patients receiving pregabalin were more likely to be sedated and confused in the first two days after surgery.

Tourniquet

Five studies with 399 participants explored tourniquet use to provide a bloodless field. Two studies each were from Australia and China, and one from Denmark. All were conducted at a single centre with participants recruited between 2008 and 2015. Sample sizes ranged from 20 to 150 participants, with a median of 65. The range of mean ages of participants in randomised groups was 66 to 71 years and in 3/5 studies, a majority of participants were women.

In three RCTs, participants received TKR with or without a tourniquet. In one study with 64 patients, a difference in KOOS pain favouring tourniquet use was not significant at six or 12 months[54]. In another study with 20 patients, the OKS was not significantly different between groups at six or 12 months[56]. There were three blood transfusions in the tourniquet group, compared with none in the 'no tourniquet' group. In the third study with 100 participants, VAS-rated pain and HSS scores were similar between groups at 6 months[55]. Six cases of wound ooze occurred in the tourniquet group.

In two RCTs, short and long-duration tourniquet use were compared. In one study with 65 participants, there was weak evidence based on graphical representation of means and

confidence intervals for improved OKS at 12 months in the long-duration group and the difference in means of 5/48[57] was greater than the MCID of 4/48. Adverse events were reported by 62% of participants receiving short-duration tourniquet compared with 38% in the long-duration group. The study was terminated early as 10 blood transfusions were required in the short-duration group compared with three in the long-duration group. In the second study with 150 participants, tourniquets were used in three different periods during surgery[58]. At six months, there were no differences between groups in HSS scores.

Blood conservation

Seven studies with 829 participants evaluated strategies to limit blood loss after TKR. Two studies were from Thailand, and one each from China, France, South Korea, the UK and the USA. All were conducted at a single centre with participants recruited between 2003 and 2015 when stated. Sample sizes ranged from 48 to 180 participants, with a median of 106. One study had three trial arms. The range of mean ages of participants in randomised groups was 65 to 74 years and in all studies, a majority of participants were women.

Tranexamic acid

Five RCTs evaluated tranexamic acid.

Tranexamic acid injections or infusions were compared with saline placebo or untreated control in four RCTs[55,61,64,65]. In all studies, control patients required more blood transfusions. In one study including 180 participants comparing intravenous tranexamic acid with untreated controls, there was no significant difference in WOMAC pain scores at one year[61]. In another study with 48 participants comparing intra-articular tranexamic acid injection with saline placebo, there was no significant difference in WOMAC scores at six months[64]. One study with 135 participants compared two intra-articular tranexamic acid doses and saline control[65]. There were no significant differences in WOMAC scores at one year. Intravenous and intra-articular tranexamic was compared with untreated controls in one study with 100 participants[55]. VAS-rated pain at six months was similar between groups, but there was strong evidence favouring tranexamic acid for HSS scores (p<0.001) although the difference in means of 1.4/100 was lower than the MCID of 8.3/100 reported by Singh and colleagues[81].

In one study, continuous tranexamic acid infusion was compared with a single bolus in 106 patients[60]. There was no difference between groups in KSS at six months or blood loss.

Thrombin infusion

In one RCT with 80 participants, thrombin infusion was compared with untreated control[62]. At one year there was no difference between groups in pain measured on the KSS.

Flexion or extension

For blood management, operated knees were kept in passive flexion or passive extension after surgery in one RCT with 180 patients[63]. At one year, OKS was similar between groups. Transfusion requirement was greater in patients with passive extension.

Compression bandage

One RCT conducted at a single UK centre with 49 participants recruited between 2013 and 2014 compared compression bandaging to reduce post-operative knee swelling with standard bandaging. The mean age of participants was about 69 years and a majority were women. OKS was similar in randomised groups at six months[59].

Wound management

One RCT with recruitment in 2011 at a single centre in South Korea evaluated a wound care strategy to limit post-operative scar pain. The mean age of participants was about 69 years and a majority were women. Investigators compared silicone gel application to the surgical scar with placebo in 100 participants[75]. There were no significant differences in VAS-rated pain at six and 12 months.

Denusomab

One RCT evaluated use of the antiresorptive monoclonal antibody Denusomab to promote bone healing. The study was conducted in two centres in Sweden with recruitment of 50 participants between 2012 and 2014. The mean age of participants was about 65 years and a majority were women. At 12 and 24 months there were no significant differences between groups in KOOS pain[66].

Continuous passive motion

Two RCTs with 237 participants evaluated use of continuous passive motion (CPM) to minimise joint stiffness and improve range of movement. Studies were conducted in single centres in Australia and Turkey with participant recruitment between 1997 and 2004 and both had three trial arms. Sample sizes were 90 and 147 participants. The mean ages of participants in studies were about 63 and 72 years and a majority of participants were women. In one study, 90 participants were randomised to no CPM, CPM at low flexion from post-operative day 1–7, or

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CPM at high flexion from post-operative day 3–7[68]. There was no significant difference between groups in KSS at two years. In the other study, 147 participants were randomised to CPM with increasing range of movement from day 1–6, early flexion CPM from day 0–6, or no CPM[67]. There were no significant differences between groups in KSS at 12 months.

Electrical stimulation

Two RCTs with 106 participants conducted in single centres in Greece and Italy evaluated electrical stimulation which is believed to have anti-inflammatory activity and limit muscle atrophy. Studies included 76 and 30 participants recruited between 2005 and 2010. The mean ages of participants were 71 and 70 years and in one study that reported it, a majority of participants were female.

In one study with 76 participants receiving transcutaneous electric muscle stimulation from postoperative day two for six weeks or no intervention, Short Form 36 bodily pain showed strong evidence for greater improvement at one year in the intervention group compared to control (p<0.001)[69]. The difference in means of 12.5/100 was close to the MCID of 16.9/100 reported by Escobar and colleagues[82]. There were no differences in OKS or KSS scores. In another study with 30 participants, pulsed electromagnetic fields from post-operative day 7 were compared with untreated control[70]. At 12 months, there was some evidence that VAS-rated pain was lower in intervention patients compared with controls (p<0.05). The difference in means of 2.1/10 was greater than the MCID of 16.1/100 reported by Danoff and colleagues[83]. Knee swelling was common during the intervention.

Rehabilitation

Four RCTs with 585 participants recruited between 2000 and 2016 evaluated features of early rehabilitation focusing on regaining range of movement, functional independence and improving mobility. Two studies were conducted at single centres in China and at two and four centres in Canada and Germany respectively. Sample sizes ranged from 80 to 234 participants, with a median of 136. The range of mean ages of participants in randomised groups was 68 to 78 years and in 3/4 studies, a majority of participants were women.

Walking guidance and training

In one study, 86 participants were randomised to walking guidance and training from postoperative day two or no intervention further to standard rehabilitation[71]. At six months, there was some evidence that those receiving intervention had lower VAS-rated pain (p<0.01) and HSS score (p<0.01) than controls. The difference in mean VAS-rated pain of 2.4/10 was greater than the MCID of 16.1/100.

Flexion or extension during knee closure

Targeting improved functional recovery, wound closure performed in 90° flexion was compared with wound closure in full extension in one study with 80 participants[74]. There was no difference between groups in VAS-rated pain at six months.

Aquatic therapy

In one study with 185 participants, aquatic therapy commencing on post-operative day six was compared with aquatic therapy commencing on day 14[72]. Patients reported similar WOMAC pain at 12 and 24 months.

Supported early discharge

In one study, early discharge supported by physiotherapist home visits and outpatient or selfdirected physiotherapy was compared with two weeks of rehabilitation centre-based usual care[73]. The study included 234 individuals receiving TKR or total hip replacement. Compared with usual care, there was weak evidence that patients with early discharge had lower WOMAC pain scores at 12 months (p=0.08). The difference in means of 4 was less than the MCID of 8-9/100. Results were not presented separately but did not differ between patients with TKR or total hip replacement.

Anabolic steroids

Searches identified one study of anabolic steroids to improve post-operative muscle strength conducted in one centre in Australia with recruitment of 10 participants before 2010. The mean age of participants was about 66 years and a minority were women. Participants received intramuscular nandrolone injections or saline from post-operative day five for six months. KSS results indicated some evidence for improvement in the intervention group compared with controls at 12 months (p=0.03)[76]. The difference in means of 10.2/200 was close to the MCID of 12.3/200.

Interventions with no long-term outcome

Interventions with lack of RCT evidence are summarised in Figure 1.

While 148 RCTs of DVT prophylaxis were identified, only five reported long-term follow up, none of which included a pain or outcome score. Among 29 RCTs of antibiotic prophylaxis, 16

reported long-term follow up, but none included a pain or outcome score. Six RCTs evaluated the use of bisphosphonates and, although all reported long-term follow up, none reported pain or an outcome score. One study reported long-term follow up of an RCT of teriparatide but included no data on pain.

For some interventions, RCTs with long-term pain outcomes were identified, but none were at low risk of bias: cold therapy; guided imagery; platelet rich plasma; and trigger point needling.

Aspects of peri-operative care evaluated in RCTs but lacking long-term pain follow up were: adenosine triphosphate; alternative and Chinese medicine; assistive devices; brain stimulation; calcium supplements; cardiovascular drugs; colloids and crystalloids; comorbidity management; constipation treatment; creatine; delirium prevention; dexmedetomidine; glucocorticoids; glucose infusion; iron; laser therapy; methylprednisolone; music therapy; nausea prevention; nutritional supplements; physiological treatments; remote ischaemic preconditioning; sleep treatments; therapy dogs; and warming.

DISCUSSION

Peri-operative care for patients with osteoarthritis receiving TKR varies widely[84,85]. To guide decisions on appropriate care, the top level of evidence in the hierarchy of primary research is the RCT[86,87]. Bringing evidence from RCTs together in systematic reviews with thorough risk of bias assessment ensures that health professionals have the information they need to deliver a high-quality patient experience with safe, clinically-effective and cost-effective treatments[88]. Furthermore, systematic reviews can identify gaps in the evidence base and promote further research.

Much research in TKR aims to identify treatments that facilitate a speedy recovery with minimal short-term pain. However, patients choose to have joint replacement for long-term pain relief and reduction in functional limitations. Thus, changes to peri-operative care, supported by short-term RCT evidence, should be backed up with evidence about long-term effectiveness for reducing pain and reassurance that there are no long-term unfavourable consequences. To this end, we synthesised evidence from RCTs evaluating peri-operative interventions which have considered their long-term effects on pain outcomes.

A major focus of research into improving long-term pain after TKR has been through prevention of acute post-operative pain using multimodal analgesia. Our review provides some encouragement for further research on long-term benefits of intra-articular LIA injections, as previously shown in short-term studies[31,89], oral pregabalin, oral opioids, and in relation to neuropathic pain, ketamine infusion. As well as potential benefits for reduced long-term pain, future studies will need to consider concerns associated with these interventions which may not have been identified in small studies including infection[31], venous thromboembolism[39] and sedation[53].

Nerve blocks are effective for managing peri-operative pain[90] but we identified no long-term benefit. In single studies, there was no benefit for nefopam infusion, oral celecoxib or LIA with additional corticosteroid. Regarding future studies, standardisation of the multi-modal regimen will allow evaluation of extra or alternative components in multiple studies in different settings. With such an approach, convincing evidence will accrue to guide multimodal pain management.

Tranexamic acid is highly effective in reducing blood transfusions during TKR[91]. We found no evidence that tranexamic acid affects long-term pain or, as observed in registry studies[92,93], adverse events. Single RCTs of thrombin infusion and maintenance of knee in flexion to prevent blood loss showed no effect on long-term pain. Tourniquets improve intraoperative visualisation of the joint, reduce blood loss and facilitate cement fixation but are associated with nerve damage, delayed recovery, acute pain and need for analgesics[94,95]. The RCTs we identified showed no effects of tourniquet use on long-term pain.

Consistent with a previous review[96], there was no suggestion that CPM affects long-term pain. Studies provided encouragement for further research into walking training, anabolic steroid injection, electrical stimulation and supported discharge.

For some interventions a direct mechanism is clear, but for others, reasons for long-term impact are less obvious. This may explain why, for example, no studies evaluated DVT prophylaxis with long-term follow up excepting a small number reporting adverse events. However, treatments to prevent symptomatic DVTs which occur in about 1% of treated patients[97] also reduce the incidence of asymptomatic DVT observed in about 28% of treated patients[98] and this may have long-term benefits. Conversely, new anticoagulants are associated with bleeding[99], which may increase the risk of wound complications[100] and joint infection[101] which are associated with long-term pain[102,103].

Our study is limited by the lack of meta-analysis which was not appropriate due to intervention and outcome heterogeneity. In the context of perioperative pain management, this was noted previously[89]. Our approach to assessing the evidence was a narrative synthesis of studies with low risk of bias. While this may seem overly restrictive, Cochrane risk of bias assessment allows us to screen out studies with important issues that may affect the validity of results. The

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main potential source of bias was incomplete outcome assessment. Although studies with longterm follow up are naturally at higher risk of missing data, we maintained a standard in this domain as it is recognised that research participants who do not complete follow up assessments differ in outcomes from those with follow up data and their inclusion could change the interpretation of results[104].

Another limitation is that pain assessed with questionnaires does not take into account the effect of pain medications and assistive aids. About 58% of women and 40% of men report taking pain medications after TKR because of pain in the operated knee[105] and we must recognise that pain levels at follow up without this treatment might be considerably higher. Even with treatment, around 20% of patients report chronic pain after TKR[10] and in the context of a blinded RCT we should expect to be able to identify effects of peri-operative treatments.

We summarised p-values to assess the strength of evidence but, as statistically strong evidence may not reflect clinically important results[106], where possible we also compared effect sizes with MCIDs. Our review considered a diverse range of interventions at a specific time in the TKR pathway and, as we were unable to make clinical practice recommendations, we did not adopt the GRADE system[107] for this review.

An alternative approach to the prevention of chronic pain after TKR is the individualisation of care based on pain phenotype, genetic, psychosocial and other factors[108]. An example of this might be the peri-operative treatment only of individuals with neuropathic pain with pregabalin, as opposed to the non-stratified provision in the RCT of Buvanendran and colleagues[53]. In an RCT with pregabalin provided to patients with painful HIV-neuropathy, while no overall benefit was seen, a group with hyperalgesia responded to pregabalin treatment[109].

Our systematic review of peri-operative interventions brings together evidence on interventions in the peri-operative phase of the TKR pathway. Whilst not supportive of the inclusion of specific interventions in clinical practice to optimise long-term pain outcomes, there are clearly areas that merit research. High quality studies assessing long-term pain after peri-operative interventions are feasible and necessary to ensure that patients with osteoarthritis achieve good long-term outcomes after TKR.

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AUTHOR CONTRIBUTIONS

All authors, ADB, JD, RG-H and AWB, contributed to the conception and design of the study. ADB, JD and VW undertook the systematic review. ADB and JD carried out the risk of bias assessments. ADB drafted the article with revisions by JD, VW, RG-H and AWB. All authors approved the final version for publication.

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COMPETING INTERESTS STATEMENT

The authors report no competing interests.

DATA STATEMENT

All extracted data is included in the Supplementary material.

Legend

Figure 1. Systematic review flow diagram

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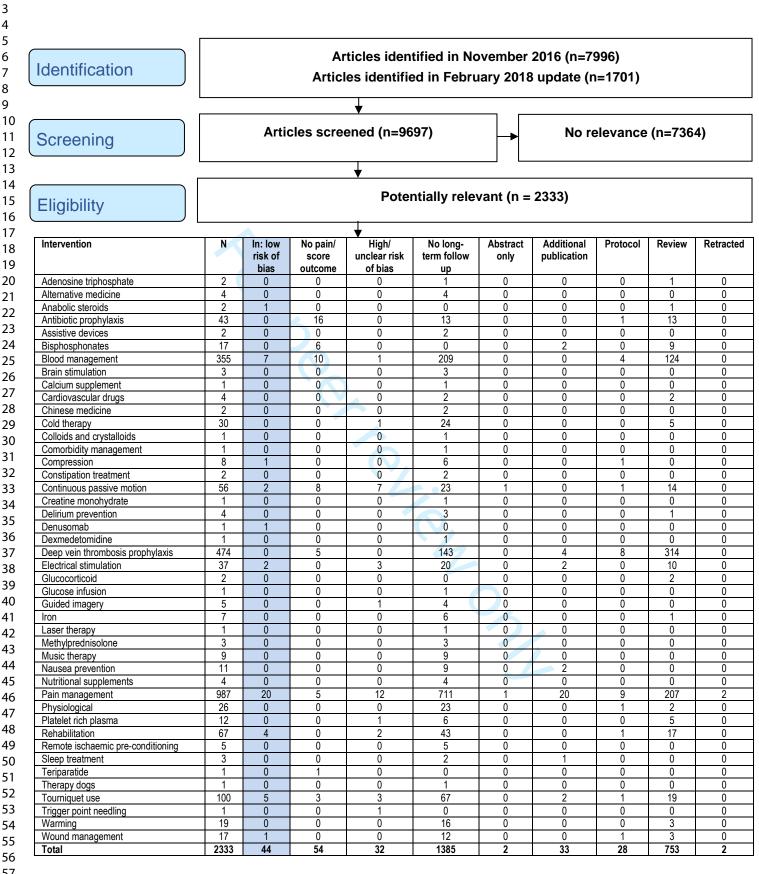
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Supplementary material. Search strategy as applied in MEDLINE on Ovid

- 1 randomized controlled trial/ or randomized controlled trial.pt.
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Supplementary material. All peri-operative interventions with long-term pain or score follow up

1. Pain management

Author	Indication	Common anaesth	esia		Follow up	
Country Recruitment dates Setting Number randomised intervention; control Age % female		Group 1 (intervention)	Group 2 (intervention)	Group C (control)	Losses to follow up intervention control Risk of bias issues Key results	
FNB single vs No F	NB	6				
Widmer et al. 2012[43] Australia Before 2012 2 surgeons	Elective primary unilateral TKR 27; 28 Median 72.1 (IQR 64.4, 76.5); 69.4 (63.4, 75.5) 44.4%; 44.4%	sevoflurane genera LIA with 200mg rop saline. PCA 20µg fentanyl morning POD2. The hours. Daily COX II hours as tolerated.	I anaesthetic. ivacaine and 0.5i at 5-minute interven, oral oxycodor inhibitor and par For breakthrough ate release every FNB Sham caine in identif	. Propofol induction and mg adrenaline in 100ml vals on demand until ne SR 10mg every 12 acetamol 1g every 6 pain, 5-10mg 3 hours as needed. setup for FNB. No ication or injection of al sheath	1 year No losses to follow up reported Low risk of bias WOMAC pain (high score favourable) at 1 year: FNB and LIA median 2.0 (IQR 0, 2.8); LIA no FNB 1.0 (0, 2.0). p=0.74 No adverse events occurred in either group	
FNB single vs ONB						
Bergeron et al. 2009[110] Canada 2005-2006 1 centre	Elective primary unilateral TKR 19; 20; 20 Mean 65.1 (SE 2.0); 72 (1.8); 67 (1.3) 79%; 80%; 75%	Intraoperative sedation with iv propofol at discretion of anaesthesiologist. Lumbar spinal anaesthesia with 12mg 0.5% bupivacaine. Postoperative i.v. PCA with fentanyl 50µg/ml set to deliver 25µg every 5 min as needed. Celecoxib 100mg and acetaminophen 650mg on arrival in recovery room and every 12 and 6 hrs respectively. Breakthrough medication with intramuscular ketorolac 10 mg every 4 hrs.		1 year Overall 32 lost to follow up High risk of bias: only 27/59 patients followed up due to resource limitations. No difference in HSS pain at rest of during activity at 1 year between the study groups.		

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		FNB with stimulator. 20ml 0.5% bupivacaine with 1/200,000 epinephrine.	ONB with stimulator. 20ml 0.5% bupivacaine with 1/200,000 epinephrine.	No injection but inguinal area prepared, and sham block performed behind drapes.	No long-term complications attributable to anaesthetic regimen
	ow dose vs FNB contin	•			
Shum et al. 2009[111] Singapore Before 2009 1 hospital	Unilateral TKR for osteoarthritis 20 (17 received treatment); 20 (18 received treatment); 20	bupivacaine. Intraop increments of 0.5mg Intravenous PCA mo	induced with 2-3ml hy perative sedation with g. prphine (1mg/ml, on-o 5 minute lockout, may	midazolam in demand bolus	2 years 16.4% of patients who received intervention lost to follow up Unclear risk of bias due to differences in OKS and weight at
	Mean 66.7 (SD 8.4); 65.4 (8.4); 67.8 (5.5) 88%; 72%; 80%	Low dose continuous FNB at conclusion of TKR with ropivacaine 0.15% (10 ml/hr in the first 24 hours, followed by 5ml/hr in the next 24 hours)	High dose continuous FNB at conclusion of TKR with ropivacaine 0.2% (10 ml/hr in the first 24 hours, followed by 5 ml/hr in the next 24 hours)	No FNB	baseline, and limited methodologica details. No separate pain outcome but mean OKS slightly more favourable in group with no FNB, 18.2 (SD 3.7) compared with combined FNB groups, 19.8 (5.4) but this was not significant. No complications attributable to use of FNB
•	SNB continuous vs con				1
Wegener et al. 2013[42] The Netherlands 2008-2010 1 centre	Unilateral TKR 29; 30; 30 (90 randomised) Median 65 (range 43-81); 66 (43-83); 62 (50-79) 62%; 70%; 73%	Lorazepam 1mg 2 ho before surgery. FNB dose 20 ml levobupiv a continuous infusior General anaesthesia infusion and remifent with 2-3 µg/ml at 0.1- changed to patient or lockout; basal rate 6 needed. Postoperativ times daily. Diclofena daily. Tramadol 100r Morphine pain relief	with stimulating cath vacaine 0.375% and a n of levobupivacaine (induced with 3-5 µg/ tanil 0.5 µg/kg/min an -0.25 µg/kg/min. Post ontrolled FNB, 5ml bo ml/hr. i.v. morphine a ve analgesia with ace ac 50mg or tramadol ng before removal of	eter: loading after 45 minutes 0.125% 10 ml/hr. /ml propofol nd maintained toperatively, FNB blus, 30-minute administered if etaminophen 1g 4 50mg 3 times	12 months 2;7;5 lost to follow up Low risk of bias Median WOMAC pain scores at 12 months: SNB injection 80 (range 25- 100), SNB continuous 90 (55-100) and PCA only 90 (35-100), p=0.81. No difference between groups in VA pain at rest (p=0.90) or during mobilisation (p=0.43). No information on adverse events.

General anaesthesia	a vs FNB single vs FN	Group Fs: SNB single injection. SNB loading dose of 20 ml levobupivacaine 0.375%.	Group FCS: SNB continuous infusion. SNB loading dose of 20 ml levobupivacaine 0.375%. Continuous infusion of levobupivacaine 0.125% 10 ml/hr started 45 mins after catheter placement. SNB maintained for 36 hours postoperatively (10 ml/hr).	Group F: No SNB. PCA via femoral nerve catheter	
Gao et al. 2017[37] China 2014-2015	Primary unilateral TKR for osteoarthritis 50; 50; 50	Pre-operative and post-operative celecoxib 0.2g twice daily. 100ml intra-operative LIA with ropivacaine 200mg and epinephrine 0.25 mg.			6 months 2; 1; 0 Low risk of bias
1 centre	Mean 65.8 (SD 6.7); 66.4 (7.4); 67.6 (6.3) 81%; 80%; 76%	General anaesthesia	Ultrasound guided FNB 5g/l ropivacaine 20ml plus 0.1mg epinephrine	Ultrasound guided FNB 5g/l ropivacaine 20 ml plus 0.1mg epinephrine and SNB 5g/l ropivacaine 20ml plus 0.1mg epinephrine	Mean HSS at 6 months: 87.1 (SD 6.9); 87.4 (7.3); 88.5 (6.7). No significant difference. Nausea and vomiting: 4; 2; 1, urinary retention: 3; 1; 2.
	d vs No LIA/ placebo				
Wylde et al. 2015 [50] UK	Primary unilateral TKR for osteoarthritis	FNB with nerve stimulator and/ or ultrasound guidance (20ml 0.25% bupivacaine). Spinal or general anaesthetic. Intra-operative analgesia provided by titration of i.v. fentanyl initially and morphine if necessary. 1g intravenous			6 and 12 months 24;19 at 12 months (including those who did not receive treatment)

2009-2012 1 centre	157; 159 (143; 137 received treatment)	paracetamol 30 minutes before the end of operation. Immediately post-operative 400mg oral ibuprofen.	Low risk of bias
1 centre	Mean 69.5 (SD 9.4); 68.7 (7.9) 52%; 54%	PCA with morphine 1mg/ml, 1 mg bolus dose and a 5- minute lock-out. If necessary morphine bolus up to 0.2mg/kg as rescue analgesia. During hospital stay, visit from pain specialist nurse. Oral or i.v. paracetamol every 6 hours and ibuprofen 400mg every 8 hours. When PCA no longer needed, oral codeine phosphate 30-60mg every 6 hours, tramadol 50-100mg every 6 hours and oramorph 10-20mg as rescue analgesia. 60ml intra-operative LIA with 0.25% bupivacaine and 1/200,000 adrenaline injected into the posterior capsule, medial and lateral capsule, fascia and muscle, and subcutaneous tissues.	At 12 months WOMAC pain score (0 100) in LIA group median 90 (IQR 30), Control 85 (35); ITT-CC linear regression coefficient 3.83 (95%CI - 0.83, 8.49), p=0.107. At 6 months WOMAC pain score ITT-CC linear regression coefficient 4.10 (95%CI - 0.22, 8.43), p=0.063. Mean differences lower than MCID of 8- 9[77]. Superficial and deep wound infectior rate in LIA group 3.2% and 1.9% in control group, p=0.500. No differences in serious adverse events between groups
Williams et al. 2013[49] Canada Before 2013 1 centre, 2 surgeons	Primary unilateral TKR for osteoarthritis 35; 32 (26; 25 received treatment) Mean 66 (SD 9.7); 67 (12.5) 58%; 60%	Sedation with i.v. midazolam and propofol. Intraoperative LIA loading dose of 20ml 0.25% bupivacaine/ epinephrine injection, 10ml into medial and lateral subcutaneous tissue around the incision and 10ml intra-articular after closure. Infiltrate delivered by pain pump into lateral recess of intra- articular space. Spinal anaesthetic with 10-15 mg of 0.75% or 0.5% plain bupivacaine and 20µg fentanyl. Postoperative morphine PCA. 7.5mg i.v ketorolac preoperatively plus 15mg every 6 hours postoperatively for 48 hours, then oral ketorolac 10mg every 6 hours for 2 days. Gabapentin 600mg given preoperatively plus 300mg twice daily for 48 hours postoperative. Oral paracetamol 650mg every 4 hours for 72 hours. Infusion of 0.5% bupivacaine at 2ml/hr for 48 hrs	6 and 12 months 3;1 of those who received treatment Low risk of bias Mean VAS pain score at 6 months 1.2 (SD 1.3); 1.2 (1.2). p=0.836. At 12 months 0.9 (1.2); 1.0 (1.1). p=0.767 No short-term differences in adverse events except control patients more likely to be drowsy at 48 hrs. Long- term adverse events not reported.
Niemeläinen et al. 2014[47] Finland 2011-2012	Primary unilateral TKR for osteoarthritis 30; 30 (27; 29 received treatment)	Oral paracetamol 1g given 1 hour before surgery. Spinal anaesthesia with 15mg bupivacaine in 3ml. After surgery oral paracetamol 1g every 6 hours and oral meloxicam (15mg) every 24 hours. PCA with oxycodone 2mg, lock-out time 8 min.	12 months 1; 4 Low risk of bias No pain measure separate from OK Weak evidence of more favourable

1 hospital	Mean 65 (SD 4.9); 64 (6.7)	Rescue levobupivacaine medic epidural catheter	ation through a lumbar	OKS (0-48) in the LIA group at 12 months, mean difference -2.7 (95%
	56%; 48%	Intra-operative periarticular LIA of 100ml saline with levobupivacaine (150mg) mixed with ketorolac (30mg) and adrenaline (0.5mg).	Intra-operative periarticular LIA of 100ml saline	CI -5.48, 0.07). Difference lower than MCID of 4.0[78]. Infection: 0; 0. Severe pain treated with epidural analgesia: 0; 3. Nausea: 1; 1
Motififard et al. 2017[46] Iran 2014-2015 1 hospital	Primary unilateral TKR for osteoarthritis 60; 60 Mean 66.4 (6.4); 64.5 (6.0) 86.0%; 94.3%	Spinal anaesthesia. No FNB or SNB. Pain medication provided as re meloxicam (15 mg daily), celec acetaminophen (1g every 8 hou 8 hours), ketorolac (30 mg slow dose max), and morphine (5–1	6 months 3; 7 Low risk of bias No separate pain measure. Weak evidence for improved KSS (0-200) ir LIA group at 6 months, mean 115.55 (SD 15.506); 101.40 (16.117).	
		Peri-articular injection, 15 minutes before incision, of 100ml saline containing 50 mg bupivacaine hydrochloride 0.5%, 1 ml morphine sulphate 10 mg/ml, 300 µg epinephrine (1:1000) and 30 mg ketorolac	100ml saline containing 300 μg epinephrine (1:1000)	P=0.07. Difference of 14.15 greater than MCID of 12.3[79]. Difference was significant at 6 weeks, p<0.001 No complications related to TKR or LIA. Low back pain (1; 2), stroke (0 1), CHF (1; 0)
McDonald et al. 2016[45] UK 2010-2011 1 hospital	Primary unilateral TKR for osteoarthritis 113; 109 received common spinal anaesthesia (121; 121 randomised) Median 68 (IQR 62, 72); 67 (62, 73) 59%; 55%	Oral premedication with 10-20r ranatidine, 10mg dexamethaso paracetamol. Spinal anaesthesia Intra-articular and subcutaneous infiltration during surgery of 200 ml of 2mg/ml ropivacaine without adrenalin or additives. Catheter inserted, and 20 ml infiltrate injected following wound closure. Further boluses of 40 ml 2 mg/ml ropivacaine via infusion pump 4 hours after leaving theatre and morning of POD1. Two		12 months 9; 11 of those receiving treatments Low risk of bias No separate pain outcome. Mean OKS at 12 months: median 41 (IQR 35, 44); 41 (34;44). P=0.915 Suspected infection 2; 1. MI 0; 1. GI bleed 1; 0. renal failure 1; 0. Died 2; 0)

		additional top ups of 40 ml 2mg/ml ropivacaine were prescribed if required.		
Celecoxib vs placeb	0			
Meunier et al. 2007[51] Sweden 2004-2005 1 centre	Elective primary unilateral TKR for osteoarthritis 25; 25 (24; 20 received treatment) Mean 68 (SD 6.3); 69 (7.7)	Spinal anaesthesia with bupivacaine 17.5-20mg. i.v.midazolam or propofol sedation if needed. Paracetamol 1 gpreoperatively and then with tramadol 50-100 mg 4 times aday during hospital stay. Ketobemidone (2.5-5mg i.v. orsubcutaneous) on demand. Paracetamol and tramadolused as required after discharge.Oral celecoxib 200mg 1 hourpreoperatively and twice dailyhour preoperatively and		12 months No losses to follow up after surgery reported Low risk of bias No effect of celecoxib on VAS or KOOS pain at 1 year. DVT: 0; 1. Deep infection: 0; 0.
	71%; 40%	for 3 weeks	twice daily for 3 weeks	
Ketamine vs placebo	0			•
Perrin and Purcell2009 [112]Elective unilateral TKRAustralia16 (5; 7 completed study per protocol)Before 2009study per protocol)1 centre (pilot study)Mean 65.6 (SD 10.2); 60.3 (11.9) 40%; 43%	Intrathecal injection of 15mg bu morphine. General anaesthesia paracetamol and then 750mg e morphine 2mg boluses with 10 rescue 2.5mg intravenously as ibuprofen 800mg.	 6 months 3 protocol breaches and 1 patient with uncontrolled pain. High risk of bias due to non-ITT reporting and recruitment difficulties 2/5 ketamine group had mild/moderate pain on the WOMAC 		
		Ketamine 0.5mg/kg bolus followed by 4µg/kg/min infusion. Commenced before surgical incision and continued until wound bandaged or syringe empty.	Saline infusion. Commenced before surgical incision and continued until wound bandaged or syringe empty.	pain scale at 26 weeks or failed to improve compared with 5/7 controls 1 adverse psycho-mimetic effect no attributed to intervention or control treatment
Ketamine vs Nefopa	•			
Aveline et al. 2014[52] France 2005 1 centre	Elective primary unilateral TKR for osteoarthritis 25; 25; 25 Mean 73 (SD 9); 72 (9); 70 (7) 67%; 60%; 63%	General anaesthesia induced with 1.5-2mg/kg propofol, 1µ/kg remifentanil and a single bolus of cisatracurium 0.15mg/kg. Remifentanil infusion at 0.15µg/k/min until skin closure. Anaesthesia maintained with sevoflurane 0.9- 1.2% with 50% nitrogen in oxygen. 20 mins before skin closure, 0.15mg/kg i.v. morphine bolus and 0.625mg droperidol. PCA with morphine hydrochloride 1 mg i.v. bolus with 7-min lockout. On arrival in recovery room, 3 mg i.v. morphine boluses at 5 minute intervals.		6 and 12 months 3; 1; 2 Low risk of bias Median DN4 at 12 months: 1 (IQR 1 2); 1 (0, 1); 2 (1, 3). p=0.02 for difference between ketamine and placebo groups. Number of patients with VAS pain on movement score

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	<i>K</i> 0,	0.2mg/kg nefopam administered over 20 min before incision; 2mg/ml nefopam continuous infusion at 120µg/kg/hr until end of surgery and 60µg/kg/hr for 48 hours	0.2mg/kg ketamine administered ove 20 min before incision; 2mg/ml ketamine continuous infusion at 120µg/kg/hr until end of surgery and 60µg/kg/hr for 48 hours	Saline administered over 20 minutes before incision; saline continuous infusion until second post- operative day	 ≥40mm at 12 months by group: nefopam (3/22, 13.7%), ketamine (3/24, 12.5%), and placebo group (6/23, 26.1%). Ketamine reduced DN4 pain (p=0.02) compared with placebo. At 12 months only 7/69 patients had DN4≥4 indicative of neuropathic pain. Infection: 0; 0; 0. Revision: 0; 0; 0.
Pregabalin vs place Buvanendran et al.	Primary unilateral	Sedation with mida			6 months
2010[53]	TKR for	spinal-epidural ana			7; 5
USA	osteoarthritis.	bupivacaine with 2 Catheter inserted f			Low risk of bias
2006-2007 Single centre Nean 64.0 (SD 8.3); 63.3 (8.9) 76%; 70%	LIA 60 ml 0.25% bupivacaine with epinephrine infiltrated into the wound at capsule closure. From completion of surgery until 32-42 hours post-operative, epidural infusion of fentanyl (5µg/ml) and bupivacaine (1mg/ml) initiated using continuous basal infusion of 6ml/hr with epidural PCA bolus doses (maximum 10ml/hr). Patients transitioned to oral opioid (morphine, oxycodone, and hydromorphone) as required. All patients received preoperative oral celecoxib 400mg 1–2 hours before surgery and 200mg twice daily for 3 days in hospital.			Mean VRS pain score at 6 months: pregabalin 0.41 (SD 1.20); control 0.95 (1.80). p=0.0084. Distributions skewed but nonparametric Wilcoxon significant (p=0.0176). Difference of 0.54 less than MCID of 1.0. In the pregabalin group the incidence of neuropathic pain measured using S-LANSS was 0% (0/113) and 5.2% (6/115) in the placebo group (p=0.014).	
		Oral pregabalin 30 h before surgery, 1 twice daily for the f postoperative days twice daily on days 12, and 50mg twice days 13 and 14	50mgsurgefirst 10first 1s, 75mgtwices 11 and12, ar	placebo 1–2 h before ry, twice daily for the 0 postoperative days, daily on days 11 and nd twice daily on days d 14	No clinically significant adverse events up to 6 months and no falls. Sedation, confusion and dry mouth more frequent in pregabalin than placebo group on day of surgery and first postoperative day.

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Ilfeld et al. 2009[113] USA 2005-2007 2 centres	Primary unilateral TKR for osteoarthritis 25; 25 Median 66 (IQR 60, 70); 64 (60, 69) 56%; 60%	Femoral catheter inserted usin 0.2% ropivacaine infusion (8ml controlled bolus; 30-minute loc POD1. 1 week oral acetaminophen (9 sustained release oral opioid (0 hours), and either oral aspirin ((200mg every 12 hours). Oral o or i.v. morphine sulfate 2-4 mg At 6 a.m. POD1, infusion pump replaced with infusion pump with 0.2% ropivacaine. At 6 p.m. POD2 pump replaced with portable infusion pump (400ml 0.2% ropivacaine). Catheter removed evening of POD4.	6 and 12 months 4; 1 lost to follow up High risk of bias: uneven loss to follow up between groups; muscle weakness resulted in lower dose of infusion on POD1 (10 continuous; saline) Groups had similar WOMAC pain scores at 6 and 12 months (p>0.05). MI: 1; 0. PE: 1; 0. Fall: 1; 0. Catheter leak, dislodged: 1; 2	
Ilfeld et al. 2011[114] USA 2007-2009 2 centres	Primary unilateral cemented TKR for osteoarthritis 40; 40 (39; 38 included in RCT) Median 61 (IQR 58, 67); 66 (60, 70) 67%; 66%	Femoral catheter inserted usin 0.2% ropivacaine infusion (6ml controlled bolus; 30-min lockou 1 week oral acetaminophen (9 sustained release oral opioid (1 hours), and either oral aspirin ((200mg every 12 hours). Oral (tablets) and/ or i.v. opioids (mo breakthrough pain.	12 months 11; 12 incomplete follow up High risk of bias: 11;12 did not ha 4 measures out of 6 up to 12 months; graph suggests WOMAC pain lower pre-intervention in continuous infusion group. No difference in WOMAC pain	
		At 6 a.m. POD2, infusion pump replaced and 0.2% ropivacaine continued. At 6 p.m. POD2 pump	At 6 a.m. POD2, infusion pump replaced but saline substituted. At 6 p.m. POD2 pump	scores between randomised grou (p>0.05). Falls: 4; 0
		replaced with portable infusion pump (400ml 0.2% ropivacaine). Catheter removed evening of POD4	replaced with portable infusion pump (saline). Catheter removed evening of POD4	
Choy et al. 2011[35] Korea 2006-2007	Primary unilateral TKR for osteoarthritis	Spinal anaesthesia. Continuou POD3. Catheter inserted with u Analgesia induced with 20ml o 2% lidocaine with 1:200,000 ep	2 years 4; 3 lost to follow up	

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1 surgeon 33; 30 (2 patients received GA and excluded) Mean 66.7 (SD 10); 67.5 (11)		infusion with 0.125% bupivacaine 5.0ml/hr. i.v. PCA (butorphanol 4mg, ketorolac 150mg, saline 50ml), programmed to deliver 1 mg bolus (lockout 10 min) with maximum dose 6mg/hr. i.v. paracetamol 2g 4 times/ day and oral ibuprofen 600mg 3 times/ day for breakthrough pain			Low risk of bias for 2 year outcome measures. At 2 years, intervention WOMAC pain mean 7.2 (SD 2), control 6.3 (SD 1); p=0.2
	97%; 93%	Continuous femoral ner block via catheter conti from POD3 to POD7		ous femoral nerve scontinued on	Superficial infection: 1; 1
FNB continuous	high concentration vs F	NB low concentration v	rs FNB single		
Albrecht et al. 2014[34] Canada 2009-2011 1 hospital	Scheduled primary unilateral TKR 32; 32; 35 Mean 61 (CI 57, 64); 63 (60, 67);63 (60, 66) 46%; 44%; 52%	Stimulating catheter ins Immediately after catheter was injected through the ropivacaine 0.2%. Spin- isobaric bupivacaine 0.3 Bolus of 20ml ropivacaine 0.2% with epinephrine 1:400,000 into the femoral catheter followed by ropivacaine 0.2% at a rate of 5 ml/hr with patient-controlled boluses of 5ml available every 30minutes.	ter placement, 10r e catheter. SNB us al anaesthesia with	nl mepivacaine 2% sing 30 ml n 2.5 to 3.0 ml	12 months 4;0;2 lost to follow up Low risk of bias. No separate pain outcome. Mean WOMAC score at 12 months: high concentration FNB 17 (95% CI 7, 27); 22 (14, 30); 18 (8, 27). P=0.68 Falls: 0; 0; 1
	vs Psoas compartment			•	
Morin et al. 2005[115] Germany Before 2005 1 centre	Elective unilateral TKR 30; 30; 30	Oral pre-medication with 20mg chlorazepate. General anaesthesia with intravenous propofol and 4–8µg/kg i.v. fentanyl and desflurane in N2O. 100mg diclofenac suppository after anaesthesia induction and 2.5g intravenous metamizole before end of surgery. Post- operative 3 daily doses of oral diclofenac 50mg. i.v. PCA			9–12 months7; 6; 5High risk of bias due to large losse to follow up, non-blinded outcome collection, and differences between

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Continuous FNB Stimulating catheter used. Initial bolus of prilocaine 1% and copivacaine 1% poivacaine 1% (30ml) and 150mg compartmentalContinuous FNB stimulating catheter used. SNBContinuous FNB compartment block1,4), FNB and SNB 2 (1, 4), p=0.44 block 2 (IQR 1, 4), p=0.44 No early complications but longer term adverse events not reported. Or5%. 300mg prilocaine 1% and copivacaine 0.75%. 300mg prilocaine 1% catheter used. Initial bolus of prilocaine 1% and copivacaine 0.75%. (30ml) and 200mg prilocaine 0.75% (20ml). During first 48hrs post- operative coperative coperative coperative coperative coperative constanted from 1 centreContinuous FNB state of the from the first of the first state of the first of the first of the first down of the first	Median 68 (IQR 62, 74); 71 (63, 74); 65 (53, 73) 50%; 70%; 59%		with piritramide bolus 2mg as needed with lockout interval of 10 mins for 48 hours.			groups in BMI and anaesthetist's opinion of difficulty of catheter placement. No difference between groups in level of pain at the knee joint during
Davidson et al. 2016[116]Primary, unilateral TKR or unicompartmental 2013-2014Spinal or general anaesthesia. Intra-operative i.v. fentanyl, hydromorphone, and/or morphine.12 months 31; 29USA 2013-2014 2 studies combined from 1 centre54 (39 TKR, 16 UKR); 56 (41 TKR, 15 UKR)Spinal or general anaesthesia. Intra-operative i.v. fentanyl, hydromorphone, and/or morphine.12 months 31; 29High risk of bias due to partial follo up2 studies combined from 1 centre54 (39 TKR, 16 UKR); 56 (41 TKR, 15 UKR)Post-operative: oral acetaminophen (975 mg every 6 hr), celecoxib (200 mg every 12 hr), and sustained release oxycodone (10 mg every 12 hr). For breakthrough pain, infusion pump bolus (4 ml, 30-min lock-out). Rescue opioid titrated to pain severity. 10 ml lidocaine (2%) bolus was 		<i>k</i> 0,	Stimulating catheter used. Initial bolus of prilocaine 1% and ropivacaine 0.75%. 300mg prilocaine 1% (30ml) and 150mg ropivacaine 0.75% (20ml). During first 48hrs post- operative ropivacaine 0.2% infusion	and continuous SNB Stimulating catheter used. Initial bolus of prilocaine 1% and ropivacaine 0.75%. In each catheter: 200mg prilocaine 1% (20ml) and 75mg ropivacaine 0.75% (10ml). During first 48hrs post-operative infusion through each catheter of 0.2% ropivacaine	compartment block Stimulating catheter used. Initial bolus of prilocaine 1% and ropivacaine 0.75%. 300mg prilocaine 1% (30ml) and 150mg ropivacaine 0.75% (20ml). During first 48hrs post- operative ropivacaine 0.2%	past 4 weeks: FNB median 2.5 (IC 1, 4), FNB and SNB 2 (1, 4), Psoa block 2 (IQR 1, 4), p=0.44 No early complications but longer
2016[116] USATKR or unicompartmental 2013-2014hydromorphone, and/or morphine.31; 292013-2014 2 studies combined from 1 centreLIA with 30 ml ropivacaine (0.5%), ketorolac (30 mg), and epinephrine (5 µg/ml).High risk of bias due to partial follo upNKR); 56 (41 TKR, 15 UKR)Post-operative: oral acetaminophen (975 mg every 6 hr), celecoxib (200 mg every 12 hr), and sustained release oxycodone (10 mg every 12 hr). For breakthrough pain, infusion pump bolus (4 ml, 30-min lock-out). Rescue opioid titrated to pain severity. 10 ml lidocaine (2%) bolus was given via the perineural catheter for moderate or severe31; 2931; 29High risk of bias due to partial follo up31; 29High risk of bias due to partial follo upNKR mean 67 (SD (10); 68 (12)N; 66 (7). UKR 70 (10); 68 (12)N; 67 (10); 6	ACB continuous vs	FNB continuous				
	2016[116] USA 2013-2014 2 studies combined	TKR or unicompartmental 54 (39 TKR, 16 UKR); 56 (41 TKR, 15 UKR) TKR mean 67 (SD 8); 66 (7). UKR 70	hydromorphone, a LIA with 30 ml rop epinephrine (5 µg Post-operative: or celecoxib (200 mg oxycodone (10 mg infusion pump bol titrated to pain sev given via the perir	and/or morphine. bivacaine (0.5%), ketoro /ml). ral acetaminophen (975 g every 12 hr), and sust g every 12 hr). For brea us (4 ml, 30-min lock-o verity. 10 ml lidocaine (blac (30 mg), and is mg every 6 hr), tained release akthrough pain, ut). Rescue opioid 2%) bolus was	31; 29 High risk of bias due to partial follow up TKR and UKR combined. Pain score (0-10) at 12 months median
				11		

	TKR 59%; 66%. UKR 47%; 47%	Ultrasound guided ACB. Ropivacaine 0.2% at basal rate of 6 ml/hr, a 4-ml bolus, and a lockout of 30 minutes	Ultrasound guided continuous FNB. Ropivacaine 0.2% at basal rate of 6 ml/hr, a 4-ml bolus, and a lockout of 30 minutes	52) in pain score (p=0.80) or pain score >0 (p=0.48). Falls in hospital: 2; 5
ACB single vs FN Macrinici et al. 2017[38] USA Before 2017 1 centre	IB single Primary unilateral TKR, indication not specified (selected by the surgeon for TKA) 49; 49 Mean 67 (SD 8); 67 (8) 61%; 63%	Multimodal regimen including N analgesics, opioids. LIA 40ml N All patients received an ultraso into ACB and FNB sites. Immediately after surgery, 30ml solution with 100ml Marcaine into ACB site. 30 ml saline into FNB site	Marcaine 0.25%.	6 months 3; 4 lost to follow up. 6; 3 complications Low risk of bias VAS pain similar between groups a 6 months. No difference in functional outcomes Medical complications: 3; 0. Surgical complication: 0; 1. Temporary foot drop: 3; 2.
<i>FNB continuous</i> Nader et al. 2012[39] USA 2007-2008 1 surgeon	vs oral opioid Elective unilateral TKR 31; 31 Median (IQR) 65 (60, 76); 64 (60, 71) 58%; 77%	Before surgery, patients receiv needed. Epidural with 10mg 0. injected intrathecally. Intraoper infusion of 25-75mcg/kg/minute area, PCA epidural with basal bupivacaine and 10 mg/ml hyd activated boluses of 3 ml with a minutes and per hour maximur discontinued and epidural cath POD 1. All subjects received 5 surgery and 40 mg enoxaparin Continuous FNB inserted with use of stimulator. After discontinuation of epidural anaesthesia on the morning of POD1 10mL bolus of ropivacaine 0.25% followed by 5ml/h infusion of 0.1% ropivacaine. On morning of POD 2, ropivacaine infusion	5% isobaric bupivacaine ative sedation with propofol e. In post-anesthesia recovery infusion of 3 ml/hr (1 mg/ml romorphone) with patient- a lockout interval of 15 n of 15 ml. Infusion eter removed on morning of mg warfarin on evening of	6 and 12 months 1; 1 lost to follow up at 12 months Low risk of bias No difference in overall median NRS pain score at 6 months and 1. months: 0 (IQR 0, 1); 0 (0, 1). p=1.0. At 12 months, some evidence favouring hydrocodone for pain ascending/ descending stairs: 1 (0, 2); 0 (0, 0). p=0.01. Also, suggestion of reduced pain in hydrocodone group at night in bed (p=0.06) and sitting/ lying (p=0.07). standing upright (p=0.10). No difference walking on flat surface (p=0.41). Falls in month after surgery: 1;0. Positive joint aspirate: 3; 0. VTE: 0 4.

		discontinued. Femoral catheter removed 24 hours after previous dose of enoxaparin.	4 hours fo pain	or breakthrough	
<i>FNB continuous vs l</i> Wang et al. 2015[117] China 2012-2013 3 centres	PCA Elective unilateral TKR 82; 86 No significant differences in age or sex	General anaesthesia with mida fentanyl (1µg/kg), propofol (1-2 (0.15mg/kg). Anaesthesia mair during surgery. Intramuscular in metoclopramide and 2.5mg dro surgery. Post-surgery, celocoxi patients with severe pain, and i Continuous FNB with ultrasound stimulator. After surgery, 0.2% ropivacaine (20ml) injected through catheter. Then an analgesia pump was attached delivering 0.2% ropivacaine 8ml/hr.	mg/kg) and trained with operidol 30 r b and pare .v. morphin Epidural F ropivacair	cisatracurium sevoflurane n 10mg minutes before coxib 40mg for e if needed. PCA 0.2% ne was injected at 5 ml/hr in a 2ml	6 and 12 months 2; 4 lost to follow up at 12 months Unclear risk of bias: limited reporting of randomisation methods No differences were observed between groups at 6 or 12 months for any HSS domain including pain. No nerve injuries
Peng et al. 2014[40] China Before 2014 1 centre (2 surgical teams with 4 surgeons and 2 anaesthesiologists)	Primary unilateral TKR 140;140 Mean: 66.8 (SD 9.4); 68.0 (SD 11.2) 73%; 65%	General intravenous and inhala midazolam 0.1-0.15mg/kg (eto patients >65 years), propofol 2. 0.3-1.0µg/kg, and vecuronium of anaesthesia. Maintenance w sevoflurane and continuous int remifentanil 7-8µg/kg/hr and pr wound closure, 5-10µg intraver dose of PCA injected. i.v. inject FNB with ultrasound guidance. Initial dose of 10ml 2% lidocaine and 10ml 1% ropivacaine. 30 minutes before end of operation, catheter connected to PCA pump; patients received loading dose of 5ml of 0.15% ropivacaine followed by infusion of 0.15% ropivacaine at 5ml/hr, with bolus of 5mL	midate 0.15 0-2.5mg/kg 0.08-0.12m ith inhalatic ravenous in opofol 25-7 nous sufent ion of 4mg i.v. PCA v 800mg, flu 100mg, a dexameth saline to a Loading of followed b	-0.2mg/kg for g, sufentanil citrate g/kg for induction on of 1%-3% fusion of 5µg/kg/min. After anil and loading ondansetron. with tramadol urbiprofen axetil nd a volume of 80ml. lose of 2ml oy an infusion rate with bolus of 2 ml.	6 and 12 months 31; 38 at 12 months Low risk of bias Chronic post-operative pain (NRS 1+) in 38.5% of PCA group at 6 months compared with 25.7% in FNB group (p=0.021). No difference at 12 months (p=0.273). Authors only reported short term adverse events associated with use of PCA.

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		and lock time of 30 min. Preoperatively, a loading dose of 30ml was injected for intraoperative analgesia.			
Wu and Wong 2014[44]Unilateral elective TKR, 98% for osteoarthritis2009-2011 1 centre40; 39 (30; 30 after post randomisation exclusions) Mean 68.8 (SD 6.4); 68.9 (7.5) 73%; 73%		Paracetamol, sustained release diclofenate, opioids (codeine or morphine). Spinal anaesthesia Catheter inserted under nerve stimulation and ultrasound guidance. Standardised bolus of 15 mL 0.5% Intravenous PCA morphine after the operation levobupivacaine. Continuous infusion of 8 to 12 mL/h 0.08% levobupivacaine postoperatively until POD 3 Intravenous of a state of the operatively until POD 3		6 months 2; 2 not pre- and peri-operative exclusions Low risk of bias No separate pain outcome but improvement of KSS from pre- operative was FNB 48.73 and PCA 44.7 (p=0.513) Including patients not followed up. Deaths: 0; 0. Infection: 1;1. DVT: 2 3. Shock: 3;2. Transfusion: 2;3. Als from excluded cases. Atrial fibrillation and confusion: 0; 1. PE: 0; 1. Sepsis: 1;0. ICU admission fo	
FNB and SNB cor	ntinuous vs epidural PC	A		1	
Anastase et al. 2014[118] Germany 2010-2011 1 centre	Primary unilateral TKR 55; 50 Mean 68.2 (SD 9.2); 69.7 (SD 8.7) 65%; 69%	Premedication with 10 mg ora anaesthesia with light sedatio Supplemental postoperative a piritramid After spinal anaesthesia installed, SNB and FNB catheters inserted with ultrasound guidance. 5 ml bolus 0.2% ropivacaine. FNB with an hourly rate of 5 ml, bolus administration of 5 ml by the patient and the lock-out interval of 20 mins. SNB 5 ml/h to a maximum of 8 ml/h, 5 ml bolus administered by the patient	n: 12.5mg 0.5% bupivacaine.	6 and 12 months 15; 14 High risk of bias due to large loss to follow up Pain during previous 4 weeks: 1 no pain, 2 very little, 3 little, 4 moderate, 5 loud, 6 very loud (translation from German). No difference at 6 months p=0.37. At 12 months, FNB/SNB median 2.00 (1.00, 2.00), PCA 2.00 (2.00, 2.00) p=0.004 favouring FNB/SNB. No falls associated with quadriceps weakness. 6 and 12 month adverse events not reported.	

		and lock-out interval of 20 minutes.		
FNB single vs LIA				•
Fan et al. 2016[36] China 2012-2014 Single hospital, 2 surgeons	Primary unilateral TKR (75% osteoarthritis; 25% rheumatoid arthritis) 80; 80 (78; 79 in analysis) Mean 68.4 (SD 8.8); 67.6 (6.3) 79%; 86%	General anaesthesia in all but surgery, i.v. morphine, PCA at FNB performed pre- operatively with 20ml ropivacaine 0.5%. After cementing prostheses, 50ml of saline injected into periarticular soft tissue.		1 year 3 protocol violations Low risk of bias No separate pain outcome. Mean KSS at 1 year similar between groups: 94.2 (SD 2.6); LIA 93.9 (3.1). p=0.51 Infection: 0; 0. DVT: 1; 1. Femoral nerve injury: 1; 0.
FNB single and epic Reinhardt et al. 2014[41] USA 2010-2012 Single hospital, 2 surgeons	Elective unilateral TKR for osteoarthritis 51; 51 (49; 45 received allocated intervention) Mean 67.9 (SD 10.9); 66.6 (10.1) 59.2%; 57.8%	Spinal anaesthetic (2.5ml 0.5% daily. Oral Perocet or Vicodin Dilaudid for severe breakthrou Combined spinal-epidural (500ml hydromorphone 10µg/ml and bupivacaine HCI 0.06%). Single intra-operative FNB injection (30ml 0.25% bupivacaine). Continuous 48-hour epidural infusion (4ml/hr with 4ml per demand dose, locked out every 10 minutes with an hourly limit of 20ml). Epidural infusion weaned to 2ml/hr on POD1 and to 0 ml/hr at 5 p.m. on POD1. Demand dose with	as required. Subcutaneous igh pain. Intravenous Toradol. Intra-articular knee catheter placed intraoperatively with continuous 0.2% ropivacaine infusion at 7 ml/hr until POD2. Placebo epidural catheter, no FNB, and postoperative placebo continuous epidural infusion of saline.	1 year 0: 0 of patients who received allocated intervention Low risk of bias VAS pain at 1 year similar betwee groups (noted in text and shown graphically) No wound-related complications of infections. 1 DVT and 1 DVT plus PE in epidural group. Arthrofibrosi 2; 1

LIA with corticostere	bid vs LIA with no ca	lockout parameters continued for 48 hours. Placebo intraarticular knee catheter placed intra- operatively with continuous saline 7ml/hr infusion until POD2. orticosteroid		
Seah et al. 2011[48] Singapore 2004-2005 1 hospital	50; 50 Mean 65.4; 67.9 Sex not stated	General or spinal anaesthesia. and PCA (with morphine bolus of minutes, and maximum dose 8 Intraoperative periarticular injection of 0.5ml/kg 1:200,000 epinephrine and 0.5% bupivacaine diluted with 30ml of normal saline. 40mg of corticosteroid (triamcinolone acetonide) was added to half the mixture. The solution with the corticosteroid was injected into the deep tissues. The remaining solution was injected into the skin incision before closure.	of 1mg, lock-out time 5	6 months and 2 years No losses to follow up reported Low risk of bias No separate pain outcome but no statistically significant difference in OKS between groups at 2 years Deep infection: 1; 1
Yue et al. 2013[119] China 2011-2012 1 hospital	for osteoarthritis 36; 36 Mean 70.2 (SD 6.4); 69.3 (5.7) 89%; 89%	General anaesthesia. PCA (25 bolus, 6 minutes lock-out, and 5 hours after surgery. 5-10mg intr rescue. Celecoxib pre- and pos Injections with local anaesthetic agent and adrenaline (0.75% ropivacaine 30ml, 1:1000 adrenaline 0.5ml, and isotonic sodium chloride solution 70ml) plus corticosteroid (1ml betamethasone).	img/hr maximum) for 72	6 and 12 months No loss to follow up reported Unclear risk of bias. No separate pain outcome. No difference in mean KSS between groups at 6 or 12 months No incision infection or tendon rupture complications

		Another 50ml syring without corticosteroi infiltrated into the sk	d was withou	er 50ml syringes fluid t corticosteroid was ted into the skin	
LIA including ketoro Spreng et al. 2012[120], Spreng et al. 2010[121] Norway 2007–2009 1 hospital	Unilateral, non- cemented TKR with no patella resurfacing 34; 34; 34 66.5 (SD 11.); 67.2 (SD 8.9); 65.8 (SD 10.1) 61%;61%;67%	anaesthesia with 13-15mg bupivacaine 5mg/ml with 20µg fentanyl. If indicated, up to 10ml/hr 10mg/ml propofol for sedation. Acetaminophen 1g every 6 hours. i.v. PCA morphine for 48 hours after surgery (2mg bolus with 10 minutes lockout time). When PCA stopped, 10mg slow release oxycodone twice daily. 5mg oxycodone as rescue analgesia. i.v. injection of ketorolac 1ml (30mg/ml) and Infiltration with immediately			12 months 13 did not provide complete data Unclear risk of bias due to limited reporting (long-term outcome only reported as conference abstract). Perioperative analgesic treatment did not have any significant influence on any KOOS outcomes. Infection: 0; 0; 1. No long-term advers
		(30mg/ml) and morphine 5ml (1mg/ml). Infiltration with ropivacaine 150mg, epinephrine 0.5mg, ketorolac 30mg and morphine 5mg in 150ml saline. After closure, catheter placed into knee joint and 10ml infiltrate injected. 22-24 hours after surgery, 20ml injection through catheter of ropivacaine 19ml (7.5mg/ml) and ketorolac 1ml (30mg/ml). i.v. injection of	Infiltration with ropivacaine 150mg, epinephrine 0.5mg, ketorolac 30mg and morphine 5mg in 150ml saline. After closure, catheter placed into knee joint and 10 ml infiltrate injected. 22-24 hours after surgery, 20ml injection through catheter of ropivacaine 19ml (7.5mg/ml) and saline 1ml. i.v. injection of saline 1ml. Sham epidural catheter.	before spinal anaesthesia. When spinal anaesthesia started to wear off, epidural infusion for 48 hrs with 6-10 ml/hr fentanyl 2ug/ml	events reported

Spinal with added	Ligh doso morphing	ketorolac 1ml (30mg/ml). Sham epidural catheter.	with added low dos	o morphino sulpha	te vs spinal with no morphine
sulphate	i nign dose niorphine	sulphale vs spillar		e morphine sulpha	ite və əhindi witir no morphine
Foadi et al. 2017[122] Germany Before 2017 1 centre	Unilateral TKR or THR for osteoarthritis 16; 16; 17 Mean 67.63 (SE	Post-operative 1 g r	esia with 0.5% bupiva netamizole (orally or morphine (intravence escue	intravenously)	6 months "only a few dropouts". >70% questionnaire return rate. Unclear risk of bias due to limited reporting of pilot RCT.
	2.45); 67.33 (2.87); 63.71 (3.14) 56%; 44%; 65%	0.2mg morphine sulphate added to spinal anaesthesia	0.1mg morphine sulphate added to spinal anaesthesia	No morphine sulphate added to spinal anaesthesia	No difference in WOMAC pain between groups at 6 months. No adverse events noted
2. Myofascial	trigger point dry nee	dling	10		

Myofascial trigger point dry needling 2.

Author	Indication	Common pain managemer	it 🖉	Follow up
Country Recruitment dates Setting		Group 1 (intervention)	Group C (control)	Losses to follow up intervention; control Risk of bias issues
	Age % female		0	Key results
Mayoral et al. 2013[123] Spain 2007-2008 Single centre	Unilateral TKR for osteoarthritis 20; 20 Mean 71.7 (SD 6.1); 72.9 (7.9) 72.5%	General or spinal anaesthes After anaesthesia and surgery started, dry needling applied 20 times to all myofascial trigger points by a trained and experienced physical therapist.	ia If spinal anaesthesia used, dry needling simulated behind screen	6 months 4; 5 High risk of bias due to large losses to follow up WOMAC pain at 6 months: mean 3.24 (SD 3.03); 3.13 (2.72). Difference not statistically significant No difference between groups in VA pain (p=0.725) or proportion of patients reporting significant VAS pain at 6 months.

		No complications related to the dry needling intervention. Other adverse events not collected.
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3. Tourniquet

Author	Indication	Common blood conservation	on strategies	Follow up Losses to follow up intervention; control Risk of bias issues Key results
Recruitment dates Setting	Number randomised intervention; control Age % female	Group 1 (intervention)	Group C (control)	
Ejaz et al. 2014[54] Denmark 2011-2012 1 centre	Primary unilateral TKR for osteoarthritis 35; 35 (33; 31 received intervention) Mean 68 (SD 8.0); 68 (7.8) 45.5%; 45.2%	Before surgery, oral tranexar (0.5g) 3 hours after surgery a postoperatively. Appropriately sized thigh tourniquet applied. Limb exsanguination by elevation for 2 minutes and cuff inflated to 250mm Hg.	nic acid (1g). Tranexamic acid and 6 and 12 hours Appropriately sized thigh tourniquet applied but not inflated. Served as safety device in case of uncontrollable bleeding.	6 and 12 months 0; 0 of those who received intervention Low risk of bias Statistically significant difference in KOOS pain intensity at 2 months favouring TKR without a tourniquet (p < 0.001). Small difference between groups not statistically significant at 6 and 12 months. Small number of adverse events did not suggest extra risk in the group
Liu et al. 2014[56] Australia Before 2014 1 surgeon	Unilateral TKR for osteoarthritis 10; 10 Mean 67.0; 70.0 30%; 10%	PCA. No CPM Tourniquet inflated to 300 mmHg before skin incision. Tourniquet deflated after wound closure and dressing.	Tourniquet placed but not inflated	with no tourniquet. 6 and 12 months 0; 0 Low risk of bias No separate pain measure. Total OKS not significantly different at 6 and 12 months Blood transfusions: 3; 0.
Mittal et al. 2012[57] Australia 2008-2010	Primary unilateral TKR 31; 34	Autologous blood re-infused Short duration. Tourniquet set at 300mm Hg inflated	if required Long-duration. Tourniquet set at 300mm Hg inflated before	1 year 5; 2

1 centre	Mean 67.5 (SD 8.9); 66.6 (8.4) 81%:74%				Low risk of bias. However, RCT terminated early due to increased need for blood transfusion in short duration tourniquet group.	
	×.					No separate pain outcome. Total OKS (0-48) at 52 weeks higher in long-duration group reflecting better recovery than short duration group but not significantly (p=0.12). Mean difference approximately 5 which is greater than MCID of 4[78]. Transfusions: 10; 2. Patient reported adverse event: 26; 12
Abdel-Salam and	Primary unilateral	Tourniquet pla	ced around thig	gh		1 and 2 years
Eyres 1995[124] UK Date not stated 1 surgeon	TKR of which 91% osteoarthritis 40; 40 Mean 72 (range 65-80); 74 (64- 82) 57.5%; 62.5%	Limb exsangu minutes and to inflated to twic blood pressure	ourniquet e systolic	Tourniquet not	inflated	0; 0 Unclear risk of bias due to limited reporting of methods. No pain measure or PROM Surgeon recorded HSS score at 1 year 90 (78-97); 91 (80-97). Not significantly different at 1 or 2 years. Blood loss similar between groups. Wound infections: 5;0. DVT: 4;0
Şükür et	Primary unilateral			to 125mm Hg al	oove systolic	6 months
al.2016[125]	TKR, in women with osteoarthritis	blood pressure				0;0;0;0
Turkey 2015	30; 30; 30; 30	Knee in 90° flexion and	Knee in 90° flexion and	Knee in full extension	Knee in full extension	High risk of bias. KSS outcome noted
2015 1 surgeon	Mean 67.0 (SD	tourniquet	tourniquet	and	and	in methods but not presented in results.
, surgeon	7.0); 66.9 (8.5); 68.4 (6.9); 68.4 (6.8) 100%	deflated during wound closure	inflated during wound closure	tourniquet deflated during wound closure	tourniquet inflated during wound closure	KSS results not reported at 6 months but no significant differences between groups at 3 months. Surgical and wound complications similar between groups. No infections, fractures or instability requiring revision within 6 months
		Blood transfus	ion if required	•	•	3-22 months, mean 12;13 months

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Zhang et al.2016	Primary TKR for	Tourniquet		No tourni	quet	Not clear
[126]	osteoarthritis					High risk of bias. Variable follow u
China	84; 82					HSS outcome noted in methods b
2014-2015	Not reported					not presented in results.
1 hospital	Not reported					HSS not reported.
	Ŕ					Transfusion rates similar between groups. At mean follow up of 12 -1 months, patients operated on with a tourniquet had a lower rate of D' (2.4%) compared with those with a tourniquet (10.7%).
Zhang et al.	Primary unilateral	Tourniquet inflated t	o 300-337	mm Hg. Tr	anexamic acid not	6 months
2017[58]	cemented TKR for osteoarthritis	generally used	·			0; 0; 0
China		Tourniquet for	Tourniqu		Tourniquet from	Low risk of bias
2008-2011 1 surgeon	50; 50; 50 Mean 70.3 (SD 6.6); 71 (10.2);	entire operation	removed wound cl	losure	first bone osteotomy until wound closure	No separate pain outcome. HSS similar between groups at 6 month (p=0.839).
	68.2 (6.8) 54%; 60%; 50%		10			At 2 weeks DVT: 0; 0; 1. Intramuscular vein thrombosis: 4; 3. Transfusions: 30%; 26%; 10%
Huang et al.	Primary unilateral	Tranexamic acid				6 months
2017[55]	TKR for osteoarthritis	Tourniquet		No tourni	quet	0; 0
China						Low risk of bias
2015 1 centre	50; 50 Mean 66.2 (SD 8.3); 65.1 (6.8)					VAS pain similar between groups months (p=0.728). Mean HSS sco 90.3 (SD 3.2); 91.2 (2.5). P=0.151
	64%; 68%					DVT: 0; 0. PE: 0; 0. Intramuscular venous thrombosis: 6; 4. Superfici infection: 1; 0. Wound secretion: 6 No significant difference in blood I between groups.

4. Compression bandage

Author	Indication	Common treatments	Follow up

Country Recruitment dates Setting	Number randomised intervention; control Age % female	Intervention	Control	Losses to follow up intervention; control Risk of bias issues Key results
Brock et al. 2017[127] UK 2013-2014 1 hospital Blood conser	Primary unilateral TKR for osteoarthritis 25; 25 (24 received intervention) Mean 67.3 (SD 8.2); 69.5 (6.8) 66.7%; 64.0%	Hydrocolloid dressing left in p 10-14 Soft inner layer with compressive outer layer bandage. Removed after 24 hours.	lace until clips removed on day Standard bandaging with soft inner layer and crepe bandage outer layer. Removed after 24 hours and cryocuff used.	6 months 0; 0 of patients receiving intervention Low risk of bias No separate pain outcome. Mean OKS similar between groups at 6 months: 35.8 (SD 7.7); 34.3 (10.6). P=0.58 No infections or thromboembolic events in either group
Author	Indication	Common blood conservation	on strategies	Follow up
Country Recruitment dates Setting	Number randomised intervention; control	Intervention	Control	Losses to follow up intervention; control Risk of bias issues
	Age % female		06	Key results
Tranexamic acid	1			
Sa-Ngasoongsong et al. 2011[64] Thailand 2008-2009 1 hospital	Primary knee osteoarthritis with unilateral primary cemented computer assisted TKR 24; 24 69.0 (SD 8.2); 69.2 (7.6) 91.7%; 75%	Drain and compressive dress 25ml saline solution containing 250mg tranexamic acid injected into knee joint after fascial closure	ing 25ml saline solution injected into knee joint after fascial closure	6 months 0; 0 Low risk of bias No separate pain score reported but WOMAC overall score mean 18.6 (SD 7.6); 20.8 (6.4). P=0.282 Lower peri-operative blood loss in tranexamic acid group and need for blood transfusion, 1/24 compared with 8/24 in control group. No DVT,

						wound complications or infection reported in either group	
Kim et al. 2014[61] Korea 2009-2011	Primary unilateral TKR for osteoarthritis	Tourniquet, drain, cor transfusion and intrav required				1 year 0; 0 Low risk of bias	
1 hospital	90; 90 Mean 73.5 (SD 5.5); 71.9 (SD	10 mg/kg body weigh tranexamic acid in 10 normal saline given a intravenous injection	0 mL of s slow	No tranex placebo	amic acid and no	WOMAC pain mean 3.2 (2.6); 2. (2.3). Difference not statistically significant	
	5.9) 88%; 87%	before tourniquet defl and the same amoun hours later.	ation,			Lower blood loss and need for allogenic transfusion in tranexan acid group. No DVT. 1 PE in cor group.	
Sa-Ngasoongsong	Primary unilateral	Drain and compressiv	/e dressir	ng		1 year	
et al. 2013[65] Thailand 2010-2011 1 hospital	cemented TKR for osteoarthritis 45; 45; 45 Mean 68.1 (SD 6.2); 67.6 (8.7); 66.2 (7.3) 88.9%; 93.3%; 95.6%	25ml saline solution containing 500mg tranexamic acid injected into knee joint after fascial closure via drain tube.	tranexar injected joint afte	ng 250mg	25ml saline solution injected into knee joint after fascial closure	0; 0; 0 Low risk of bias No separate pain outcome but WOMAC mean 14.5 (7.1); 15.1 (15.5 (6.6). P=0.42 Total blood and Hb loss lower in intervention groups than control. Fewer transfusions in 500mg (0) 250mg tranexamic acid group (6) control group (10). 2 DVT in 500r group. 1 DVT in 250mg group. 1 and 3 DVT in control group. No infections.	
Hourlier et al. 2015[60]	Primary unilateral TKR for	Tourniquet, electrocautery, routine haemostasis, superficial drain. No blood salvage system.			6 months 0; 0		
France 2009-2010 1 hospital	osteoarthritis 52; 54 74 (SD 6); 72 (7) 62%; 63%	10 mg/kg intra-operative tranexamic infusion. After 2 hours, continuous infusion of tranexamic acid 2 mg/kg/hr for 20 hours via electricsingle bo tranexami intraoper 2 hours, continuous		tranexami intraopera 2 hours, p	us of 30 mg/kg c acid as an tive infusion. After lacebo saline s infusion via ringe	Low risk of bias. No separate pain score but KSS clinical score mean 90 (SD 6); 9 (13). P=0.90 No difference between groups ir blood loss. 1 MUA in single treat	

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			group. No deep infections or revisions.
Primary unilateral TKR for osteoarthritis 50; 50 Mean 66.2 (SD 8.3); 65.8 (6.3) 64%; 70%			6 months 0; 0 Low risk of bias VAS pain similar between groups at a months (p=0.728). Mean HSS score (0-100) better in tranexamic acid group than controls: 90.3 (SD 3.2); 88.9 (3.0). P<0.001. Mean difference 1.4 lower than MCID of 8.29[81] Greater blood loss in control group than tranexamic group (p<0.001). DVT: 0; 0. PE: 0; 0. Intramuscular venous thrombosis: 6; 3. Superficial infection: 1; 3. Wound secretion: 6; 9
on l			, , , , , , , , , , , , , , , , , , , ,
Primary unilateral TKR for osteoarthritis 40; 40 Mean 64.6 (SD 10.2); 64.5 (7.3) 82.5%; 67.5%	Tourniquet, drain, Esmarch ba 20,000 IU thrombin infusion (1,000 IU/mL) through fascial defect	ndage, electrocautery Closure and drain placement protocol without the thrombin infusion.	1 year (6 months and 2 years also reported) 0; 0 Low risk of bias No separate pain outcome. KSS mean 95.5; 96.0. p=0.45 Lower drop in Hb in thrombin group. Blood transfusion in 4 intervention and 7 control patients. 1 control patient had haematoma. No hospital readmissions
sion			·
Primary unilateral TKR of which 89% for osteoarthritis 90; 90	No drains or tranexamic acid Flexion. Operated knee kept in passive flexion (120°) post-operatively for 6 hours using a jig. Wound redressed and placed in flexion over a	Extension. Operated knee kept in full passive extension	1 year 5; 1 (12 did not attend follow up) Low risk of bias. No separate pain outcome. OKS mean 20.5 (SD9.0); 22.1 (9.7). P=0.27
	TKR for osteoarthritis50; 50Mean 66.2 (SD 8.3); 65.8 (6.3)64%; 70%64%; 70%Primary unilateral TKR for osteoarthritis40; 40Mean 64.6 (SD 10.2); 64.5 (7.3) 82.5%; 67.5%sionPrimary unilateral TKR of which 89% for osteoarthritis	TKR for osteoarthritis 50; 50and deflated after wound closu Intravenous tranexamic acid 20mg/kg before incision and tranexamic acid 10mg/kg at 3, 6, 12 and 24 hours. 1g tranexamic acid in 50ml saline irrigated into wound during operationmTourniquet, drain, Esmarch ba 20,000 IU thrombin infusion (1,000 IU/mL) through fascial defectprimary unilateral TKR for osteoarthritis 40; 40Tourniquet, drain, Esmarch ba 20,000 IU thrombin infusion (1,000 IU/mL) through fascial defectsionNo drains or tranexamic acid Flexion. Operated knee kept in passive flexion (120°) post-operatively for 6 hours	TKR for osteoarthritis and deflated after wound closure 50; 50 Intravenous tranexamic acid 20mg/kg before incision and tranexamic acid 10mg/kg at 3, 6, 12 and 24 hours. 1g tranexamic acid in 50ml saline irrigated into wound during operation No treatment with tranexamic acid 01 Primary unilateral TKR for osteoarthritis 40; 40 Tourniquet, drain, Esmarch bandage, electrocautery 20,000 IU thrombin infusion (1,000 IU/mL) through fascial defect Closure and drain placement protocol without the thrombin infusion. sion Primary unilateral TKR of which 8% for osteoarthritis No drains or tranexamic acid Fiexion. Operated knee kept in passive flexion (120°) post-operatively for 6 hours Extension. Operated knee kept in full passive extension

Country	Number	Group 1 (intervention)	Group C (control)	Losses to follow up intervention;
Author	Indication	Common blood conservati	on strategies	Follow up
. Platelet ricl	h plasma		On On	groups.
		10/16	Vio.	7% of auto-transfusion group requir allogenic transfusion compared with 28% in control group. Fewer infections, readmissions and GP visits in auto-transfusion group. No significant differences in other serio adverse events or mortality betweer
1 hospital	70.0 (40-88) 62%; 53%	before re-infusion using a centrifugal cell washing machine		No separate pain outcome. No significant difference in EQ-5D between groups.
UK Not stated	Mean 69.3 (range 32-95);	drainage if volume >125ml post-operative. Blood washed and re-suspended		Unclear risk of bias due to limited details of methods and follow up.
2001[128]	115; 116	Auto-transfusion of wound	Wound drainage discarded	Losses to follow up not reported
Thomas et al.	Unilateral TKR	Allogenic transfusion if Hb fe	ll below 9g/dl	6 months
Auto-transfusion	of washed blood			weakness in extension group. More transfusions in extension group (p=0.002)
	74%; 64%	morning.		infection and 1 extensor muscle
	Mean 70.4 (SD 9.9) 71.0 (7.6)	single pillow until POD1 morning.		1 MI and 1 DVT in each group. 1 haematoma in flexion group. 1 deep

Platelet rich plasma 6.

Author	Indication	Common blood conservation strategies		Follow up
Country Recruitment dates Setting	Number randomised intervention; control Age % female	Group 1 (intervention)	Group C (control)	Losses to follow up intervention; control Risk of bias issues Key results
Aggarwal et al. 2014[129]	Primary unilateral surgery or first surgery of staged	Tourniquet. No tranexamic acid or suction drain. Blood transfusion if necessary due to intraoperative blood loss or postoperative haemoglobin <8g/dl.		6 months No losses to follow up reported

patients had excellent or good

No adverse events reported in

either group during functional

of controls (p=0.032).

training

knee function compared with 69%

India 2010-2011 1 surgeon	bilateral TKR for osteoarthritis 7; 14 Mean 56.43 (SD 7.59); 53.79 (9.75) Sex not stated	8 ml PRP, prepared from patient's blood. Calcium chloride for activation given in a separate syringe in 4:1 ratio. PRP and calcium chloride injected into the posterior recess, gutters and capsule, and repaired extensor mechanism and prepatellar fat.		High risk of bias due to unexplained differences in numbers of patients in randomised groups. No separate pain outcome. WOMAC total at 6 months PRP mean 7.14 (SE 0.69), controls 7.86 (1.23), p=0.173 PRP group had lower fall in haemoglobin and need for blood transfusion
7. Cryotherapy Author	Indication	Common treatment		Follow up
Country Recruitment dates Setting	Number randomised intervention; control	Group 1 (intervention)	Group 1 (intervention)	Losses to follow up intervention; control Risk of bias issues Key results
	Age			Neyreauta
	% female			
Wang 2017[130]	% female Unilateral TKR for osteoarthritis	CPM for 2 weeks		6 months

8. Denusomab

Author	Indication	Common treatment		Follow up
Country Recruitment dates Setting Number randomised intervention; control Age % female	Group 1 (intervention)	Group 1 (intervention)	Losses to follow up intervention; control Risk of bias issues Key results	
Ledin et al. 2017[66] Sweden 2012-2014 2 centres	Elective cemented primary unilateral TKR for osteoarthritis 25; 25 Mean 66 (SD 6.3); 64 (5.5) 60%; 60%	Injection of 60mg denusomab 1 day after surgery and after 6 months	Injection of placebo 1 day after surgery and after 6 months	 12, 24 months 0; 2 Low risk of bias No significant differences in KOOS pain or other KOOS domains between groups 12 12 or 24 months No suspected unexpected adverse reactions in either group
). Continuous p Author	bassive motion	Common treatment	10	Follow up

9. Continuous passive motion

Author	Indication	Common treatment		C	1	Follow up	
Country Recruitment dates Setting	Number randomised intervention; control Age % female	Group 1 (intervention)	Group 2 (intervent	ion)	Group C (control)	Losses to follow up intervention; control Risk of bias issues Key results	
Leach et al. 2006[131] UK Before 2005 1 hospital	Unilateral cruciate retaining rotating platform TKR for osteoarthritis 85 overall Mean 71.2 (range 53-84); 72.9 (52- 89)	Physiotherapy protoc exercises to improve exercises. CPM commenced on postoperative day set range 0–30 and used hour twice per day. E	ROM and q first t at a for 1			6 and 12 months 25 patients lost to follow up High risk of bias due to large loss to follow up and use of date of birth randomisation No difference in mean VAS pain at 1 year, CPM 0.6; control 0.9. p=0.49	

	50%; 54%	range was increased by 10° with discharge at POD 5-7.			Adverse events not reported
Sahin et al. 2006[132] Turkey Before 2006 1 hospital	Primary unilateral TKR for osteoarthritis 15; 16 Mean 61 (SD 6.0); 61.6 (7.5) 86%; 86%	Standard physiotherapy From POD 1, CPM 2.5 hours 2x/day. Initially 0-40° flexion and increased by 10° each day until POD 7	No CPM		6 months 3 lost to follow up Unclear risk of bias as patients were followed up by treating physician. Mean difference in VAS pain 0.1/10 slightly favouring no CPM group (95% CI -0.8, 0.9; P=0.87) Adverse events not known
Pope et al. 1997[133] Australia 1988-1999 1 hospital	Primary unilateral or bilateral TKR of which 86% for osteoarthritis 62 (70 knees). Authors excluded those not followed up so groups were 18; 20; 19 Mean 72.5 (95% CI 64.4, 74.98); 72.7 (70.4, 75.0); 69.4 (64.4, 74.98) 64.7%; 50%; 72.2%	Physiotherapy commenced on p Patients had an initial CPM range of 0-40° increased by 10° twice, on day after surgery and day 2, so that 0-60° flexion achieved before removal of machine at 48 hours	ad an <i>I</i> range of eased by on day ery and that 0-90° hieved noval of	e day 1 Knee placed in an extension splint in the recovery room	 6 and 12 months 8 patients (12 knees) excluding 1 death High risk of bias due to losses to follow up and limited reporting of methods No separate pain outcome. However, "pain disability" contributed up to 50 points out of a total of 70-point functional score (70 best outcome). No difference between groups in functional score: CPM 0-40 median 56 (range 20, 70); CPM 0-70 52 (10, 70); no CPM 52 (25, 70). p=0.80 CPM groups had greater blood loss than controls, p=0.008). 1 manipulation under anaesthesia in no CPM group, 2 revisions due to patellar dislocation in the 0-40 CPM group, 1 PE death in the 0-70 CPM group.
Beaupré etal. 2001[134]	Primary unilateral TKR of which	Standardised exercise during ho a slider board session.	spital admi	ssion which included	6 months

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Canada 1997-1998 1 hospital	92% for osteoarthritis 40; 40; 40 Mean 68 (SD 9); 68 (9); 69 (8) 52.5%; 50%; 30%	3 sessions (2 hours) with CPM machine per day from POD2. Range increased from starting range 0-30 degrees as tolerated.		a addition the sed Active on and in sitting positions d ently as	No intervention further than standardised exercise.	6; 8; 6 Unclear risk of bias due to losse to follow up Mean WOMAC pain at 6 months 76 (15); 85 (15); 79 (16). No difference over time between groups, p=0.62. Long-term adverse events. Need for MUA: 1; 1; 0. DVT: 0; 1; 0. Cellulitis: 0; 0; 1. Infection 0; 0; 1
Kumar et al. 1996[135] USA Before 1996 1 hospital	Primary unilateral TKR for osteoarthritis 40 (46 knees); 33 (37) Mean 69 (range 52-86); 68 (42-88) 58%; 67%	Standard physiothera CPM from POD 0. In hours/ day 0-90° unti discharge	itially 10	movemen to 90° 2x/	Passive range of t ("drop and dangle") day initially for 20 ater 30-45 minutes.	6 months 15; 13 lost to follow up High risk of bias due to large losses to follow up No separate pain outcome. KSS CPM 82.7; Drop and dangle 80. p=0.78 Haematoma 3;1. Closed manipulation 1;3. DVT 0;0. PE 0
Worland et al. 1998[136] USA 1996 1 hospital	Unilateral or bilateral TKR for osteoarthritis. 91 patients (114 knees randomised). After post- randomisation exclusions: 37 (49 knees); 43 (54 knees) Mean 70.2 (range 44-84) 66.25%	CPM and physiother At home after discha machine 3 hours per replaced knee for 10	rge, CPM day on	Physical t	nission herapist home visit 1 e times per week for	6 months 11 patients (11 knees) Unclear risk of bias due to post- operative exclusions not reporter separately for groups and limiter reporting of methods. No separate pain outcome. At 6 months, mean HSS score CPM 95.3 (SD 2.8); physiotherapy 95 (3.0). P=0.49. Adverse events not reported.

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MacDonald et al. 2000[137]	Primary unilateral TKR for	Active ROM, passive using walker or crutc	ROM exercises, mobi hes.	lised as tolerated	6 and 12 months Not reported
Canada Before 2000 1 hospital	osteoarthritis 40; 40; 40 Age and sex not reported	CPM commenced POD 0. Initially 0- 50 degrees. Provided for 18-24 hour/ day. Increased by 10 degrees/ hour as tolerated. Continued until POD 1	CPM commenced POD 0. Initially 70- 110 degrees. Provided for 18-24 hr/ day. Not increased. Continued until POD 1	No CPM	Unclear risk of bias due to limited and selective reporting. No separate pain outcome. No statistical differences between groups for KSS at 6 and 12 months. Adverse events not reported
Bennett et al. 2005[67] Australia 1997-2000 1 hospital	Primary unilateral TKR for osteoarthritis 47; 48; 52 70.7; 71.4; 71.7 72.3%; 64.6%; 67.3%	Standard in hospital Standard CPM from 0° to 40° for 2x3 hours on POD 1 increased by 10° per day until POD 6. Extension splint applied overnight	physiotherapy program Early flexion CPM commenced in recovery room from 90° to 50° knee flexion. Increased gradually to CPM 90° to 0° for 2x3 hours in day 4-6.	ime No CPM	12 months1 patient excluded due to inabilityto achieve 90° flexionLow risk of biasNo separate pain outcome. Nosignificant difference in KSSbetween groups at 1 year.No difference in wound healingbetween groups
Ersözlü et al. 2009[68] Turkey 2003-2004	Primary unilateral TKR for osteoarthritis 30; 30; 30 Mean 65 (range 54-73); 61 (49- 80); 62 (52-78) 66%; 55%; 57%	Conventional physica CPM set at 30-40° from POD1. Increased as tolerated to POD7. 1 hour CPM 3x/day.	al therapy CPM set at 60-70° from POD3. Increased by 10°/ day to POD7. 1 hour CPM 3x/day.	No CPM	2 years 1; 1; 2 Low risk of bias No separate pain outcome. KSS scores 98; 95; 92. No significant difference between groups p=0.67. Infection 0; 0; 1. Arrhythmia 0; 1; 0. No difference in complications between groups

10. Electrical stimulation

Author	Indication	Common rehabilitation strategies	
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Country Recruitment dates Setting	Number randomised intervention; control Age	Intervention	Intervention	Common rehabilitation strategies
	% female			
Avramidis et al. 2011[69] Greece 2005-2006 1 hospital	Elective primary unilateral TKR for osteoarthritis 38; 38 Mean 70.54 (SD 4.68); 70.66 (3.73) 80%; 82.9%	Standard physiotherapy for 6 we Transcutaneous electric muscle stimulation of the vastus medialis muscle from POD2 2x/ day for 2 hours for 6 weeks.	No intervention	1 year 3 (intervention intolerance); 3 Low risk of bias Improved SF-36 bodily pain at 1 year in intervention group compared with control, mean 92 (SD 10.57); 79.48 (12.72). P<0.001. Difference of 12.52 close to MCID of 16.86[82]. No difference in OKS or American KSS Adverse events not reported
Stevens-Lapsley et al. 2012[138] USA 2006-2010 1 hospital	Primary unilateral TKR for osteoarthritis 35; 31 Mean 66.2 (SD 9.1); 64.8 (7.7) 57.1%; 51.6%	Standard inpatient rehabilitation therapy Neuromuscular electrical stimulation commenced on POD2 for 6 weeks 2x/ day.	home and outpatient physical No intervention	6 months and 1 year 5; 6 Unclear risk of bias due to baseline differences in WOMAC No difference in resting pain (points) at 1 year intervention mean 0.6 (SD 1.4); control 0.4 (1.5). Also similar at 6 months. Mean WOMAC total score bette at 1 year in intervention group compared with control, 5.7 (5.9) 10.0 (12.2) and at 6 months. However, probably explained by baseline differences. Authors state no differences for change WOMAC. DVT 1; 0. Unspecified complication 1; 0. Infection 0; 2. Revision 0; 1

Levine et al.	Elective unilateral	2 sessions of ROM exercise		6 months
2013[139] USA Before 2013 1 surgeon	TKR for osteoarthritis 35; 35 Mean 68.1; 65.1 76%; 62%	Neuromuscular electrical stimulation commenced 14 days pre-operatively until 1 day before surgery. Recommenced at POD1 for 60 days. After hospital discharge no direct contact with a physical therapist	Formal physical therapy programme with progressive resistive exercises and strengthening in hospital and after discharge supervised by physical therapist.	5; 9 Unclear risk of bias due to large uneven losses to follow up KSS pain favoured intervention a 6 months but not significantly 79.08 (SD 10.97); 75.5 (14.77); 95%CI for difference -3.78, 10.93 Similar for WOMAC total score, 95%CI for difference -3.19, 14.81 Confusion 2; 0
Moretti et al.	Primary unilateral	Rehabilitation protocol including	СРМ	6 and 12 months
2012[70] Italy 2008-2010 1 hospital	TKR for osteoarthritis 15; 15 Mean 70.0 (SD 10.6); 70.5 (8.1) Not reported		No intervention	No losses to follow up Low risk of bias Mean VAS pain (10-point scale) lower at 12 months in intervention group compared with control, 0.5 (SD 1.3); 3.6 (3.9). p< 0.05. Mean difference of 2.1 (10-point scale) greater than MCID of 16.1 (100- point scale)[83] Difference also at 6 months. More swelling of the knee in intervention patients than controls, statistically significant at 1 and 2 months
Adravanti et al. 2014[140] Italy 1 hospital	Primary unilateral TKR for osteoarthritis 16; 17 Mean 66 (SD 13); 73 (5) 62.5%; 52.9%	Standard rehabilitation protocol: Pulsed electromagnetic fields (I-ONE therapy) by POD7 for 4 hours/ day for 60 days	active and passive mobilisation No intervention	6 months 4; 3 High risk of bias: small study, proportionately high losses to follow up At 6 months, mean VAS pain in intervention group lower than in controls (p<0.05). At 3 years, 1/1 intervention patients and 4/12 controls reported severe pain

			No difference between groups in swelling at 6 months.
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11. Rehabilitation

Author	Indication	Common rehabilitation stra	ategies	Follow up
Country Recruitment dates Setting	Number randomised intervention; control Age % female	Intervention Control		Losses to follow up intervention; control Risk of bias issues Key results
Walking guidance a	nd training	No		
Li et al. 2017[71] China 2015-2016 1 hospital	Primary unilateral TKR for osteoarthritis 43; 43 Mean 76.33 (SD 5.28); 78.47 (5.50) 55.8%; 51.2%	muscle strength, use of aids methods and precautions. Knee passive flexion and ex muscle strength training com straight leg raising exercises increased joint activities and	ce on joint activities, quadriceps , diet guidance, correct walking tension to 90° and quadriceps menced on POD 1. POD 3-7, 2. 2 weeks after replacement, muscle strength training, centre nb weight training, and walking No additional rehabilitation	6 months 0; 0 Low risk of bias Mean VAS pain at 6 months: 0.51 (SD 0.74); 2.83 (0.88) favouring walking intervention group, p<0.01. Difference of 2.42 (10 point scale) greater than the MCID of 16.1 (100- point scale)[83]. HSS scores at 6 months favoured intervention, p<0.01. No infection, allergic reaction or immune reaction in either group. Intervention not associated with swelling, pain, prosthesis loosening, thrombosis, or delayed wound healing
Aquatic therapy				
Liebs et al. 2012[72] Germany 2003-2004 4 hospitals	Elective primary unilateral TKR for osteoarthritis 87;98	suction drains. Programme of motion activities; exercises for the second s	nce, coordination and gait; and	6, 12 and 24 months 13.8%; 19.4% excluding deaths and unexplained reasons Low risk of bias

	Mean 68.5 (SD 8.6); 70.9 (7.5) 70.1%;73.5%	Aquatic therapy for 30 minutes 3 times a week up to postoperative week 5. Pool exercises aimed at training of proprioception, coordination and strengthening with aid of float cuffs, training kickboards and bar floats.				WOMAC pain at 12 months: early aquatic mean 13.2 (SD 15.0); late aquatic 17.4 (22.4) p=0.22. No difference at 6 and 24 months.	
	A	Aquatic therapy beginn on the 6th postoperativ day with the wound covered with a waterpr adhesive dressing.	/e ex	ercise af	erapy as pool fter the completion nealing on the 14th ive day	5 early aquatic therapy patients and late aquatic therapy patient readmitted to hospital within 3 months. 2 early aquatic patients and 1 late aquatic patient readmission directly or indirectly related to the intervention.	
Rahmann et al. 2009[141] Australia 2003-2005 1 hospital with 2 surgeons	Unilateral primary TKR or THR for osteoarthritis (50% TKR) 18;19;17 (11 had been excluded post- randomisation due to complications in hospital Mean 69.4 (SD 6.5); 69.0 (8.9); 70.4 (9.2) 44.4%; 63.2%; 70.6%	physiotherapy treatmentwith an occlusive, wateFrom day 4, 1 to 1Findividualinphysiotherapy.plAquaticWphysiotherapyplprogramme togrmaximize functionnrand strength. 40spmins/ day. Fastrepace metronomear80-88 bpmpr	individual physiotherapy. Aquatic physiotherapy programme to maximize function and strength. 40 mins/ day. Fast pace metronome individual physiotherapy. Water exercise programme with general exercises not targeted at specific functional retraining in the aquatic		I wounds covered 0 mins/ day. From day 4, 1 to 1 individual ward- based physiotherapy. 40	6 months 4;2;0 for combined THR and TKR Unclear risk of bias as TKR patients more likely to receive ward-based control intervention. THR and TKR analysed together	
Supported early dis	-						
Mahomed et al. 2008[142] Canada 2000-2002 2 centres	Primary unilateral TKR or THR for osteoarthritis (approximately 50% TKR) 119:115	KR or THR for isteoarthritis approximately 0% TKR)Discharged home when able to independently transfer supine to sitting and sitting to standing, walk 30 metres and climb stairs if necessary.T re d d				12 months No losses to follow up Low risk of bias (analysis by actual treatment received showed similar results)	
	68					WOMAC pain at 12 months marginally favoured home-based	

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Hill et al. 2000[143] UK 1997-1998 1 centre	About 67% women Unilateral, primary TKR, irrespective of diagnosis or concomitant disease 70 randomised, with 32;28 eligible for trial at	subsequent management along a multidisciplinary clinical pathway (4-16 visits). Then outpatient physiotherapy or self- directed programme. Care pathway for medical, nurs from admission until day 5 Outreach team domiciliary visit prior to admission with assessment of home environment. At days 5–7, patients assessed to ensure discharge safe. Outreach team visit on day of	sing and physiotherapy care Inpatient care until removal of skin clips and wound healing.	rehabilitation mean 87 (SD 16); 83 SD (20), p=0.08 but this was not statistically significant. Mean difference of 4 less than MCID of 8- 9[77]. Results did not differ between TKR and THR patients. Similar rates of dislocation, DVT and readmissions between groups. 2% inpatient group developed infections compared with 0 in home group 1 year No losses to follow up reported after commencement of intervention Unclear risk of bias due to limited reporting of methods. No pain outcome or patient reported outcome. Control group had better mean KSS scores, but this did not reach statistical significance at 1 yea
	day 5	discharge with further visits as required. 1+ physiotherapist visit linked with nurses to monitor knee performance. Discharge when skin clips removed, wound healed and specialist orthopaedic assistance not required, usually day 10–12	ien on	or earlier. 1;1 serious infection, other wound infections 1;6, painful joints 9;4, othe minor complications similar between groups
Flexion or extension	n during knee closu	re		
Wang et al.	Primary unilateral	No patellar replacement or late	ral retinacular release	6 months
2014[74]	TKR for osteoarthritis	Articular capsule, soft tissue	Wound closure performed in	No losses to follow up
China	40; 40	and skin enclosed in 90° flexion which was maintained	full extension	Low risk of bias
2009-2010 1 centre	Mean 68.34 (SD 7.09), 67.87 (6.47)	for 1-2 min after wound closure.		Mean VAS pain in flexion group 1.13 (SD 0.73); extension group 1.12 (0.68), p=0.64
	17.5%; 22.5%			

	No wound complications, patella fracture or infection requiring surgery in either group
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Wound management 12.

Author	Indication	Common wound manageme	nt strategies	Follow up
Country Recruitment dates Setting	Number randomised intervention; control Age % female	Intervention	Control	Losses to follow up intervention; control Risk of bias issues Key results
Kong et al. 2014[75] South Korea 2011 1 surgeon	Primary cemented unilateral TKR for osteoarthritis 50; 50 Mean 69.0 (SD 7.7); 68.0 (4.8) 89.6%; 87.5%	Skin staples removed on day applied for 5 days After removal of wound closure strip, patients managed operation scars with application of silicone gel for 1 month after stitches removed	10 and wound closure strip After removal of wound closure strip, patients managed operation scars with application of petroleum gel for 1 month after stitches removed	6 and 12 months 2; 2 lost to follow up Low risk of bias At 12 months, VAS pain in silicone gel group mean 2.50 (SD 1.16); control 2.92 (1.90). P=0.201. No difference at 6 months, p=0.886. No wound dehiscence or infection associated with application of silicone gel or petroleum
3. Anabolic ster	oids Indication	Common rehabilitation strat	regies	Follow up
Country	Number	Intervention	Control	Laccas to follow up intervention

13. Anabolic steroids

Author	Indication	Common rehabilitation strat	egies	Follow up
Country Recruitment dates Setting	Number randomised intervention; control Age % female	Intervention	Control	Losses to follow up intervention; control Risk of bias issues Key results
		Cold compression and CPM	·	6, 9 and 12 months

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2010[76] Australia Before 2010 1 surgeon	TKR for osteoarthritis 5; 5 Mean 66.2 (range 58, 72); 65.2 (59, 72) 20%; 40%	injection of 50 mg Nandrolone decanoate solution. Patients visited every 2 weeks and injections continued for 6 months.	injection of saline. Patients visited every 2 weeks and injections continued for 6 months.	Low risk of bias (but small feasibility study) No separate pain outcome. KSS at 12 months in intervention group mean 91.4 (SD 3.5); control 81.2 (SD 7.1). p=0.03. Difference also at 6 months (p=0.04), marginal at 9 months (p=0.06). Difference in means at 12 months of 10.2 close to MCID of 12.3[79]. Intervention group had smaller
		D _R		decrease in bone mineral density at 6 months than controls but not significant

14. **Guided imagery**

Author	Indication	Common rehabilitation strat	egies	Follow up	
Country Recruitment dates Setting	Number randomised intervention; control Age % female	Intervention	Control	Losses to follow up intervention; control Risk of bias issues Key results	
Jacobson et al. 2016[144] USA 2011-2012 1 surgeon	Primary unilateral TKR for osteoarthritis 42; 40 (41; 39 received treatment) Mean 65.0 SD 8.6) 62.2%	Participants listened to a 19- 21-minute CD each day for 2 weeks before and 3 weeks after surgery. Content covered concerns and hopes about TKR with aim to facilitate mind–body connections to promote optimal TKR outcomes.	Participants listened to a 17- 21-minute CD each day for 2 weeks before and 3 weeks after surgery. Content comprised poetry, short stories and essays	6 months 12; 10 of patients receiving treatments High risk of bias due to large losses to follow up Mean WOMAC pain 2.7 (SD 3.1); 3.5 (SD 3.3). P<0.001 Adverse events not reported	

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CD compact disc; CPM Continuous passive motion; DN4 Douleur Neuropathique 4; FNB Femoral nerve block; HSS Hospital for Special Surgery; i.v. intravenous; KOOS Knee injury and Osteoarthritis Outcome Score; KSS Knee Society Score; LIA local infiltration analgesia; NRS Numerical rating scale; OKS Oxford Knee Score; ONB obturator nerve block; PCA Patient controlled analgesia; PNB psoas nerve block; SF-36 Short Form 36 Health Survey; S-LANSS Leeds assessment of Neuropathic Symptoms and Signs Pain Scale; SNB Sciatic nerve block; TKR Total knee replacement; VAS Visual analogue scale; VTE Venous thromboembolism; WOMAC Western Ontario and McMaster Universities Osteoarthritis Index.

ITT, ITT CC, POD, MI, PE

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Supplementary material. Risk of bias assessment

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blind outcome assessment	Incomplete outcome data	Selective reporting	Other bias	Summary
Pain manageme	ent			·				
Albrecht et al. 2014[34]	Computer generated	Anaesthetist blind to allocation	Physiotherapists, surgeons, research assistants collecting data, and members of the Acute Pain Service were kept blinded to group allocation.	Physiotherapists, surgeons, research assistants collecting data, and members of the Acute Pain Service were kept blinded to group allocation.	ITT analysis low losses to follow up	No but not checked protocol	Study was terminated early with 61% of planned recruitment completed due to change in standard anaesthesia at hospital	Low
Anastase et al. 2014[118]	Method of the Ulm Institute of Statistics	Method of the Ulm Institute of Statistics	No	No	15:14 lost to follow up	No but not checked protocol	ASA comorbidities differed between groups	High
Aveline et al. 2014[52]	Computer generated	opaque sealed envelopes	Blinded syringes prepared by nurse not involved in study	Yes	Low losses to follow up	Consistent with short term follow up paper	No	Low
Bergeron et al. 2009[110]	Blocks of different sizes according to list preprepared by study epidemiologist	Not described	Anaesthetist not blind. Patients blind	Nurse observers collecting data blind to allocation	32/59 lost to follow up	No but not checked protocol	No	High
Buvanendran et al. 2010[53]	computer generated	Yes, physicians and nurses blind	Yes	Yes	ITT	Protocol not checked	No	Low

Choy et al. 2011[35]	Computer generated	sealed envelope	No, the catheter was removed at either day 3 or 7	Patient reported outcome. Other outcomes by blinded independent physician	Low losses to follow up	Protocol not checked but reasonable range of outcomes	No	Low
Davidson et al. 2016[116]	Computer generated	Sealed opaque envelopes	Subjects and investigators were not masked to treatment group	Subjects and investigators were not masked to treatment group. PROM	31; 29 lost to follow up	None apparent but protocol not checked	Combined data from 2 RCTs	High
Fan et al. 2016[36]	No details	sealed opaque envelopes	Patients and assessors blind to randomisation	Patients and assessors blind to randomisation	2% protocol violation	No but not checked protocol	No	Low
Foadi et al. 2017[122]	Computer generated	Not described	Not described	Patient reported outcome	>70% questionnaire return	None apparent but protocol not checked	Described as pilot study	Unclea
Gao et al. 2017[37]	Random number table	Not described	Blind to patients	Blind to observers	2; 1; 0	None apparent but protocol not checked	Groups similar at baseline	Low
llfeld et al. 2009[113]	Computer generated	Investigators, patients, and all clinical staff were unaware of treatment group assignments	Investigators, patients, and all clinical staff were unaware of treatment group assignments	Investigators, patients, and all clinical staff were unaware of treatment group assignments	4:1 lost to follow up	No but not checked protocol	Basal infusion halved on POD1 in 10 intervention patients compared with 3 controls	High
llfeld et al. 2011[114]	Computer generated tables	Solutions prepared by investigational pharmacist	Yes. Intervention and control solutions indistinguishable	Patient reported outcomes. Staff masked to treatment group	11;12 did not have 4 measures out	Protocol not checked	WOMAC and WOMAC domain scores	High

				assignment performed all measures and assessments	of 6 up to 12 months	but seems reasonable	somewhat lower pre- intervention in extended infusion group. Authors report change scores	
Macrinici et al. 2017[38]	Computer generated	Staff performing injections blind	Anaesthesiologist, surgeons, patients and physical therapists blind to allocation	Yes	3; 4 lost to follow up. 6; 3 complications	None apparent but protocol not checked	Groups similar at baseline	Low
McDonald et al. 2016[45]	Computerised blocked	Study coordinator independent of care and surgery	Patients blind. Surgeon aware of study	Outcome assessment blind to allocation	1; 4 unexplained	None apparent, protocol not checked	Groups similar at baseline	Low
Meunier et al. 2007[51]	Computer generated	Sealed envelope	Randomisation code broken after 1 year	Yes	ITT reported except for 12 month pain outcome	No but not checked protocol	M/F ratio differed	Low
Morin et al. 2005[115]	Allocated randomly	Sealed envelope	All patients received some form of nerve block. Anaesthesiologist not blind to intervention	Observers not blinded	Per protocol analysis	No but not checked protocol	Difference between groups in anesthetist's opinion of difficulty of catheter placement. BMI differed between groups	High
Motififard et al. 2017[46]	Computer generated	Study coordinator independent of care and surgery	Patients blind. Surgeon aware of study	Outcome assessment blind to allocation	3; 7 (1; 4 unexplained)	None apparent, protocol not checked	Groups similar at baseline	Low

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Nader et al. 2012[39]	Computer generated	Opaque envelope	No	Patient reported outcome	1:1 lost to follow up	Protocol not checked but reasonable range of outcomes	FNB group somewhat higher BMI	Low
Niemeläinen et al. 2014[47]	No details	Opaque sealed envelopes	Only research nurse preparing infiltrate aware of randomisation. All other personnel unaware until after 1 year follow up	Only research nurse preparing infiltrate aware of randomisation. All other personnel unaware until after 1 year follow up	All patients who received intervention completed follow up	No but not checked protocol	No	Low
Peng et al. 2014[40]	Computer generated	Not possible	Not possible	Patient reported outcome	31:38 lost at 12 months but ITT and per- protocol analysis	No but not checked protocol	No	Low
Perrin and Purcell 2009[112]	No details	Sealed syringe code stored in pharmacy department	yes	Yes	4 failed to complete protocol	No but not checked protocol	Pilot investigation. High risk of bias due to recruitment difficulties leading to small trial	High
Reinhardt et al. 2014[41]	Computer generated	Maintained by pharmacy department for blinding	Patients blind to intervention	Blinded research assistant and partially physical therapist	0 reported lost to follow up of those who received interventions	No but not checked protocol	No	Low
Seah et al. 2011[48]	Randomisation tables	Sealed envelopes. Anaesthetist and surgeon blind before opening of	Blinding of patients not stated	Blind outcome assessors and PROMs	No losses to follow up reported	No but not checked protocol	No	Low

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		sealed envelope						
Shum et al. 2009[111]	No details	No details	Anaesthetist performing the blocks was not involved in the postoperative follow-up and data collection	Patient reported	14% and 20%	No but not checked protocol	Mean patient weight lower in no FNB group. More favourable mean OKS in no FNB group. Two groups combined for 2 year outcome but not for earlier	High
Spreng et al. 2012[120], Spreng et al. 2010[121]	Hospital pharmacy	Epidural catheter or sham set-up taped along the back of the patient and connected to an infusion pump covered in an opaque bag. Also sham knee catheter	Patients blind	Blind outcome assessment	13%	Limited reporting in conference abstract	Conference abstract only so limited information additional to early follow up paper	Uncle
Wang et al. 2015[117]	No details	No details	Not stated	Not stated	2:4 lost to follow up	No but not checked protocol	No	Uncle
Wegener et al. 2013[42]	No details	Opaque envelope	Patients, surgeons and researchers not blind to intervention	Patients not blinded	2:7:5 lost to follow up	No. Protocol checked	no	Low
Widmer et al. 2012[43]	Coded envelope	Coded envelope	Except for anaesthetist and surgeon	Both the investigators and patients were blinded	None reported as incomplete	No but protocol not checked	No	Low

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Williams et al. 2013[49]	Computer generated	Not stated	Patients and assessors blind	Patients and assessors blind	3:1 of those who received treatment	No but not checked protocol	No	Low
Wu and Wong 2014[44]	Computer	Sealed envelopes	No	No	Available cases	No but not checked protocol	No	Low
Wylde et al. 2015[50]	Trials unit	Trials unit	Surgeon and anaesthetist not blind to allocation, Patients blind	Patients and research nurses blind to allocation	ITT with imputed data	No as per protocol	No	Low
Yue et al. 2013[119]	No details	No details	Surgeons and patients were double-blinded to the injection administered	surgeons and patients were double-blinded to the injection administered	Losses to follow up not reported	Limited reporting	No	Unclear
Myofascial trig	ger point dry nee	edling						
Mayoral et al. 2013[123]	Computerised	Not described	Patient and other researchers apart from physical therapist blind	Patient outcomes	4: 5 loss to follow up	None apparent but protocol not checked	No	High
Tourniquet								
Abdel-Salam and Eyres 1995[124]	Card system	Not described	No	No	No losses to follow up	None apparent but protocol not checked	No	Unclear
Ejaz et al. 2014[54]	Block randomised	Sealed envelopes	Patients unaware	PROM	No losses to follow up of those who received treatments	None apparent but protocol not checked	No	Low
Huang et al. 2017[55]	Computer generated	Sealed opaque envelopes	Surgeons not blind. Patients blind to allocation	Data collector blind to allocation	No losses to follow up reported	None apparent but protocol	Groups similar at baseline	Low

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Liu et al. 2014[56]	Excel	Not described	Patients blind	PROM	No losses	None apparent but protocol not checked.	No	Low
Mittal et al. 2012[57]	Computer generated	Sealed opaque envelopes	Patient blind	Outcome assessors blind. PROM	5:2	None apparent but protocol not checked	Study stopped because of high risk of transfusion in short tourniquet duration group	Low
Şükür et al.2016[125]	Computer generated	Not described	Possibly patients	Outcome assessors blind	No losses to follow up	KSS outcome noted in methods but not presented in results	No	High
Zhang et al. 2017[58]	Excel	Randomisation by blinded researcher.	Patients and nurses on ward blind	Not clear	No losses reported	None apparent but protocol not checked	Groups similar at baseline	Low
Zhang et al.2016[126]	Randomly allocated	Not clear	Not clear	Not clear	Not clear	HSS outcome noted in methods but not presented in results	No	Hig

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Brock et al. 2017[127]	Web-based	Not specified	Not possible	No but PROMs	4; 2 of those receiving intervention	None apparent but protocol not checked	Groups similar at baseline	Low
Blood conserva			1	- 	1			
Hourlier et al. 2015[60]	Computer generated	Opaque envelopes	Anaethsetist, surgeon and patient blind to treatment allocation	Assessors blind	No missing data	None apparent but protocol not checked	No	Low
	Computer generated	Sealed opaque envelopes	Surgeons not blind. Patients blind to allocation	Data collector blind to allocation	No losses to follow up reported	None apparent but protocol not checked	Groups similar at baseline	Low
Kim et al. 2014[61]	Computer generated	Not stated	patients blind to allocation	Clinical investigator blind to allocation	No missing data	None apparent but protocol not checked	No	Low
Kusuma et al. 2013[62]	Computer generated	Sealed envelopes	Surgeon and patient blind	Outcome assessor blind	No missing data	None apparent but protocol not checked	No	Low
Napier et al. 2014[63]	Computer generated	Sealed envelopes	Unlikely	Not stated but PROM	low losses to follow up	None apparent but protocol not checked	No	Low
Sa- Ngasoongsong et al. 2011[64]	Computer generated	Sealed envelopes	Surgeon and patient blind	Outcome assessor blind	No missing data	None apparent but	No	Low
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						protocol not checked		
Sa- Ngasoongsong et al. 2013[65]	Computer generated	Sealed envelopes	Surgeon and patient blind	Outcome assessor blind	No missing data	None apparent but protocol not checked	Some difference between groups in pre- operative Hb	Low
Thomas et al. 2001[128]	Not described	not stated	Not reported	Not reported but PROM	Not reported but ITT	None apparent but protocol not checked	No	Unclear
Platelet rich pla		1 -				Г		
Aggarwal et al. 2014[129]	Not described	Opaque envelopes	Patients blind	Patients and examiners blind	No losses to follow up reported	None apparent but protocol not checked	Odd numbers in groups from randomisation	High
Cryotherapy								
Wang 2017[130]	No details	No details	No details	No details	No losses to follow up	None apparent but protocol not checked	Groups similar at baseline	Unclea
Denusomab	Devilenting		Le sellestere est	11.1.1.1.1.1.1.1.1.1.1.1.1.1.1.1.1.1.1.1		NUMBER		
Ledin et al. 2017[66]	Randomisation list produced by the study monitor	Syringes prepared independently	Investigators and patients blind	Unblinding was done after all the data had been locked	0; 2	None apparent but protocol not checked	No	Low
Continuous pas			1			1		
Beaupré etal. 2001[134]	Computer generated	Sealed envelopes	No	Researcher unaware and PROMs	6:8:6. Results carried	No	4 controls; 1 SB	Unclea

					forward for missing data		reassigned to CPM	
Bennett et al. 2005[67]	Block	Not stated	Operating surgeon blind. Patient not	Independent assessor blind	1 not included in analyses as not able to achieve 90 degree flexion	No	No	Low
Ersözlü et al. 2009[68]	Divided into groups by random selection	Not described	No	Surgeon score	A diabetic patient from the control group was excluded because of a superficial wound infection, a patient with a cardiac problem in group II due to dysrhythmia, and two patients due to insufficient follow-up.	Not apparent	No differences baseline	Unclear
Kumar et al. 1996[135]	Random number generator	Not stated	No	Not described	Large loss to follow up	Not all data clearly reported	No	High
Leach et al. 2006[131]	Allocation by date of birth	No	No	Blinded evaluation	Large loss to follow up	No	No	High
MacDonald et al. 2000[137]	Computer generated	Allocation concealed	No	Not described	Not reported	Yes, not all outcomes reported in full	No	Unclea
Pope et al. 1997[133]	Not described	Not described	Not described	Not described	No separate reporting. 8 patients (12 knees)	None apparent but protocol	No	High

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					excluding 1 death	not checked		
Sahin et al. 2006[132]	Not described	Not stated	No	Followed up by treating physician	Low loss to follow up	No	No	Unclea
Worland et al. 1998[136]	Not described	Not described	No	Researcher blind	Not reported separately	None apparent but protocol not checked	No	Unclea
Electrical stime								T
Adravanti et al. 2014[140]	Computer generated	Not described	Research assistant not involved in patient assessment	Principal investigator and all physicians in charge of clinical controls were blinded to patient allocation	78% retained at 6 months	Not apparent but protocol not checked	No	High
Avramidis et al. 2011[69]	Computer generated	Not described	No	Independent assessors blind	3 (intolerance of intervention); 3	Not apparent	Baseline similar	Low
Levine et al. 2013[139]	Drawing papers from hat	Not described	No	Not described. WOMAC PROM	5:9 for KSS pain and WOMAC	Not apparent but protocol not checked	No	Unclea
Moretti et al. 2012[70]	Computer generated	Not described	Physicians, as well as medical assessors, were blinded to the allocation of patients in the study groups	Physicians, as well as medical assessors, were blinded to the allocation of patients in the study groups	No losses reported	Not apparent but protocol not checked	No	Low
Stevens- Lapsley et al. 2012[138]	Stratified	Concealed	No	no but standardised scripts used	5; 6	Not apparent but protocol	WOMAC, BMI unequal at baseline	Unclea

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Rehabilitation						onoonou		
Hill et al. 2000[143]	Not described	Not stated	Not possible	Not described	No losses to follow up after initial 23222	No but protocol not checked	No	Unclea
Li et al. 2017[71]	Random number table	Not stated	Not possible	Not described but PROM	No losses to follow up	No but protocol not checked	Groups similar at baseline	Low
Liebs et al. 2012[72]	Computer generated	Allocation concealed	Not possible	No but PROM	Low losses to follow up (<20% if deaths and other explained reasons not counted)	No but protocol not checked	No	Low
Mahomed et al. 2008[142]	Block randomisation	Not stated	Not possible	PROM	No loss	No but protocol not checked	ITT gave similar results to analysis according to actual discharge destination (20 inpatient group received home based)	Low
Rahmann et al. 2009[141]	Not described	Sealed numbered envelopes	Not possible	Assessor blind to intervention. Patient reported outcome	Low losses to follow up	No but protocol not checked	TKR patients more likely to receive ward- based control intervention. THR and TKR analysed together	Unclea
Wang et al. 2014[74]	Computer generated	Surgeons did not participate	Surgery was performed by the	Postoperative evaluation was	No loss to follow up	None apparent	No baseline differences	Low

		in pre- operative grouping	physicians who did not participate in the preoperative grouping and postoperative evaluation	conducted by the physicians who were unaware of the grouping.		but protocol not checked		
Wound manage Kong et al. 2014[75]	Not described	Not described	Placebo used	Patient outcome	Low loss to follow up	None apparent but protocol not checked	Similar at baseline	Low
Anabolic stero Hohmann et al. 2010[76]	Internet based	Not reported	Placebo trial	Double-blind design minimized systemic error and eliminated observer and experimenter's bias	0 loss to follow up	None apparent	None apparent but small study	Low
Guided imager Jacobson et al. 2016[144]	y Permuted blocks	Opaque CD holders	Personnel yes, participants no	Yes	12; 10 of patients receiving treatment	None apparent but protocol not checked	No	High

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Reporting checklist for systematic review and meta-analysis.

Based on the PRISMA guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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31				Page
32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60			Reporting Item	Number
		#1	Identify the report as a systematic review, meta-analysis, or both.	1
	Structured summary	#2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number	2/5
	Rationale	#3	Describe the rationale for the review in the context of what is already known.	4-5
	Objectives	#4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
	Protocol and registration	#5 For p	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address) and, if available, provide registration information including the registration number. beer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	5

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1 2 3 4 5	Eligibility criteria	#6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rational	5
6 7 8 9 10	Information sources	#7	Describe all information sources in the search (e.g., databases with dates of coverage, contact with study authors to identify additional studies) and date last searched.	6
11 12 13 14 15	Search	#8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	See note 1
16 17 18 19 20 21	Study selection	#9	State the process for selecting studies (i.e., for screening, for determining eligibility, for inclusion in the systematic review, and, if applicable, for inclusion in the meta-analysis).	5,6
22 23 24 25 26	Data collection process	#10	Describe the method of data extraction from reports (e.g., piloted forms, independently by two reviewers) and any processes for obtaining and confirming data from investigators.	6
27 28 29 30 31	Data items	#11	List and define all variables for which data were sought (e.g., PICOS, funding sources), and any assumptions and simplifications made.	5/6
32 33 34 35 36 37 38	Risk of bias in individual studies	#12	Describe methods used for assessing risk of bias in individual studies (including specification of whether this was done at the study or outcome level, or both), and how this information is to be used in any data synthesis.	6
39 40 41 42	Summary measures	#13	State the principal summary measures (e.g., risk ratio, difference in means).	7
43 44 45 46 47	Planned methods of analyis	#14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I2) for each meta-analysis.	7
48 49 50 51 52 53 54 55 56 57 58	Risk of bias across studies	#15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6
	Additional analyses	#16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	7
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1 2 3 4 5	Study selection	#17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	See note 2
6 7 8 9 10	Study characteristics	#18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citation.	See note 3
11 12 13 14	Risk of bias within studies	#19	Present data on risk of bias of each study and, if available, any outcome-level assessment (see Item 12).	See note 4
15 16 17 18 19 20 21	Results of individual studies	#20	For all outcomes considered (benefits and harms), present, for each study: (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot.	See note 5
22 23 24 25 26	Synthesis of results	#21	Present the main results of the review. If meta-analyses are done, include for each, confidence intervals and measures of consistency.	16-23
27 28 29 30	Risk of bias across studies	#22	Present results of any assessment of risk of bias across studies (see Item 15).	See note 6
31 32 33 34	Additional analysis	#23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	16-23
35 36 37 38 39 40	Summary of Evidence	#24	Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., health care providers, users, and policy makers	16-23
41 42 43 44 45 46	Limitations	#25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias).	24-25
47 48 49 50	Conclusions	#26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	23-25
51 52 53 54 55	Funding	#27	Describe sources of funding or other support (e.g., supply of data) for the systematic review; role of funders for the systematic review.	26
56 57 58	Author notes			

- 1. 5, Supplemetary material
- 2. 7, Figure 1

- 3. 8-15, Table1, Supplementary material
- 4. 7, Supplementary material
- 5. 8-15, Table1, Supplementary material

6. 8-15, Supplementary material

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Are peri-operative interventions effective in preventing chronic pain after primary total knee replacement? A systematic review

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Are peri-operative interventions effective in preventing chronic pain after primary total knee replacement? A systematic review

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ABSTRACT

Objectives

For many people with advanced osteoarthritis, total knee replacement (TKR) is an effective treatment for relieving pain and improving function. Features of peri-operative care may be associated with the adverse event of chronic pain six months or longer after surgery; effects may be direct, e.g. through nerve damage or surgical complications, or indirect through adverse events. This systematic review aims to evaluate whether non-surgical peri-operative interventions prevent long-term pain after TKR.

Methods

We conducted a systematic review of peri-operative interventions for adults with osteoarthritis receiving primary TKR evaluated in a randomised controlled trial (RCT). We searched *The Cochrane Library*, MEDLINE, Embase, PsycINFO and CINAHL to February 2018. After screening, two reviewers evaluated articles. Studies at low risk of bias according to the Cochrane tool were included.

Interventions

Peri-operative non-surgical interventions; control receiving no intervention or alternative treatment.

Primary and secondary outcome measures

Pain or score with pain component assessed at six months or longer post-operative.

Results

44 RCTs at low risk of bias assessed long-term pain. Intervention heterogeneity precluded meta-analysis and definitive statements on effectiveness. There was good-quality evidence for a small benefit for reduced long-term pain with local infiltration analgesia (3 studies), ketamine infusion (1 study), pregabalin (1 study), and electric muscle stimulation (2 studies). No concerns relating to long-term adverse events were reported. In 5 RCTs, tranexamic acid to prevent blood loss was not associated with long-term pain. Many extensively researched interventions including venous thromboembolism prevention have not been evaluated in relation to long-term pain.

Conclusions

To prevent chronic pain after TKR, peri-operative interventions including components of multimodal analgesia, early rehabilitation and supported discharge, electrical stimulation and anabolic steroids show small benefits meriting further research. Tranexamic acid use is not associated with chronic pain but the long-term consequences of many widely researched treatments have not been reported.

STRENGTHS AND LIMITATIONS

• For the first time, this systematic review brings together contemporary evidence on aspects of peri-operative care for people with total knee replacement and their effects on long-term pain.

• Only studies assessed to be at low risk of bias were included in the narrative synthesis.

• Intervention and outcome heterogeneity precluded meta-analysis.

KEYWORDS

Total knee replacement; Systematic review; Randomised controlled trial; Peri-operative care; Long-term pain

BACKGROUND

In the US about 13% of men and 19% of women will be diagnosed with knee osteoarthritis and over half will receive a total knee replacement (TKR)[1]. For people with advanced osteoarthritis unresponsive to pharmacological or conservative treatments, TKR aims to relieve pain and improve function. In the UK nearly 100,000 primary TKRs were performed in 2017[2,3] and in the USA in 2010, an estimated 4.7 million people were living with a TKR[4]. Despite good outcomes for many, some people report long-term pain and are disappointed with their surgery[5,6]. After TKR, pain levels plateau from about 6 months[7,8] after which persistent pain is considered "chronic"[9] and is reported by 10-34% of patients[10].

The mechanisms that influence the development of chronic pain after total knee replacement may be biological, mechanical and psychosocial. Biological causes include the sensitising impact of long-term pain from osteoarthritis[11,12], inflammation, infection and localised nerve injury[13]. Mechanical causes include altered gait, prosthesis loosening, and effects on ligaments[14,15]. Psychological factors including depression and catastrophizing may also influence outcomes[16-19]. Much research has focused on pre-operative predictors of outcomes and these include pain intensity, presence of widespread pain, anxiety, depression and catastrophizing.[10,20] However, attempts to target or modify pre-operative care have, as yet, shown no benefit regarding chronic pain or other long-term patient outcomes[10,21-23].

Peri-operative risk factors suggest that appropriate interventions may reduce long-term pain. For example, acute post-operative pain, which may be a direct consequence of the operation, anaesthetic protocol and subsequent analgesia, or related to particular aspects of care, is an acknowledged risk factor for chronic post-surgical pain[24].

In the peri-operative period from hospital admission to the early stages of recovery, care focuses on acute pain management, prevention of adverse events, facilitation of early mobilisation and timely discharge. However, for people with osteoarthritis the key aim of TKR is the achievement of a long-term painless and well-functioning knee with no adverse events. All aspects of peri-operative care should work together to achieve this.

Any treatment in the peri-operative period including pain management, blood conservation, deep vein thrombosis (DVT) and infection prevention, and inpatient rehabilitation could potentially affect patient recovery and chronic pain, either directly or indirectly. Direct mechanisms may be through prevention of nerve damage[25], post-thrombotic syndrome[26], reperfusion injury[27] and articular bleeding[28]. For other treatments, pathways leading to long-

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term pain may be indirect, possibly being mediated through increased risks of adverse events[29]. Irrespective of mechanism, chronic pain is a highly prevalent adverse event after TKR and should be considered along with infection, DVT and other complications in the safety profile of interventions.

Our systematic review of randomised controlled trials (RCTs) aims to evaluate the effectiveness of treatments in the peri-operative period in preventing long-term pain after TKR. By focusing on studies with low risk of bias we aim to identify interventions with robust evidence of long-term effectiveness and identify gaps in the research base.

METHODS

The systematic review protocol was registered (PROSPERO CRD42017041382) and PRISMA reporting guidelines used[30]. A checklist is included as Supplementary material.

Patient and public involvement

As part of the STAR programme of research (NIHR RP-PG-0613-20001), this review benefited from extensive patient and public involvement. Advice was sought from patients and stakeholders at a group discussion in March 2016 with decisions made on inclusion criteria and outcomes. Our patient advisory group comprises five patients with experience of long-term pain after TKR, supported by a dedicated co-ordinator. This group will advise on dissemination of the study results to a general audience including plain language summaries.

Eligibility criteria

Studies were eligible if they satisfied PICOS criteria defined in the protocol. Participants were adults receiving unilateral primary TKR with osteoarthritis in at least 75% of patients. Pharmacological or non-pharmacological interventions commenced in the peri-operative setting with "peri-operative" reflecting the time from hospital admission to immediately post-discharge. Interventions relating to implant designs and surgical procedures were excluded. The comparator was usual care, placebo or an alternative intervention. Outcomes were, in preference, patient-reported joint-specific pain intensity measured by tools such as the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) or Oxford Knee Score (OKS). If joint-specific measures were unavailable, pain dimensions from quality of life measures were used or pain rated on a visual analogue scale (VAS) or numerical rating scale (NRS). We also considered composite patient-reported outcome measures and surgeon scores which included a pain intensity component, such as the American Knee Society Score (KSS) and Hospital for Special Surgery (HSS) score. Measures specifically of neuropathic pain were also used. The occurrence of adverse events was summarised. The studies included were RCTs with follow up at ≥6 months after surgery and a pain outcome or score including pain. Authors of studies were contacted regarding incomplete pain outcome data.

Database searches

We established an Endnote database of all RCTs in TKR. On 14th February 2018, a search from database inception was conducted in: *The Cochrane Library*; MEDLINE, Embase and PsycINFO on Ovid; and CINAHL on EBSCOhost. The MEDLINE search strategy is included as supplementary material. Citations of key articles were tracked in Web of Science. No language restrictions were applied, and translations made. Studies reported as abstracts or unobtainable using inter-library loans and author contact were excluded.

Screening and data extraction

We imported records into Endnote X7 (Thomson Reuters). An initial screen by one reviewer excluded clearly irrelevant articles. Subsequently, abstracts and full articles were screened independently by two reviewers and reasons for exclusion recorded.

Data were extracted onto piloted forms and an Excel spreadsheet by one reviewer, specifically: country; dates; participants (indication, age, sex); inclusion and exclusion criteria; intervention and control content; setting, timing, duration and intensity of intervention; follow up intervals; losses to follow up; pain outcome data; and serious adverse events. Data was checked against source material by a second reviewer.

Authors were contacted for missing data, and data provided for previous reviews was used[10,31].

Quality assessment

Potential sources of bias were assessed by two experienced reviewers using the Cochrane risk of bias tool[32], specifically: the randomisation process; deviations from intended interventions; missing outcome data (>20%), measurement of the outcome; and selection of the reported result. Studies with serious concerns relating to risk of bias were considered high risk and those with limited reporting unclear risk. Studies with high or unclear risk of bias were excluded from the narrative synthesis but are included in supplementary summary tables with reasons for exclusion.

Data analysis

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Insufficient studies with similar interventions and outcomes were identified for meta-analysis, and a narrative synthesis is presented. Results reported with p-values ≤0.001 were considered "strong" evidence of effectiveness[33], p-values 0.001-0.05 "some" evidence, and p-values 0.05-0.1 "weak" evidence. When authors reported results "statistically significant" with no p-value, this was noted. Where possible, effect sizes were compared with published minimal clinically important differences (MCID). Concerns relating to adverse events were summarised.

RESULTS

Figure 1 shows review progress and reasons for exclusion. Of 1515 RCTs of interventions in the peri-operative setting, 1385 had no long-term follow up. Peri-operative interventions with follow up of \geq six months were evaluated in 130 RCTs of which 76 reported a pain outcome or score with a pain component. Detailed intervention and study characteristics and risk of bias assessments are provided as supplementary material. Studies excluded had concerns for risk of bias pertaining to at least one of: large baseline differences in group characteristics or numbers in groups (n=4); incomplete outcome data (n=15); limited or selective reporting (n=12); or unblinded surgeon follow up (n=1).

Details of 44 studies assessed to be at low risk of bias are summarised in Table 1. In 34 studies, patients received TKR exclusively for osteoarthritis and in three, 75% or more patients. In seven studies there was no information on reason for surgery but there was no suggestion that patients had an indication other than osteoarthritis. Interventions focused on pain management (n=20), tourniquets (n=5), compression bandages (n=1), blood conservation (n=7), denusomab (n=1), continuous passive motion (n=2), electrical stimulation (n=2), rehabilitation (n=4), wound management (n=1) and anabolic steroids (n=1). Primary pain outcome measures reported were VAS or NRS pain (n=12), WOMAC pain (n=7), KOOS pain (n=3), Leeds assessment of Neuropathic Symptoms and Signs Pain Scale (S-LANSS) (n=1), SF-36 bodily pain (n=1), or composite scores including a pain measure, OKS or WOMAC (n=10), KSS or HSS (n=10). Latest outcomes were recorded at 6 months (n=12), 12 months (n=26) and 24 months (n=6). Reporting of adverse events covered the entire follow up period in 27 studies, short-term after surgery in 15 studies, but were not reported in two studies.

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Table 1. Perioperative interventions with follow up for pain or score at6 months or later and assessed to be at low risk of bias

Study	Treatment common to	Intervention	Number patients	Follow up
	randomised groups		patiente	Group difference
Pain management: nerve	blocks			
Albrecht et al. 2014[34]	SNB	1. FNB continuous high	99	1 year
Canada, 2009-2011,		2. FNB continuous low		WOMAC score: no difference
1 hospital		3. FNB single		(p=0.68)
Choy et al. 2011[35]	PCA	1. FNB continuous long	61	1 year
Korea, 2006-2007,		2. FNB continuous short		WOMAC pain: no difference
1 surgeon				(p=0.2)
Fan et al. 2016[36]	PCA	1. FNB single	157	1 year
China, 2012-2014,		2. LIA		KSS: no difference (p=0.51)
2 surgeons				
Gao et al. 2017[37]	LIA	1. General anaesthesia	150	6 months
China, 2014-2015,		2. FNB single		HSS score: no significant
1 centre		3. FNB/ SNB single		difference (p> 0.05)
Macrinici et al. 2017[38]	LIA	1. ACB single	98	6 months
USA, Before 2017		2. FNB single		VAS pain: no difference
1 centre				
Nader et al. 2012[39]	PCA	1. FNB continuous	62	1 year
USA, 2007-2008,		2. Oral opioid		NRS pain stair: some evidence
1 surgeon				favouring opioid (p=0.01) but not consistent. Overall NRS pain: no difference (p=1.0)
				VTE: concern opioid
Peng et al. 2014[40]		1. FNB continuous	280	6 months and 1 year
China, Before 2014,		2. PCA		NRS pain: some evidence favouring FNB at 6 months
		8		

1 centre				(p=0.021); no difference at 1 year (p=0.273)
Reinhardt et al. 2014[41]		1. FNB single/ epidural	94	1 year
USA, 2010-2012,		2. LIA 48 hours		VAS pain: no difference
2 surgeons				
Wegener et al. 2013[42]	FNB	1. SNB single	89	1 year
The Netherlands, 2008-2010,		2. SNB continuous		WOMAC pain: no difference
1 centre		3. PCA		(p=0.81)
Widmer et al. 2012[43]	LIA, PCA	1. FNB single	55	1 year
Australia, before 2012,		2. Control no FNB		WOMAC pain: no difference (p=0.74)
2 surgeons		1. FNB continuous	60	C months
Wu and Wong 2014[44]			60	6 months
China, 2009-2011,		2. PCA		KSS: no difference (p=0.513)
1 centre		6		
Pain management: LIA				
McDonald et al. 2016[45]		1. LIA	222	1 year
UK, 2010-2011		2. PCA		OKS: no difference (p=0.915)
1 hospital				
Motififard et al. 2017[46]		1. LIA pre-emptive	120	6 months
Iran, 2014-2015		-		KSS: weak evidence favouring
1 hospital		2. Control saline with epinephrine		LIA (p=0.07). Difference between groups (14.2/200) less than MCID (12.3/200).
Niemeläinen et al. 2014[47]	PCA	1. LIA	56	1 year
Finland, 2011-2012		2. Control saline		OKS: weak evidence from
1 hospital				means and confidence intervals favouring LIA. Difference (2.7/48) less than MCID (4.0/48)
Seah et al. 2011[48]	PCA	1. LIA with corticosteroid	100	6 months and 2 years
Singapore, 2004-2005		2. LIA no corticosteroid		OKS: no difference

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1 hospital				
Williams et al. 2013[49]	LIA, PCA	1. LIA 48 hours	51	6 months and 1 year
Canada, Before 2013		2. Control saline		VAS pain: no difference (6 months p=0.836, 1 year
2 surgeons				p=0.767)
Wylde et al. 2015[50]	FNB, PCA	1. LIA	280	6 months and 1 year
UK, 2009-2012		2. Control no LIA		WOMAC pain: weak evidence favouring LIA at 6 months
1 centre				p=0.063; 1 year p=0.107. Mean difference at 1 year (3.8/100) lower than MCID (8– 9/100)
Pain management: Celeco.	xib			
Meunier et al. 2007[51]	PCA	1. Celecoxib	44	1 year
Sweden, 2004-2005		2. Control placebo		KOOS/VAS pain: no difference
1 centre				
Pain management: Ketami	ne/ Nefopam	0,		
Aveline et al. 2014[52]	PCA	1. Ketamine infusion	75	6 months and 1 year
France, 2005		2. Nefopam infusion		DN4/VAS pain: some evidence favouring ketamine (for DN4
1 centre		3. Control saline		p=0.02). Few patients had neuropathic pain at 12 months
Pain management: Pregab	alin	(9	
Buvanendran et al. 2010[53]	LIA, PCA	1. Pregabalin	240	6 months
USA, 2006-2007		2. Control placebo		NRS pain: some evidence favouring pregabalin at 6
Single centre				months (p=0.0176)
				S-LANSS pain: no neuropathi pain reported in pregabalin group compared with 5.2% of patients in control group
				(p=0.014) Sedation and confusion day 0
				and day 1: concern pregabalin

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Tourniquet				
Ejaz et al. 2014[54]	Tranexamic	1. Tourniquet	64	6 months and 1 year
Denmark, 2011-2012	acid	2. Tourniquet not inflated		KOOS pain: no significant
1 centre				difference
Huang et al. 2017[55]	Tranexamic	1. Tourniquet	100	6 months
China, 2015	acid	2. No tourniquet		VAS pain: no difference (p=0.728)
1 centre				Wound: concern tourniquet
Liu et al. 2014[56]	0,	1. Tourniquet	20	6 months and 1 year
Australia, Before 2014		2. Tourniquet not inflated		OKS: no significant differenc
1 surgeon				Transfusion: concern tourniquet
Mittal et al. 2012[57]		1. Tourniquet short	65	1 year
Australia, 2008-2010		duration		OKS: weak evidence from
1 centre		2. Tourniquet long duration		means and Cis on graph favouring long duration at 1 year. Mean difference (5) greater than MCID (4)
				Transfusions/ adverse events
Zhang et al. 2017[58]		1. Tourniquet for entire	150	6 months
China, 2008-2011		operation		HSS score: no difference
1 surgeon		2. Tourniquet removed before wound closure		(p=0.839)
		3. Tourniquet from first		Transfusions: concern late tourniquet start in groups 1
		bone osteotomy until closure		and 2
Compression bandage				
Brock et al. 2017[59]	Hydrocolloid	1. Compression bandage	49	6 months
UK, 2013-2014	dressing	2. Standard crepe		OKS: no difference (p=0.58)
1 hospital		bandage		
Blood conservation				
		11		

1 2 3 4 5 6 7 8 9 10 1 12 13 14 15 16 17 8 19 20 21 22 32 4 5 26 7 8 9 10 1 12 13 14 15 16 17 8 19 20 21 22 32 4 5 26 7 8 9 30 3 12 33 4 35 36 7 8 9 40 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4	
44 45 46 47 48	

tourniquet, electrocautery Tourniquet	tranexamic acid 2. Control saline 1. Intravenous and topical tranexamic acid 2. No tranexamic acid	100	KSS: no difference (p=0.90) 6 months VAS pain: no difference (p=0.728)
Tourniquet	1. Intravenous and topical tranexamic acid	100	VAS pain: no difference
Tourniquet	tranexamic acid	100	VAS pain: no difference
			•
	2. No tranexamic acid		(p=0.728)
			HSS score: strong evidence favouring tranexamic acid (p<0.001). Mean difference (1.4/100) lower than MCID (8.3/100)
			Blood loss: control concern
Tourniquet,	1. Tranexamic acid	180	1 year
compressive	2. No tranexamic acid		WOMAC pain: no significant difference
aressing			
			Transfusion: control concern
Tourniquet, Esmarch	1. Thrombin infusion	80	6 months, 1 and 2 years
bandage,	2. No thrombin infusion		KSS: no difference (p=0.45)
electrocautery			
	1. Passive flexion	180	1 year
	2. Passive extension		OKS: no difference (p=0.27)
			Transfusion: extension concern
Drain and	1. Tranexamic acid	48	6 months
compressive dressing	2. Control saline		WOMAC score: no difference (p=0.282)
			Transfusion: control concern
Drain and	1. Tranexamic acid	135	1 year
dressing	2. Tranexamic acid		WOMAC score: no difference (p=0.42)
	250mg 3. Control saline		Transfusions: control and 250mg group concerns
	drain, compressive dressing Tourniquet, Esmarch bandage, electrocautery Drain and compressive dressing Drain and compressive	drain, compressive dressing2. No tranexamic acidTourniquet, Esmarch bandage, electrocautery1. Thrombin infusion2. No thrombin infusion electrocautery2. No thrombin infusion1. Passive flexion 2. Passive extension1. Passive flexion 2. Passive extensionDrain and compressive dressing1. Tranexamic acid 2. Control salineDrain and compressive dressing1. Tranexamic acid 500mg 2. Tranexamic acid 250mg	drain, compressive dressing2. No tranexamic acidTourniquet, Esmarch bandage, electrocautery1. Thrombin infusion802. No thrombin infusion electrocautery2. No thrombin infusion801. Passive flexion 2. Passive extension180Drain and compressive dressing1. Tranexamic acid482. Control saline1. Tranexamic acid135Drain and compressive dressing1. Tranexamic acid135Drain and compressive dressing1. Tranexamic acid135Drain and compressive dressing1. Tranexamic acid135Drain and compressive dressing1. Tranexamic acid135Jong dressing3. Control saline135

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Denusomab				
Ledin et al. 2017[66]		1. Denusomab	50	1 and 2 years
Sweden, 2012-2014		2. Placebo		KOOS pain: no significant
2 centres				difference
Continuous passive motio	n			
Bennett et al. 2005[67]	Physiotherapy	1. Standard CPM	147	1 year
Australia, 1997-2000		2. Early flexion CPM		KSS: no significant difference
1 hospital		3. No CPM		
Ersözlü et al. 2009[68]	Physiotherapy	1. CPM low and	90	2 years
Turkey, 2003-2004		increasing		KSS: no difference (p=0.67)
1 hospital		2. CPM high and increasing		
		3. No CPM		
Electrical stimulation				
Avramidis et al. 2011[69]	Physiotherapy	1. Transcutaneous	76	1 year
Greece, 2005-2006		electric muscle stimulation		SF-36 bodily pain: strong
1 hospital		2. No treatment		evidence favouring electrical stimulation (p<0.001). Mean difference (12.5/100) close to
				MCID (16.9/100). OKS/ KSS: no difference
Moretti et al. 2012[70]	Rehabilitation	1. Pulsed electromagnetic	30	6 months and 1 year
Italy, 2008-2010	protocol	fields		VAS pain: some evidence
-		2. No treatment		favouring electrical stimulation
1 hospital				(p<0.05). Mean difference (2.1/10) greater than MCID
				(16.1/100)
				Knee swelling: electrical stimulation concern
Rehabilitation				
Li et al. 2017[71]	Standard	1. Walking guidance and	86	6 months
China, 2015-2016	rehabilitation	training		
		13		

1 hospital		2. No treatment		VAS pain/ HSS score: some evidence favouring walking (both p<0.01). Mean VAS pair difference (2.4/100) greater than MCID (16.1/100)		
Liebs et al. 2012[72]	CPM,	1. Early aquatic therapy	185	6 months, 1 and 2 years		
Germany, 2003-2004	physiotherapy, post-discharge aquatic	2. Delayed aquatic therapy		WOMAC pain: no difference (p=0.22 at 12 months)		
4 hospitals	therapy			(p)		
Mahomed et al. 2008[73]	Physiotherapy	1. Multidisciplinary	234 hip	1 year		
Canada, 2000-2002		supported early discharge and home physiotherapy	or knee replace	WOMAC pain: weak evidence favouring supported discharge		
2 centres		2. Transfer to rehabilitation centre	ment	(p=0.08). Mean difference (4) less than MCID (8-9)		
Wang et al. 2014[74]		1. Wound closure in	80	6 months		
China, 2009-2010		flexion 2. Wound closure in		VAS pain: no difference		
1 centre		extension		(p=0.64)		
Wound management		()				
Kong et al. 2014[75]	Skin staples	1. Silicone gel	100	6 months and 1 year		
South Korea, 2011	and closure strip	2. Petroleum gel		VAS pain: no difference (6 months p=0.886, 1 year		
1 surgeon				p=0.201)		
Anabolic steroids		C				
Hohmann et al. 2010[76]	CPM. Cold compression,	1. Intramuscular nandrolone injections	10 tions	6 and 9 months, 1 year		
Australia, Before 2010		2. Saline injections		 KSS: some evidence favou nandrolone (6 months p=0. 		
1 surgeon				9 months p=0.06, 12 months p=0.03). Difference at 12 months (10.2) close to MCID (12.3)		
				Bone mineral density: weak evidence favouring nandrolon		
ACB adductor canal blo	ock; CPM Continuou	us passive motion; DN4 Doule	eur Neurop	athique 4; FNB		
Femoral nerve block; H	ISS Hospital for Spe	ecial Surgery; KOOS Knee inj	al Surgery; KOOS Knee injury and Osteoarthritis Outcome			
Score; KSS Knee Socie	ety Score; LIA local	infiltration analgesia; MCID n	ninimal clin	ically important		
		14				

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difference; NRS Numerical rating scale; OKS Oxford Knee Score; PCA Patient controlled analgesia; SF-36 Short Form 36 Health Survey; S-LANSS Leeds assessment of Neuropathic Symptoms and Signs Pain Scale; SNB Sciatic nerve block; VAS Visual analogue scale; VTE Venous thromboembolism; WOMAC Western Ontario and McMaster Universities Osteoarthritis Index.

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Pain management

We identified 20 RCTs with 2393 participants evaluating components of multi-modal pain management. Four studies each were from China and the USA, two each from Canada and the UK and one each from Australia, Finland, France, Iran, Singapore, South Korea, Sweden and The Netherlands. All were conducted at a single centre and, in those with dates, participants were recruited between 2004 and 2015. Sample sizes ranged from 44 to 280 participants, with a median of 96. Four studies had three trial arms and 16 had two. The range of mean or median ages of participants in randomised groups was 61 to 73 years and, in 17/19 studies with data, a majority of participants were women.

Femoral nerve block

Femoral nerve blocks (FNB) were studied in 10 RCTs.

Three RCTs compared FNB with no FNB. In one study with 55 patients, WOMAC pain scores at one year were similar in patients receiving single-shot FNB and untreated controls[43]. All patients received local anaesthetic infiltration (LIA) and patient-controlled analgesia (PCA). In another study with all participants receiving LIA, 150 were randomised to receive single-shot FNB with or without sciatic nerve block (SNB), or general anaesthesia[37]. There were no differences in HSS scores between groups at six months. Continuous FNB was compared with oral hydrocodone opioid in 62 patients receiving PCA[39]. There was some evidence for 'pain using stairs' favouring hydrocodone (p=0.01) but no difference in overall NRS-rated pain at one year and concern over venous thromboembolism in 4/31 participants treated with hydrocodone.

In two RCTs, continuous FNB was compared with PCA. In one study with 60 participants, the KSS at six months was similar between groups[44]. In another study with 280 participants, there was some evidence for higher incidence of NRS-rated pain at six months in the PCA group than the FNB group (p=0.021) but not at 12 months (p=0.273).[40]

Two RCTs compared FNB with LIA. In one study, all 157 participants also received PCA[36]. At one year, KSS values were similar in single-shot FNB and LIA groups. In the other study, 94 participants were randomised to receive single-shot FNB with continuous epidural infusion or LIA through an intra-articular catheter[41]. VAS-rated pain was similar between groups at one year.

In two RCTs, FNB procedures were compared. In one study with 99 patients randomised to two FNB concentrations, there was no difference in WOMAC score between groups at 12 months[34]. In another study with 61 participants allocated to two different durations of FNB,

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there was no difference in WOMAC pain scores at one year[35]. In these studies, all participants received either SNB[34] or PCA[35].

Single-shot FNB was compared with single adductor canal block in one RCT with 98 participants, all receiving LIA[38]. At six months there was no difference in VAS-rated pain.

Sciatic nerve block

In one study, 89 patients were randomised to single-shot SNB, continuous SNB, or PCA[42]. All patients received FNB. At 12 months, there were no differences in pain for single-shot SNB and continuous SNB on the WOMAC pain scale or VAS-rated pain at rest or during mobilisation. Similarly, there were no differences between single-shot SNB and PCA in WOMAC pain scale or VAS-rated pain at rest or during mobilisation, or between continuous SNB and PCA.

Local anaesthetic infiltration

Four RCTs compared LIA with placebo. In one study, all 280 participants received FNB and PCA[50]. There was weak evidence that WOMAC pain scores were better in the LIA group at six (p=0.063) but not at 12 months (p=0.107) when the difference in means of 3.8/100 was lower than the MCID of 8-9/100 reported by Ehrich and colleagues[77]. In another study, 56 patients received LIA including ketorolac, or saline placebo, and all received PCA[47]. At one year, mean differences and confidence intervals provided weak evidence that OKS scores were better in the LIA group but the difference in means of 2.7/48 was less than the MCID of 4/48 reported by Beard and colleagues[78]. LIA before surgical incision was compared with placebo in one study with 120 participants[46]. None received FNB or PCA. There was weak evidence for a better KSS (function and knee score components) at six months in those receiving LIA (p=0.07) with a difference in means of 14.2/200 exceeding the MCID of 12.3/200 reported by Lee and colleagues[79]. In another study, all 51 participants received LIA intra-operatively, followed by PCA[49]. Those randomised to post-operative catheter-delivered LIA with ketorolac, or saline placebo had similar VAS-rated pain at six and 12 months.

LIA delivered as an injection and post-operative infusion was compared with epidural PCA in one study with 222 patients[45]. There was no difference between groups in OKS at 12 months. In one study of 100 participants, LIA with or without corticosteroid were compared[48]. All

patients received PCA. At two years there was no difference in OKS between groups.

Oral celecoxib

In one RCT, 44 participants received oral celecoxib or placebo[51], as well as PCA. There were no differences between groups in KOOS or VAS-rated pain at 12 months.

Ketamine or nefopam infusion

In one RCT, ketamine infusion, nefopam infusion and saline placebo were compared in 75 patients, all of whom received PCA[52]. VAS-rated pain on movement did not differ between groups at 12 months. For the Douleur Neuropathique 4 (DN4) measure of neuropathic pain, there was some evidence favouring ketamine over placebo at six and 12 months (p=0.02), but overall, few patients reported neuropathic pain at 12 months.

Pregabalin

Oral pregabalin was compared with placebo in one RCT with 240 participants[53]. All received LIA and PCA. At six months, there was some evidence for better NRS pain in patients receiving pregabalin compared with placebo (p=0.0176) but the difference in means of 0.54/10 was less than the MCID of 1/10 reported by Salaffi and colleagues[80]. No participants receiving pregabalin reported neuropathic pain when assessed using the S-LANSS, compared with 5.2% of those receiving placebo (p=0.014). Patients receiving pregabalin were more likely to be sedated and confused in the first two days after surgery.

Tourniquet

Five studies with 399 participants explored tourniquet use to provide a bloodless field. Two studies each were from Australia and China, and one from Denmark. All were conducted at a single centre with participants recruited between 2008 and 2015. Sample sizes ranged from 20 to 150 participants, with a median of 65. The range of mean ages of participants in randomised groups was 66 to 71 years and in 3/5 studies, a majority of participants were women.

In three RCTs, participants received TKR with or without a tourniquet. In one study with 64 patients, a difference in KOOS pain favouring tourniquet use was not significant at six or 12 months[54]. In another study with 20 patients, the OKS was not significantly different between groups at six or 12 months[56]. There were three blood transfusions in the tourniquet group, compared with none in the 'no tourniquet' group. In the third study with 100 participants, VAS-rated pain and HSS scores were similar between groups at 6 months[55]. Six cases of wound ooze occurred in the tourniquet group.

In two RCTs, short and long-duration tourniquet use were compared. In one study with 65 participants, there was weak evidence based on graphical representation of means and

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confidence intervals for improved OKS at 12 months in the long-duration group and the difference in means of 5/48[57] was greater than the MCID of 4/48. Adverse events were reported by 62% of participants receiving short-duration tourniquet compared with 38% in the long-duration group. The study was terminated early as 10 blood transfusions were required in the short-duration group compared with three in the long-duration group. In the second study with 150 participants, tourniquets were used in three different periods during surgery[58]. At six months, there were no differences between groups in HSS scores.

Blood conservation

Seven studies with 829 participants evaluated strategies to limit blood loss after TKR. Two studies were from Thailand, and one each from China, France, South Korea, the UK and the USA. All were conducted at a single centre with participants recruited between 2003 and 2015 when stated. Sample sizes ranged from 48 to 180 participants, with a median of 106. One study had three trial arms. The range of mean ages of participants in randomised groups was 65 to 74 years and in all studies, a majority of participants were women.

Tranexamic acid

Five RCTs evaluated tranexamic acid.

Tranexamic acid injections or infusions were compared with saline placebo or untreated control in four RCTs[55,61,64,65]. In all studies, control patients required more blood transfusions. In one study including 180 participants comparing intravenous tranexamic acid with untreated controls, there was no significant difference in WOMAC pain scores at one year[61]. In another study with 48 participants comparing intra-articular tranexamic acid injection with saline placebo, there was no significant difference in WOMAC scores at six months[64]. One study with 135 participants compared two intra-articular tranexamic acid doses and saline control[65]. There were no significant differences in WOMAC scores at one year. Intravenous and intra-articular tranexamic was compared with untreated controls in one study with 100 participants[55]. VAS-rated pain at six months was similar between groups, but there was strong evidence favouring tranexamic acid for HSS scores (p<0.001) although the difference in means of 1.4/100 was lower than the MCID of 8.3/100 reported by Singh and colleagues[81].

In one study, continuous tranexamic acid infusion was compared with a single bolus in 106 patients[60]. There was no difference between groups in KSS at six months or blood loss.

Thrombin infusion

In one RCT with 80 participants, thrombin infusion was compared with untreated control[62]. At one year there was no difference between groups in pain measured on the KSS.

Flexion or extension

For blood management, operated knees were kept in passive flexion or passive extension after surgery in one RCT with 180 patients[63]. At one year, OKS was similar between groups. Transfusion requirement was greater in patients with passive extension.

Compression bandage

One RCT conducted at a single UK centre with 49 participants recruited between 2013 and 2014 compared compression bandaging to reduce post-operative knee swelling with standard bandaging. The mean age of participants was about 69 years and a majority were women. OKS was similar in randomised groups at six months[59].

Wound management

One RCT with recruitment in 2011 at a single centre in South Korea evaluated a wound care strategy to limit post-operative scar pain. The mean age of participants was about 69 years and a majority were women. Investigators compared silicone gel application to the surgical scar with placebo in 100 participants[75]. There were no significant differences in VAS-rated pain at six and 12 months.

Denusomab

One RCT evaluated use of the antiresorptive monoclonal antibody Denusomab to promote bone healing. The study was conducted in two centres in Sweden with recruitment of 50 participants between 2012 and 2014. The mean age of participants was about 65 years and a majority were women. At 12 and 24 months there were no significant differences between groups in KOOS pain[66].

Continuous passive motion

Two RCTs with 237 participants evaluated use of continuous passive motion (CPM) to minimise joint stiffness and improve range of movement. Studies were conducted in single centres in Australia and Turkey with participant recruitment between 1997 and 2004 and both had three trial arms. Sample sizes were 90 and 147 participants. The mean ages of participants in studies were about 63 and 72 years and a majority of participants were women. In one study, 90 participants were randomised to no CPM, CPM at low flexion from post-operative day 1–7, or

CPM at high flexion from post-operative day 3–7[68]. There was no significant difference between groups in KSS at two years. In the other study, 147 participants were randomised to CPM with increasing range of movement from day 1–6, early flexion CPM from day 0–6, or no CPM[67]. There were no significant differences between groups in KSS at 12 months.

Electrical stimulation

Two RCTs with 106 participants conducted in single centres in Greece and Italy evaluated electrical stimulation which is believed to have anti-inflammatory activity and limit muscle atrophy. Studies included 76 and 30 participants recruited between 2005 and 2010. The mean ages of participants were 71 and 70 years and in one study that reported it, a majority of participants were female.

In one study with 76 participants receiving transcutaneous electric muscle stimulation from postoperative day two for six weeks or no intervention, Short Form 36 bodily pain showed strong evidence for greater improvement at one year in the intervention group compared to control (p<0.001)[69]. The difference in means of 12.5/100 was close to the MCID of 16.9/100 reported by Escobar and colleagues[82]. There were no differences in OKS or KSS scores. In another study with 30 participants, pulsed electromagnetic fields from post-operative day 7 were compared with untreated control[70]. At 12 months, there was some evidence that VAS-rated pain was lower in intervention patients compared with controls (p<0.05). The difference in means of 2.1/10 was greater than the MCID of 16.1/100 reported by Danoff and colleagues[83]. Knee swelling was common during the intervention.

Rehabilitation

Four RCTs with 585 participants recruited between 2000 and 2016 evaluated features of early rehabilitation focusing on regaining range of movement, functional independence and improving mobility. Two studies were conducted at single centres in China and at two and four centres in Canada and Germany respectively. Sample sizes ranged from 80 to 234 participants, with a median of 136. The range of mean ages of participants in randomised groups was 68 to 78 years and in 3/4 studies, a majority of participants were women.

Walking guidance and training

In one study, 86 participants were randomised to walking guidance and training from postoperative day two or no intervention further to standard rehabilitation[71]. At six months, there was some evidence that those receiving intervention had lower VAS-rated pain (p<0.01) and HSS score (p<0.01) than controls. The difference in mean VAS-rated pain of 2.4/10 was greater than the MCID of 16.1/100.

Flexion or extension during knee closure

Targeting improved functional recovery, wound closure performed in 90° flexion was compared with wound closure in full extension in one study with 80 participants[74]. There was no difference between groups in VAS-rated pain at six months.

Aquatic therapy

In one study with 185 participants, aquatic therapy commencing on post-operative day six was compared with aquatic therapy commencing on day 14[72]. Patients reported similar WOMAC pain at 12 and 24 months.

Supported early discharge

In one study, early discharge supported by physiotherapist home visits and outpatient or selfdirected physiotherapy was compared with two weeks of rehabilitation centre-based usual care[73]. The study included 234 individuals receiving TKR or total hip replacement. Compared with usual care, there was weak evidence that patients with early discharge had lower WOMAC pain scores at 12 months (p=0.08). The difference in means of 4 was less than the MCID of 8-9/100. Results were not presented separately but did not differ between patients with TKR or total hip replacement.

Anabolic steroids

Searches identified one study of anabolic steroids to improve post-operative muscle strength conducted in one centre in Australia with recruitment of 10 participants before 2010. The mean age of participants was about 66 years and a minority were women. Participants received intramuscular nandrolone injections or saline from post-operative day five for six months. KSS results indicated some evidence for improvement in the intervention group compared with controls at 12 months (p=0.03)[76]. The difference in means of 10.2/200 was close to the MCID of 12.3/200.

Interventions with no long-term outcome

Interventions with lack of RCT evidence are summarised in Figure 1.

While 148 RCTs of DVT prophylaxis were identified, only five reported long-term follow up, none of which included a pain or outcome score. Among 29 RCTs of antibiotic prophylaxis, 16

reported long-term follow up, but none included a pain or outcome score. Six RCTs evaluated the use of bisphosphonates and, although all reported long-term follow up, none reported pain or an outcome score. One study reported long-term follow up of an RCT of teriparatide but included no data on pain.

For some interventions, RCTs with long-term pain outcomes were identified, but none were at low risk of bias: cold therapy; guided imagery; platelet rich plasma; and trigger point needling.

Aspects of peri-operative care evaluated in RCTs but lacking long-term pain follow up were: adenosine triphosphate; alternative and Chinese medicine; assistive devices; brain stimulation; calcium supplements; cardiovascular drugs; colloids and crystalloids; comorbidity management; constipation treatment; creatine; delirium prevention; dexmedetomidine; glucocorticoids; glucose infusion; iron; laser therapy; methylprednisolone; music therapy; nausea prevention; nutritional supplements; physiological treatments; remote ischaemic preconditioning; sleep treatments; therapy dogs; and warming.

DISCUSSION

Much research in TKR aims to identify treatments that facilitate a speedy recovery with minimal short-term pain. However, patients choose to have joint replacement for long-term pain relief and reduction in functional limitations. Thus, changes to peri-operative care, supported by short-term RCT evidence, should be backed up with evidence about long-term effectiveness for reducing pain and reassurance that there are no long-term unfavourable consequences. To this end, we synthesised evidence from RCTs evaluating peri-operative interventions which have considered their long-term effects on pain outcomes.

Consistent with its status as a key peri-operative risk factor, a major focus of research into improving long-term pain after TKR has been through prevention of acute post-operative pain using multimodal analgesia. Our review provides good quality evidence for a small benefit for intra-articular LIA injections, as previously shown in short-term studies[31,84], oral pregabalin, oral opioids, and in relation to neuropathic pain, ketamine infusion. As well as potential benefits for reduced long-term pain, future studies will need to consider concerns associated with these interventions which may not have been identified in small studies including infection[31], venous thromboembolism[39] and sedation[53].

Nerve blocks are effective for managing peri-operative pain[85] but we identified no long-term benefit. In single studies, there was no benefit for nefopam infusion, oral celecoxib or LIA with additional corticosteroid. Regarding future studies, standardisation of the multi-modal regimen

will allow evaluation of extra or alternative components in multiple studies in different settings. With such an approach, convincing evidence will accrue to guide multimodal pain management.

Some interventions targeted the prevention of adverse events and facilitation of early mobilisation. Tranexamic acid is highly effective in reducing blood transfusions during TKR[86] and we found no evidence that tranexamic acid affects long-term pain or, consistent with registry studies[87,88], adverse events. Single RCTs of thrombin infusion and maintenance of knee in flexion to prevent blood loss showed no effect on long-term pain. Tourniquets improve intraoperative visualisation of the joint, reduce blood loss and facilitate cement fixation but are associated with nerve damage, delayed recovery, acute pain and need for analgesics[89,90]. The RCTs we identified showed no effects of tourniquet use on long-term pain.

As shown in a previous review[91], there was no suggestion that CPM affects long-term pain. There was good quality evidence for a small benefit for reduced long-term pain in patients receiving walking training, anabolic steroid injection, electrical stimulation and supported discharge.

For some interventions a direct mechanism is clear, but for others, reasons for long-term impact are less obvious. This may explain why, for example, no studies evaluated DVT prophylaxis with long-term follow up excepting a small number reporting adverse events. However, treatments to prevent symptomatic DVTs which occur in about 1% of treated patients[92] also reduce the incidence of asymptomatic DVT observed in about 28% of treated patients[93] and this may have long-term benefits. Conversely, new anticoagulants are associated with bleeding[94], which may increase the risk of wound complications[95] and joint infection[96] which are associated with long-term pain[97,98].

Our study is limited by the lack of meta-analysis which was not appropriate due to intervention and outcome heterogeneity. In the context of perioperative pain management, this was noted previously[84]. Our approach to assessing the evidence was a narrative synthesis of studies with low risk of bias. While this may seem overly restrictive, Cochrane risk of bias assessment allows us to screen out studies with important issues that may affect the validity of results. The main potential source of bias was incomplete outcome assessment. Although studies with longterm follow up are naturally at higher risk of missing data, we maintained a standard in this domain as it is recognised that research participants who do not complete follow up assessments differ in outcomes from those with follow up data and their inclusion could change the interpretation of results[99].

Another limitation is that pain assessed with questionnaires does not take into account the effect of pain medications and assistive aids. About 58% of women and 40% of men report taking pain medications after TKR because of pain in the operated knee[100] and we must recognise that pain levels at follow up without this treatment might be considerably higher. Even with treatment, around 20% of patients report chronic pain after TKR[10] and in the context of a blinded RCT we should expect to be able to identify effects of peri-operative treatments.

We summarised p-values to assess the strength of evidence but, as statistically strong evidence may not reflect clinically important results[101], where possible we also compared effect sizes with MCIDs. Our review considered a diverse range of interventions at a specific time in the TKR pathway and, as we were unable to make clinical practice recommendations, we did not adopt the GRADE system[102] for this review.

An alternative approach to the prevention of chronic pain after TKR is the individualisation of care based on pain phenotype, genetic, psychosocial and other factors[103]. An example of this might be the peri-operative treatment only of individuals with neuropathic pain with pregabalin, as opposed to the non-stratified provision in the RCT of Buvanendran and colleagues[53]. In an RCT with pregabalin provided to patients with painful HIV-neuropathy, while no overall benefit was seen, a group with hyperalgesia responded to pregabalin treatment[104].

Our systematic review of peri-operative interventions brings together evidence on interventions in the peri-operative phase of the TKR pathway. There was good quality evidence for some interventions of a small benefit for reduced long-term pain, and whilst not supportive of the inclusion of specific interventions in clinical practice, there are clearly areas that merit research. High quality studies assessing long-term pain after peri-operative interventions are feasible and necessary to ensure that patients with osteoarthritis achieve good long-term outcomes after TKR.

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AUTHOR CONTRIBUTIONS

All authors, ADB, JD, RG-H and AWB, contributed to the conception and design of the study. ADB, JD and VW undertook the systematic review. ADB and JD carried out the risk of bias assessments. ADB drafted the article with revisions by JD, VW, RG-H and AWB. All authors approved the final version for publication.

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COMPETING INTERESTS STATEMENT

The authors report no competing interests.

DATA STATEMENT

All data relevant to the study are included in the article or uploaded as supplementary 1.en information.

Legend

Figure 1. Systematic review flow diagram

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dentification	Articles identified in searches of <i>The Cochrane Library</i> , MEDLINE, Embase PsycINFO and CINAHL from inception to February 2018 (n = 9697)								ise,	
				•						
Screening		Artic	les scree	ened (n = 90	697)		No re	levance	(n = 736	64)
				+						
Eligibility		Potentially relevant (n = 2333)								
		. .		•						
Intervention	N	In: low risk of bias	No pain/ score outcome	High/ unclear risk of bias	No long- term follow up	Abstract only	Additional publication	Protocol	Review	Ret
Adenosine triphosphate	2	0	0	0	1 1	0	0	0	1	
Alternative medicine	4	0	0	0	4	0	0	0	0	
Anabolic steroids	2	1	0	0	0	0	0	0	1	
Antibiotic prophylaxis	43	0	16	0	13	0	0	1	13	
Assistive devices	2	0	0	0	2	0	0	0	0	
Bisphosphonates	17	0	6	0	0	0	2	0	9	
Blood management	355	7	10	1	209	0	0	4	124	
Brain stimulation	3	0	0	0	3	0	0	0	0	
Calcium supplement	1	0	0	0	1	0	0	0	0	
Cardiovascular drugs	4	0	0	0	2	0	0	0	2	
Chinese medicine	2 30	0	0	0	2 24	0	0	0	0	
Cold therapy	30	0	0	1	24	0	0	0	5 0	
Colloids and crystalloids Comorbidity management	1	0	0	0	1	0	0	0	0	
Compression	8	1	0	0	6	0	0	0	0	
Constipation treatment	2	0	0	0	2	0	0	0	0	
Continuous passive motion	56	2	8	7	23	1	0	1	14	
Creatine monohydrate	1	0	0	0	1	0	0	0	0	
Delirium prevention	4	0	0	0	3	0	0	0	1	
Denusomab	1	1	0	ů 0	0	0	0	0	0	
Dexmedetomidine	1	0	0	0	1	0	0	0	0	
Deep vein thrombosis prophylaxis	474	0	5	0	143	0	4	8	314	
Electrical stimulation	37	2	0	3	20	0	2	0	10	
Glucocorticoid	2	0	0	0	0	0	0	0	2	
Glucose infusion	1	0	0	0	1	0	0	0	0	
Guided imagery	5	0	0	1	4	0	0	0	0	
Iron	7	0	0	0	6	0	0	0	1	
Laser therapy	1	0	0	0	1	0	0	0	0	
Methylprednisolone	3	0	0	0	3	0	0	0	0	
Music therapy	9	0	0	0	9	0	0	0	0	
Nausea prevention	11	0	0	0	9	0	2	0	0	
Nutritional supplements	4 987	0 20	0	0 12	4 711	0	0 20	0 9	0 207	
Pain management Physiological	26	20	5 0	0	23	0	20	9	207	
Platelet rich plasma	12	0	0	1	6	0	0	0	5	
Rehabilitation	67	4	0	2	43	0	0	0	17	
Remote ischaemic pre-conditioning	5	0	0	0	43	0	0	0	0	
Sleep treatment	3	0	0	0	2	0	1	0	0	
Teriparatide	1	0	1	0	0	0	0	0	0	
Therapy dogs	1	0	0	0	1	0	0	0	0	1
Tourniquet use	100	5	3	3	67	0	2	1	19	1
Trigger point needling	1	0	0	1	0	0	0	0	0	
Warming	19	0 0	0 0	0	16	0	0	0	3	
Wound management	17	1	0	0	12	0	0	1	3	
Total	2333	44	54	32	1385	2	33	28	753	

Supplementary material. Search strategy as applied in MEDLINE on Ovid

- 1 randomized controlled trial/ or randomized controlled trial.pt.
- 2 controlled clinical trial.pt.
- 3 randomized.ab.
- 4 placebo.ab.
- 5 randomly.ab
- 6 trial.ab
- 7 randomised.tw
- 8 1 or 2 or 3 or 4 or 5 or 6 or 7

9 review/

- 10 'systematic review\$'.mp
- 11 9 or 10
- 12 8 or 11
- 13 Arthroplasty, Replacement, Knee/
- 14 Knee Prosthesis/

15 (arthoplast\$ adj3 knee\$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

16 (knee\$ adj3 replac\$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

17 (knee adj3 implant\$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

18 13 or 14 or 15 or 16 or 17

19 12 and 18

Supplementary material. All peri-operative interventions with long-term pain or score follow up

1. Pain management

Author	Indication	Common anaesthe	esia			Follow up
Country Recruitment dates Setting Number randomised intervention; control Age % female		Group 1 (intervention) Group 2 (intervention) Group C (control)		Losses to follow up intervention control Risk of bias issues Key results		
FNB single vs No F	NB	6				
Widmer et al. 2012[43] Australia Before 2012 2 surgeons	Elective primary unilateral TKR 27; 28 Median 72.1 (IQR 64.4, 76.5); 69.4 (63.4, 75.5) 44.4%; 44.4%	Premedication 1-3mg i.v. midazolam. Propofol induction and sevoflurane general anaesthetic.LIA with 200mg ropivacaine and 0.5mg adrenaline in 100ml saline.PCA 20µg fentanyl at 5-minute intervals on demand until morning POD2. Then, oral oxycodone SR 10mg every 12 hours. Daily COX II inhibitor and paracetamol 1g every 6 hours as tolerated. For breakthrough pain, 5-10mg oxycodone immediate release every 3 hours as needed.Ultrasound guided FNB with 100mg ropivacaine in 30ml salineSham setup for FNB. No identification or injection of femoral sheath				1 year No losses to follow up reported Low risk of bias WOMAC pain (high score favourable) at 1 year: FNB and LIA median 2.0 (IQR 0, 2.8); LIA no FNB 1.0 (0, 2.0). p=0.74 No adverse events occurred in either group
FNB single vs ONB		T				
Bergeron et al. 2009[105] Canada 2005-2006 1 centre	Elective primary unilateral TKR 19; 20; 20 Mean 65.1 (SE 2.0); 72 (1.8); 67 (1.3) 79%; 80%; 75%	Intraoperative sedation with iv propofol at discretion of anaesthesiologist. Lumbar spinal anaesthesia with 12mg 0.5% bupivacaine. Postoperative i.v. PCA with fentanyl 50µg/ml set to deliver 25µg every 5 min as needed. Celecoxib 100mg and acetaminophen 650mg on arrival in recovery room and every 12 and 6 hrs respectively. Breakthrough medication with intramuscular ketorolac 10 mg every 4 hrs.			1 year Overall 32 lost to follow up High risk of bias: only 27/59 patients followed up due to resource limitations. No difference in HSS pain at rest or during activity at 1 year between the study groups.	

		FNB with stimulator. 20ml 0.5% bupivacaine with 1/200,000 epinephrine.	ONB with stimulator. 20ml 0.5% bupivacaine with 1/200,000 epinephrine.	No injection but inguinal area prepared, and sham block performed behind drapes.	No long-term complications attributable to anaesthetic regimen
FNB continuous lo	w dose vs FNB continu	ious high dose vs No	o FNB		
Shum et al. 2009[106] Singapore Before 2009 1 hospital	Unilateral TKR for osteoarthritis 20 (17 received treatment); 20 (18 received treatment); 20 Mean 66.7 (SD 8.4); 65.4 (8.4); 67.8 (5.5) 88%; 72%; 80%	bupivacaine. Intraop increments of 0.5mg Intravenous PCA mo doses of 1 mg with 5 mg/hr) Low dose continuous FNB at conclusion of TKR with ropivacaine 0.15% (10 ml/hr in the first 24 hours, followed by 5ml/hr in the next 24 hours)	orphine (1mg/ml, on-co minute lockout, max	midazolam in demand bolus	2 years 16.4% of patients who received intervention lost to follow up Unclear risk of bias due to differences in OKS and weight at baseline, and limited methodologica details. No separate pain outcome but mean OKS slightly more favourable in group with no FNB, 18.2 (SD 3.7) compared with combined FNB groups, 19.8 (5.4) but this was not significant. No complications attributable to use of FNB
SNB injection vs S	NB continuous vs con	rol		0	
Wegener et al. 2013[42] The Netherlands 2008-2010 1 centre	Unilateral TKR 29; 30; 30 (90 randomised) Median 65 (range 43-81); 66 (43-83); 62 (50-79) 62%; 70%; 73%	Lorazepam 1mg 2 hours and acetaminophen 2g 1 hour before surgery. FNB with stimulating catheter: loading dose 20 ml levobupivacaine 0.375% and after 45 minutes a continuous infusion of levobupivacaine 0.125% 10 ml/hr. General anaesthesia induced with 3-5 μg/ml propofol infusion and remifentanil 0.5 μg/kg/min and maintained with 2-3 μg/ml at 0.1-0.25 μg/kg/min. Postoperatively, FNB changed to patient controlled FNB, 5ml bolus, 30-minute lockout; basal rate 6 ml/hr. i.v. morphine administered if needed. Postoperative analgesia with acetaminophen 1g 4 times daily. Diclofenac 50mg or tramadol 50mg 3 times daily. Tramadol 100mg before removal of nerve catheters. Morphine pain relief as required.			12 months 2;7;5 lost to follow up Low risk of bias Median WOMAC pain scores at 12 months: SNB injection 80 (range 25- 100), SNB continuous 90 (55-100) and PCA only 90 (35-100), p=0.81. No difference between groups in VAS pain at rest (p=0.90) or during mobilisation (p=0.43). No information on adverse events.

Concrol anoorthooi	a vs FNB single vs FN	Group Fs: SNB single injection. SNB loading dose of 20 ml levobupivacaine 0.375%.	Group FCS: SNB continuous infusion. SNB loading dose of 20 ml levobupivacaine 0.375%. Continuous infusion of levobupivacaine 0.125% 10 ml/hr started 45 mins after catheter placement. SNB maintained for 36 hours postoperatively (10 ml/hr).	Group F: No SNB. PCA via femoral nerve catheter	
Gao et al. 2017[37] China 2014-2015 1 centre	Primary unilateral TKR for osteoarthritis 50; 50; 50 Mean 65.8 (SD 6.7); 66.4 (7.4); 67.6 (6.3) 81%; 80%; 76%	Pre-operative and p daily.	oost-operative celecox ve LIA with ropivacain g. Ultrasound guided FNB 5g/l ropivacaine 20ml plus 0.1mg epinephrine	-	6 months 2; 1; 0 Low risk of bias Mean HSS at 6 months: 87.1 (SD 6.9); 87.4 (7.3); 88.5 (6.7). No significant difference. Nausea and vomiting: 4; 2; 1, urinary retention: 3; 1; 2.
<i>LIA no corticostero</i> Wylde et al. 2015 [50] UK	<i>id vs No LIA/ placebo</i> Primary unilateral TKR for osteoarthritis	FNB with nerve stimulator and/ or ultrasound guidance (20ml 0.25% bupivacaine). Spinal or general anaesthetic. Intra-operative analgesia provided by titration of i.v. fentanyl initially and morphine if necessary. 1g intravenous			6 and 12 months 24;19 at 12 months (including those who did not receive treatment)

2009-2012	157; 159 (143; 137	paracetamol 30 minutes before the end of operation.	Low risk of bias
1 centre	received treatment) Mean 69.5 (SD 9.4); 68.7 (7.9) 52%; 54%	Immediately post-operative 400mg oral ibuprofen.PCA with morphine 1mg/ml, 1 mg bolus dose and a 5- minute lock-out. If necessary morphine bolus up to 0.2mg/kg as rescue analgesia. During hospital stay, visit from pain specialist nurse. Oral or i.v. paracetamol every hours and ibuprofen 400mg every 8 hours. When PCA no longer needed, oral codeine phosphate 30-60mg every 6 hours, tramadol 50-100mg every 6 hours and oramorph 10-20mg as rescue analgesia.60ml intra-operative LIA with 0.25% bupivacaine and 1/200,000 adrenaline 	At 12 months WOMAC pain score (0 100) in LIA group median 90 (IQR 30), Control 85 (35); ITT-CC linear regression coefficient 3.83 (95%CI - 0.83, 8.49), p=0.107. At 6 months
Williams et al. 2013[49] Canada Before 2013 1 centre, 2 surgeons	Primary unilateral TKR for osteoarthritis 35; 32 (26; 25 received treatment) Mean 66 (SD 9.7); 67 (12.5) 58%; 60%	Sedation with i.v. midazolam and propofol. Intraoperative LIA loading dose of 20ml 0.25% bupivacaine/ epinephrine injection, 10ml into medial and lateral subcutaneous tissu around the incision and 10ml intra-articular after closure. Infiltrate delivered by pain pump into lateral recess of intra articular space. Spinal anaesthetic with 10-15 mg of 0.75° or 0.5% plain bupivacaine and 20µg fentanyl. Postoperative morphine PCA. 7.5mg i.v ketorolac preoperatively plus 15mg every 6 hours postoperatively for 48 hours, then oral ketorolac 10mg every 6 hours for 2 days. Gabapentin 600mg given preoperatively plus 300m twice daily for 48 hours postoperative. Oral paracetamol 650mg every 4 hours for 72 hours. Infusion of 0.5% bupivacaine at 2ml/hr for 48 hrs	 3;1 of those who received treatment Low risk of bias Mean VAS pain score at 6 months 1.2 (SD 1.3); 1.2 (1.2). p=0.836. At 12 months 0.9 (1.2); 1.0 (1.1). p=0.767 No short-term differences in adverse events except control patients more likely to be drowsy at 48 hrs. Long- term adverse events not reported.
Niemeläinen et al. 2014[47] Finland 2011-2012	Primary unilateral TKR for osteoarthritis 30; 30 (27; 29 received treatment)	Oral paracetamol 1g given 1 hour before surgery. Spinal anaesthesia with 15mg bupivacaine in 3ml. After surgery oral paracetamol 1g every 6 hours and oral meloxicam (15mg) every 24 hours. PCA with oxycodone 2mg, lock-out time 8 min.	12 months 1; 4 Low risk of bias No pain measure separate from OKS Weak evidence of more favourable

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1 hospital	Mean 65 (SD 4.9); 64 (6.7)	Rescue levobupivacaine medic epidural catheter	ation through a lumbar	OKS (0-48) in the LIA group at 12 months, mean difference -2.7 (95%	
	56%; 48%	Intra-operative periarticular LIA of 100ml saline with levobupivacaine (150mg) mixed with ketorolac (30mg) and adrenaline (0.5mg).	Intra-operative periarticular LIA of 100ml saline	CI -5.48, 0.07). Difference lower than MCID of 4.0[78]. Infection: 0; 0. Severe pain treated with epidural analgesia: 0; 3. Nausea 1; 1	
Motififard et al. 2017[46]Primary unilateral TKR for osteoarthritis 60; 601 hospitalMean 66.4 (6.4); 64.5 (6.0) 86.0%; 94.3%		Spinal anaesthesia. No FNB or SNB. Pain medication provided as remeloxicam (15 mg daily), celect acetaminophen (1g every 8 hours), ketorolac (30 mg slow dose max), and morphine (5–1 Peri-articular injection, 15 minutes before incision, of 100ml saline containing 50 mg bupivacaine hydrochloride 0.5%, 1 ml morphine sulphate 10 mg/ml, 300 µg epinephrine (1:1000) and 30 mg ketorolac	6 months 3; 7 Low risk of bias No separate pain measure. Weak evidence for improved KSS (0-200) LIA group at 6 months, mean 115.55 (SD 15.506); 101.40 (16.117). P=0.07. Difference of 14.15 greater than MCID of 12.3[79]. Difference was significant at 6 weeks, p<0.001. No complications related to TKR or LIA. Low back pain (1; 2), stroke (0; 1), CHF (1; 0)		
McDonald et al. 2016[45] UK 2010-2011 1 hospital	Primary unilateral TKR for osteoarthritis 113; 109 received common spinal anaesthesia (121; 121 randomised) Median 68 (IQR 62, 72); 67 (62, 73) 59%; 55%	Oral premedication with 10-20r ranatidine, 10mg dexamethaso paracetamol. Spinal anaesthesia Intra-articular and subcutaneous infiltration during surgery of 200 ml of 2mg/ml ropivacaine without adrenalin or additives. Catheter inserted, and 20 ml infiltrate injected following wound closure. Further boluses of 40 ml 2 mg/ml ropivacaine via infusion pump 4 hours after leaving theatre and morning of POD1. Two		12 months 9; 11 of those receiving treatments Low risk of bias No separate pain outcome. Mean OKS at 12 months: median 41 (IQR 35, 44); 41 (34;44). P=0.915 Suspected infection 2; 1. MI 0; 1. GI bleed 1; 0. renal failure 1; 0. Died 2; 0)	

Celecoxib vs placeb	0	additional top ups of 40 ml 2mg/ml ropivacaine were prescribed if required.		
Meunier et al. 2007[51] Sweden 2004-2005 1 centre	Elective primary unilateral TKR for osteoarthritis 25; 25 (24; 20 received treatment) Mean 68 (SD 6.3); 69 (7.7) 71%; 40%	Spinal anaesthesia with bupiva midazolam or propofol sedation preoperatively and then with tra day during hospital stay. Ketob subcutaneous) on demand. Pa used as required after discharg Oral celecoxib 200mg 1 hour preoperatively and twice daily for 3 weeks	12 months No losses to follow up after surgery reported Low risk of bias No effect of celecoxib on VAS or KOOS pain at 1 year. DVT: 0; 1. Deep infection: 0; 0.	
Ketamine vs placebo Perrin and Purcell2009 [107] Australia Before 2009 1 centre (pilot study)	D Elective unilateral TKR 16 (5; 7 completed study per protocol) Mean 65.6 (SD 10.2); 60.3 (11.9) 40%; 43%	morphine. General anaesthesia. After surgery 1.5gparacetamol and then 750mg every 4 hours; PCA withmorphine 2mg boluses with 10-minute lockout; morphinerescue 2.5mg intravenously as required; and rescue oralibuprofen 800mg.Ketamine 0.5mg/kg bolusfollowed by 4ug/kg/min		6 months 3 protocol breaches and 1 patient with uncontrolled pain. High risk of bias due to non-ITT reporting and recruitment difficulties 2/5 ketamine group had mild/moderate pain on the WOMAC pain scale at 26 weeks or failed to improve compared with 5/7 controls. 1 adverse psycho-mimetic effect not attributed to intervention or control treatment
Ketamine vs Nefopa Aveline et al. 2014[52] France 2005 1 centre	m vs placebo Elective primary unilateral TKR for osteoarthritis 25; 25; 25 Mean 73 (SD 9); 72 (9); 70 (7) 67%; 60%; 63%	General anaesthesia induced v 1µ/kg remifentanil and a single 0.15mg/kg. Remifentanil infusio closure. Anaesthesia maintaine 1.2% with 50% nitrogen in oxyg closure, 0.15mg/kg i.v. morphine droperidol. PCA with morphine bolus with 7-min lockout. On ar i.v. morphine boluses at 5 minu	6 and 12 months 3; 1; 2 Low risk of bias Median DN4 at 12 months: 1 (IQR 1, 2); 1 (0, 1); 2 (1, 3). p=0.02 for difference between ketamine and placebo groups. Number of patients with VAS pain on movement score	

	6	0.2mg/kg nefopam administered over 20 min before incision; 2mg/ml nefopam continuous infusion at 120µg/kg/hr until end of surgery and 60µg/kg/hr for 48 hours	0.2mg/kg ketamine administered 20 min befo incision; 2m ketamine continuous infusion at 120µg/kg/hr end of surge and 60µg/kg for 48 hours	d over 2 re ir g/ml c until ery g/hr	Saline administered over 20 minutes before ncision; saline continuous infusion until second post- operative day	 ≥40mm at 12 months by group: nefopam (3/22, 13.7%), ketamine (3/24, 12.5%), and placebo group (6/23, 26.1%). Ketamine reduced DN4 pain (p=0.02) compared with placebo. At 12 months only 7/69 patients had DN4≥4 indicative of neuropathic pain. Infection: 0; 0; 0. Revision: 0; 0; 0.
Pregabalin vs place	bo			·		
Buvanendran et al. 2010[53] USA 2006-2007 Single centre	Primary unilateral TKR for osteoarthritis. 120; 120 (9; 2 did not receive post- operative treatment but ITT analysis) Mean 64.0 (SD 8.3); 63.3 (8.9) 76%; 70%	Sedation with midazolam and i.v. propofol. Combined spinal-epidural anaesthetic. 1.5ml 0.75% hyperbaric bupivacaine with 25µg fentanyl injected intrathecally. Catheter inserted for epidural drug administration. LIA 60 ml 0.25% bupivacaine with epinephrine infiltrated into the wound at capsule closure. From completion of surgery until 32-42 hours post-operative, epidural infusion of fentanyl (5µg/ml) and bupivacaine (1mg/ml) initiated using continuous basal infusion of 6ml/hr with epidural PCA bolus doses (maximum 10ml/hr). Patients transitioned to oral opioid (morphine, oxycodone, and hydromorphone) as required. All patients received preoperative oral celecoxib 400mg 1–2 hours before surgery and 200mg twice daily for 3 days in hospital.				6 months 7; 5 Low risk of bias Mean VRS pain score at 6 months: pregabalin 0.41 (SD 1.20); control 0.95 (1.80). p=0.0084. Distributions skewed but nonparametric Wilcoxon significant (p=0.0176). Difference of 0.54 less than MCID of 1.0. In the pregabalin group the incidence of neuropathic pain measured using S-LANSS was 0% (0/113) and 5.2% (6/115) in the placebo group
		Oral pregabalin 3 h before surgery, twice daily for the postoperative day twice daily on day 12, and 50mg twi days 13 and 14	150mg first 10 /s, 75mg /s 11 and	surgery, t first 10 po twice dail <u>y</u>	ebo 1–2 h before wice daily for the ostoperative days, y on days 11 and wice daily on days 4	(p=0.014). No clinically significant adverse events up to 6 months and no falls. Sedation, confusion and dry mouth more frequent in pregabalin than placebo group on day of surgery an first postoperative day.

Ilfeld et al. 2009[108] USA 2005-2007 2 centres	Primary unilateral TKR for osteoarthritis 25; 25 Median 66 (IQR 60, 70); 64 (60, 69) 56%; 60%	Femoral catheter inserted using 0.2% ropivacaine infusion (8ml controlled bolus; 30-minute loc POD1. 1 week oral acetaminophen (97 sustained release oral opioid (0 hours), and either oral aspirin ((200mg every 12 hours). Oral c or i.v. morphine sulfate 2-4 mg At 6 a.m. POD1, infusion pump replaced with infusion pump with 0.2% ropivacaine. At 6 p.m. POD2 pump replaced with portable	/hr basal; 4 ml patient- kout) from surgery until a.m. 75mg every 6 hours), Dxycontin, 10mg every 12 650mg daily) or celecoxib pxycodone 5 mg tablets and/	6 and 12 months 4; 1 lost to follow up High risk of bias: uneven loss to follow up between groups; muscle weakness resulted in lower dose of infusion on POD1 (10 continuous; 3 saline) Groups had similar WOMAC pain scores at 6 and 12 months (p>0.05). MI: 1; 0. PE: 1; 0. Fall: 1; 0. Catheter leak, dislodged: 1; 2		
llfeld et al. 2011[109] USA 2007-2009 2 centres	Primary unilateral cemented TKR for osteoarthritis 40; 40 (39; 38 included in RCT) Median 61 (IQR 58, 67); 66 (60, 70) 67%; 66%	Teplaced with portableTeplaced with portableinfusion pump (400ml 0.2% ropivacaine). Catheter removed evening of POD4.infusion pump (saline). Catheter removed evening of POD4Femoral catheter inserted using nerve stimulator. FNB with 0.2% ropivacaine infusion (6ml/hr basal; 4ml patient- controlled bolus; 30-min lockout) from surgery until POD1. 1 week oral acetaminophen (975mg every 6 hours), sustained release oral opioid (Oxycontin, 10mg every 12 hours), and either oral aspirin (650mg daily) or celecoxib (200mg every 12 hours). Oral (oxycodone 5mg or 10mg tablets) and/ or i.v. opioids (morphine sulfate 2-4mg) for breakthrough pain.		12 months 11; 12 incomplete follow up High risk of bias: 11;12 did not have 4 measures out of 6 up to 12 months; graph suggests WOMAC pain lower pre-intervention in continuous infusion group. No difference in WOMAC pain		
		At 6 a.m. POD2, infusion pump replaced and 0.2% ropivacaine continued. At 6 p.m. POD2 pump replaced with portable infusion pump (400ml 0.2% ropivacaine). Catheter removed evening of POD4	At 6 a.m. POD2, infusion pump replaced but saline substituted. At 6 p.m. POD2 pump replaced with portable infusion pump (saline). Catheter removed evening of POD4	 scores between randomised group (p>0.05). Falls: 4; 0 		
Choy et al. 2011[35] Korea 2006-2007	Primary unilateral TKR for osteoarthritis	Spinal anaesthesia. Continuous POD3. Catheter inserted with u Analgesia induced with 20ml of 2% lidocaine with 1:200,000 ep	s FNB via catheter until se of nerve stimulator. f 1:1 0.25% bupivacaine and	2 years 4; 3 lost to follow up		

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1 surgeon 33; 30 (2 patients received GA and excluded) Mean 66.7 (SD 10); 67.5 (11)		infusion with 0.125% bu (butorphanol 4mg, keto programmed to deliver maximum dose 6mg/hr oral ibuprofen 600mg 3	rolac 150mg, 1 mg bolus (lo . i.v. paracetar times/ day for	Low risk of bias for 2 year outcome measures. At 2 years, intervention WOMAC pain mean 7.2 (SD 2), control 6.3 (SD 1); p=0.2		
97%; 93%	97%; 93%					Superficial infection: 1; 1
FNB continuous Albrecht et al. 2014[34] Canada 2009-2011 1 hospital	high concentration vs Fi Scheduled primary unilateral TKR 32; 32; 35 Mean 61 (Cl 57, 64); 63 (60, 67);63 (60, 66) 46%; 44%; 52%	VB low concentration v Stimulating catheter ins Immediately after cathe was injected through th ropivacaine 0.2%. Spin- isobaric bupivacaine 0.3 Bolus of 20ml ropivacaine 0.2% with epinephrine 1:400,000 into the femoral catheter followed by ropivacaine 0.2% at a rate of 5 ml/hr with patient-controlled boluses of 5ml available every 30minutes.	Bolus of 20 r ropivacaine 0.2% with epinephrine 1:400,000 in femoral cath followed by ropivacaine 0.1% at rate 10ml/hr with patient- controlled boluses of 10	rasour t, 10m NB usi a with g intra ml nto neter o f	I mepivacaine 2% ng 30 ml 2.5 to 3.0 ml thecal morphine. Bolus of 30ml ropivacaine 0.375% with epinephrine 1:400,000 into the femoral catheter followed by normal saline at a rate of 1 ml/hr with patient-controlled boluses of 1mL available every	12 months 4;0;2 lost to follow up Low risk of bias. No separate pain outcome. Mean WOMAC score at 12 months: high concentration FNB 17 (95% CI 7, 27); 22 (14, 30); 18 (8, 27). P=0.68 Falls: 0; 0; 1
FNB continuous			-	s com		
Morin et al. 2005[110] Germany Before 2005 1 centre	Elective unilateral TKR 30; 30; 30	block vs FNB continuous and psoas compartment block Oral pre-medication with 20mg chlorazepate. General anaesthesia with intravenous propofol and 4–8µg/kg i.v. fentanyl and desflurane in N2O. 100mg diclofenac suppository after anaesthesia induction and 2.5g intravenous metamizole before end of surgery. Post- operative 3 daily doses of oral diclofenac 50mg. i.v. PCA				9–12 months7; 6; 5High risk of bias due to large losse to follow up, non-blinded outcome collection, and differences betwee

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	Median 68 (IQR 62, 74); 71 (63, 74); 65 (53, 73) 50%; 70%; 59%	with piritramide bo 10 mins for 48 hou	olus 2mg as needed wit urs.	th lockout interval of	groups in BMI and anaesthetist's opinion of difficulty of catheter placement. No difference between groups in level of pain at the knee joint during past 4 weeks: FNB median 2.5 (IQF
	6	Continuous FNB Stimulating catheter used. Initial bolus of prilocaine 1% and ropivacaine 0.75%. 300mg prilocaine 1% (30ml) and 150mg ropivacaine 0.75% (20ml). During first 48hrs post- operative ropivacaine 0.2% infusion 14ml/hr.	Continuous FNB and continuous SNB Stimulating catheter used. Initial bolus of prilocaine 1% and ropivacaine 0.75%. In each catheter: 200mg prilocaine 1% (20ml) and 75mg ropivacaine 0.75% (10ml). During first 48hrs post-operative infusion through each catheter of 0.2% ropivacaine 7ml/hr.	Continuous psoas compartment block Stimulating catheter used. Initial bolus of prilocaine 1% and ropivacaine 0.75%. 300mg prilocaine 1% (30ml) and 150mg ropivacaine 0.75% (20ml). During first 48hrs post- operative ropivacaine 0.2% infusion 14ml/hr.	1, 4), FNB and SNB 2 (1, 4), Psoas block 2 (IQR 1, 4), p=0.44 No early complications but longer term adverse events not reported.
ACB continuous vs	FNB continuous				
Davidson et al. 2016[111] USA 2013-2014 2 studies combined from 1 centre	Primary, unilateral TKR or unicompartmental 54 (39 TKR, 16 UKR); 56 (41 TKR, 15 UKR) TKR mean 67 (SD 8); 66 (7). UKR 70 (10); 68 (12)	hydromorphone, a LIA with 30 ml rop epinephrine (5 µg/ Post-operative: or celecoxib (200 mg oxycodone (10 mg infusion pump bol titrated to pain sev	ivacaine (0.5%), ketoro	blac (30 mg), and o mg every 6 hr), tained release akthrough pain, out). Rescue opioid 2%) bolus was	12 months 31; 29 High risk of bias due to partial follow up TKR and UKR combined. Pain score (0-10) at 12 months median 0.0 (IQR 0.0, 3.0); 0.5 (0.0, 2.0). P=0.80). Pain score >0: 35%; 32%. P=0.65. No difference at 4 months when follow up more complete (51;

	TKR 59%; 66%. UKR 47%; 47%	Ultrasound guided ACB. Ropivacaine 0.2% at basal rate of 6 ml/hr, a 4-ml bolus, and a lockout of 30 minutes	Ultrasound guided continuous FNB. Ropivacaine 0.2% at basal rate of 6 ml/hr, a 4-ml bolus, and a lockout of 30 minutes	52) in pain score (p=0.80) or pain score >0 (p=0.48). Falls in hospital: 2; 5
ACB single vs FN Macrinici et al. 2017[38] USA Before 2017 1 centre	Primary unilateral TKR, indication not specified (selected by the surgeon for TKA) 49; 49	Multimodal regimen including I analgesics, opioids. LIA 40ml I All patients received an ultrasc into ACB and FNB sites. Immediately after surgery, 30ml solution with 100ml	Marcaine 0.25%. ound guided needle insertion Immediately after surgery, 30ml solution with 100ml	6 months 3; 4 lost to follow up. 6; 3 complications Low risk of bias VAS pain similar between groups a 6 months. No difference in
FNB continuous	Mean 67 (SD 8); 67 (8) 61%; 63% vs oral opioid	Marcaine into ACB site. 30 ml saline into FNB site	Marcaine into FNB site. 30 ml saline into ACB site	functional outcomes Medical complications: 3; 0. Surgical complication: 0; 1. Temporary foot drop: 3; 2.
Nader et al. 2012[39] USA 2007-2008 1 surgeon	Elective unilateral TKR 31; 31 Median (IQR) 65 (60, 76); 64 (60, 71) 58%; 77%	Before surgery, patients received needed. Epidural with 10mg 0. injected intrathecally. Intraoper infusion of 25-75mcg/kg/minute area, PCA epidural with basal bupivacaine and 10 mg/ml hydro- activated boluses of 3 ml with minutes and per hour maximum discontinued and epidural cath POD 1. All subjects received 5 surgery and 40 mg enoxaparing	5% isobaric bupivacaine rative sedation with propofol e. In post-anesthesia recovery infusion of 3 ml/hr (1 mg/ml Iromorphone) with patient- a lockout interval of 15 m of 15 ml. Infusion leter removed on morning of mg warfarin on evening of a starting on POD 1	6 and 12 months 1; 1 lost to follow up at 12 months Low risk of bias No difference in overall median NRS pain score at 6 months and 1 months: 0 (IQR 0, 1); 0 (0, 1). p=1.0. At 12 months, some evidence favouring hydrocodone for pain ascending/ descending stairs: 1 (0, 2); 0 (0, 0). p=0.01. Also, suggestion of reduced pain in
		Continuous FNB inserted with use of stimulator. After discontinuation of epidural anaesthesia on the morning of POD1 10mL bolus of ropivacaine 0.25% followed by 5ml/h infusion of 0.1% ropivacaine. On morning of POD 2, ropivacaine infusion	10 mg oral hydrocodone plus 325mg acetaminophen every 4-6 hours administered for pain as needed. Sustained release oxycodone 10mg for 12 hours with oral hydromorphone 2 mg over	hydrocodone group at night in bed (p=0.06) and sitting/ lying (p=0.07) standing upright (p=0.10). No difference walking on flat surface (p=0.41). Falls in month after surgery: 1;0. Positive joint aspirate: 3; 0. VTE: 0 4.

		discontinued. Femoral catheter removed 24 hours after previous dose of enoxaparin.	4 hours for breakthrough pain		
FNB continuous vs Wang et al. 2015[112] China 2012-2013	PCA Elective unilateral TKR 82; 86 No significant	General anaesthesia with mida fentanyl (1µg/kg), propofol (1-2 (0.15mg/kg). Anaesthesia mair during surgery. Intramuscular i	mg/kg) and cisatracurium ntained with sevoflurane njection with 10mg	6 and 12 months 2; 4 lost to follow up at 12 months Unclear risk of bias: limited reporting of randomisation method	
3 centres	differences in age or sex	metoclopramide and 2.5mg dro surgery. Post-surgery, celocoxi patients with severe pain, and i Continuous FNB with ultrasound stimulator. After surgery, 0.2% ropivacaine (20ml) injected through catheter. Then an analgesia pump was attached delivering 0.2% ropivacaine 8ml/hr.	No differences were observed between groups at 6 or 12 months for any HSS domain including pain. No nerve injuries		
Peng et al. 2014[40] China Before 2014 1 centre (2 surgical teams with 4 surgeons and 2 anaesthesiologists)	Primary unilateral TKR 140;140 Mean: 66.8 (SD 9.4); 68.0 (SD 11.2) 73%; 65%	General intravenous and inhala midazolam 0.1-0.15mg/kg (eto patients >65 years), propofol 2 0.3-1.0µg/kg, and vecuronium of anaesthesia. Maintenance w sevoflurane and continuous int remifentanil 7-8µg/kg/hr and pr wound closure, 5-10µg intraver dose of PCA injected. i.v. inject	midate 0.15-0.2mg/kg for .0-2.5mg/kg, sufentanil citrate 0.08-0.12mg/kg for induction rith inhalation of 1%-3% ravenous infusion of opofol 25-75µg/kg/min. After nous sufentanil and loading	6 and 12 months 31; 38 at 12 months Low risk of bias Chronic post-operative pain (NRS 1+) in 38.5% of PCA group at 6 months compared with 25.7% in FNB group (p=0.021). No difference at 12 months (p=0.273).	
		FNB with ultrasound guidance. Initial dose of 10ml 2% lidocaine and 10ml 1% ropivacaine. 30 minutes before end of operation, catheter connected to PCA pump; patients received loading dose of 5ml of 0.15% ropivacaine followed by infusion of 0.15% ropivacaine at 5ml/hr, with bolus of 5mL	i.v. PCA with tramadol 800mg, flurbiprofen axetil 100mg, and dexamethasone 5mg with saline to a volume of 80ml. Loading dose of 2ml followed by an infusion rate of 1 ml/hr with bolus of 2 ml. Lock time 15min.	Authors only reported short term adverse events associated with u of PCA.	

		and lock time of 30 min. Preoperatively, a loading dose of 30ml was injected for intraoperative analgesia.		
Wu and Wong 2014[44] China 2009-2011 1 centre	Unilateral elective TKR, 98% for osteoarthritis 40; 39 (30; 30 after post randomisation exclusions) Mean 68.8 (SD 6.4); 68.9 (7.5) 73%; 73%	Paracetamol, sustained releas (codeine or morphine). Spinal Catheter inserted under nerve stimulation and ultrasound guidance. Standardised bolus of 15 mL 0.5% levobupivacaine. Continuous infusion of 8 to 12 mL/h 0.08% levobupivacaine postoperatively until POD 3	anaesthesia Intravenous PCA morphine after the operation	6 months 2; 2 not pre- and peri-operative exclusions Low risk of bias No separate pain outcome but improvement of KSS from pre- operative was FNB 48.73 and PCA 44.7 (p=0.513) Including patients not followed up. Deaths: 0; 0. Infection: 1;1. DVT: 2; 3. Shock: 3;2. Transfusion: 2;3. Also from excluded cases. Atrial fibrillation and confusion: 0; 1. PE: 0; 1. Sepsis: 1;0. ICU admission for shock: 1; 0.
Anastase et al. 2014[113] Germany 2010-2011 1 centre	Primary unilateral TKR 55; 50 Mean 68.2 (SD 9.2); 69.7 (SD 8.7) 65%; 69%	Premedication with 10 mg ora anaesthesia with light sedation Supplemental postoperative a piritramid After spinal anaesthesia installed, SNB and FNB catheters inserted with ultrasound guidance. 5 ml bolus 0.2% ropivacaine. FNB with an hourly rate of 5 ml, bolus administration of 5 ml by the patient and the lock-out interval of 20 mins. SNB 5 ml/h to a maximum of 8 ml/h, 5 ml bolus	n: 12.5mg 0.5% bupivacaine.	6 and 12 months 15; 14 High risk of bias due to large loss to follow up Pain during previous 4 weeks: 1 no pain, 2 very little, 3 little, 4 moderate, 5 loud, 6 very loud (translation from German). No difference at 6 months p=0.37. At 12 months, FNB/SNB median 2.00 (1.00, 2.00), PCA 2.00 (2.00, 2.00) p=0.004 favouring FNB/SNB. No falls associated with quadriceps weakness. 6 and 12 month adverse

		and lock-out interval of 20 minutes.		
FNB single vs LIA		· · · ·		
Fan et al. 2016[36] China 2012-2014 Single hospital, 2 surgeons	Primary unilateral TKR (75% osteoarthritis; 25% rheumatoid arthritis) 80; 80 (78; 79 in analysis) Mean 68.4 (SD 8.8); 67.6 (6.3) 79%; 86%	General anaesthesia in all but surgery, i.v. morphine, PCA ar FNB performed pre- operatively with 20ml ropivacaine 0.5%. After cementing prostheses, 50ml of saline injected into periarticular soft tissue.		1 year 3 protocol violations Low risk of bias No separate pain outcome. Mean KSS at 1 year similar between groups: 94.2 (SD 2.6); LIA 93.9 (3.1). p=0.51 Infection: 0; 0. DVT: 1; 1. Femoral nerve injury: 1; 0.
FNB single and epid Reinhardt et al. 2014[41] USA 2010-2012 Single hospital, 2 surgeons	Elective unilateral TKR for osteoarthritis 51; 51 (49; 45 received allocated intervention) Mean 67.9 (SD 10.9); 66.6 (10.1) 59.2%; 57.8%	Spinal anaesthetic (2.5ml 0.5% daily. Oral Perocet or Vicodin a Dilaudid for severe breakthrou Combined spinal-epidural (500ml hydromorphone 10µg/ml and bupivacaine HCI 0.06%). Single intra-operative FNB injection (30ml 0.25% bupivacaine). Continuous 48-hour epidural infusion (4ml/hr with 4ml per demand dose, locked out every 10 minutes with an hourly limit of 20ml). Epidural infusion weaned to 2ml/hr on POD1 and to 0 ml/hr at 5 p.m. on POD1. Demand dose with	as required. Subcutaneous	1 year 0: 0 of patients who received allocated intervention Low risk of bias VAS pain at 1 year similar between groups (noted in text and shown graphically) No wound-related complications o infections. 1 DVT and 1 DVT plus PE in epidural group. Arthrofibrosis 2; 1

LIA with corticostere	oid vs LIA with no o	lockout parameters continued for 48 hours. Placebo intraarticular knee catheter placed intra- operatively with continuous saline 7ml/hr infusion until POD2.		
Seah et al. 2011[48] Singapore 2004-2005 1 hospital	TKR 50; 50 Mean 65.4; 67.9 Sex not stated	General or spinal anaesthesia. and PCA (with morphine bolus minutes, and maximum dose 8 Intraoperative periarticular injection of 0.5ml/kg 1:200,000 epinephrine and 0.5% bupivacaine diluted with 30ml of normal saline. 40mg of corticosteroid (triamcinolone acetonide) was added to half the mixture. The solution with the corticosteroid was injected into the deep tissues. The remaining solution was injected into the skin incision before closure.	of 1mg, lock-out time 5	6 months and 2 years No losses to follow up reported Low risk of bias No separate pain outcome but no statistically significant difference in OKS between groups at 2 years Deep infection: 1; 1
Yue et al. 2013[114] China 2011-2012 1 hospital	Unilateral TKR for osteoarthritis 36; 36 Mean 70.2 (SD 6.4); 69.3 (5.7) 89%; 89%	General anaesthesia. PCA (25 bolus, 6 minutes lock-out, and 5 hours after surgery. 5-10mg intr rescue. Celecoxib pre- and pos Injections with local anaesthetic agent and adrenaline (0.75% ropivacaine 30ml, 1:1000 adrenaline 0.5ml, and isotonic sodium chloride solution 70ml) plus corticosteroid (1ml betamethasone).	omg/hr maximum) for 72	6 and 12 months No loss to follow up reported Unclear risk of bias. No separate pain outcome. No difference in mean KSS between groups at 6 or 12 months No incision infection or tendon rupture complications

		Another 50ml syring without corticosteroi infiltrated into the sk	id was 🛛 wi	other 50ml syringe thout corticosteroid iltrated into the skir	was
LIA including ketorolac vs epiduralSpreng et al. 2012[115], Spreng et al. 2010[116]Unilateral, non- cemented TKR with no patella resurfacing 34; 34; 34Norway 2007–2009 1 hospital34; 34; 34 66.5 (SD 11.); 67.2 (SD 8.9); 65.8 (SD 10.1) 61%;61%;67%	Premedication with anaesthesia with 13 fentanyl. If indicated sedation. Acetamino morphine for 48 hou minutes lockout time release oxycodone t analgesia. i.v. injection of ketorolac 1ml	-15mg bupivac l, up to 10ml/hr ophen 1g every urs after surgery e). When PCA	aine 5mg/ml with 2 10mg/ml propofol f 6 hours. i.v. PCA 7 (2mg bolus with 1 stopped, 10mg slov g oxycodone as res f Epidural cat inserted	iorUnclear risk of bias due to limited reporting (long-term outcome only reported as conference abstract).0 v scuePerioperative analgesic treatment did not have any significant influence on any KOOS outcomes.Infection: 0; 0; 1. No long-term adverse	
		(30mg/ml) and morphine 5ml (1mg/ml). Infiltration with ropivacaine 150mg, epinephrine 0.5mg, ketorolac 30mg and morphine 5mg in 150ml saline. After closure, catheter placed into knee joint and 10ml infiltrate injected. 22-24 hours after surgery, 20ml injection through catheter of ropivacaine 19ml (7.5mg/ml) and ketorolac 1ml (30mg/ml). i.v. injection of	Infiltration with ropivacaine 150mg, epinephrine 0.5mg, ketoro 30mg and morphine 5mg 150ml saline. After closure, catheter place into knee joint 10 ml infiltrate injected. 22-2 hours after surgery, 20ml injection throu catheter of ropivacaine 11 (7.5mg/ml) an saline 1ml. i.v injection of sa 1ml. Sham epidura catheter.	before spina anaesthesia When spina anaesthesia When spina anaesthesia started to w off, epidural infusion for hrs with 6-1 ml/hr fentan 2µg/ml, epinephrine 1µg/ml, bupivacaine 1mg/ml. No knee infiltrations. 9ml d catheter with injections	al a. Il a ear 48 0 iyl

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		ketorolac 1ml (30mg/ml). Sham epidural catheter.			
Spinal with adde sulphate	d high dose morphine	e sulphate vs spinal	with added low dos	e morphine sulpha	ate vs spinal with no morphine
Foadi et al.	Unilateral TKR	3ml spinal anaesthe	sia with 0.5% bupiva	caine	6 months
2017[117]	or THR for	Post-operative 1 g r	netamizole (orally or	intravenously)	"only a few dropouts". >70%
Germany	osteoarthritis		morphine (intraveno	ous or	questionnaire return rate. Unclear risk of bias due to limited
Before 2017	16; 16; 17	subcutaneous) as re	escue		
1 centre	Mean 67.63 (SE	medication			reporting of pilot RCT.
	2.45); 67.33 (2.87); 63.71 (3.14) 56%; 44%; 65%	0.2mg morphine sulphate added to spinal anaesthesia	0.1mg morphine sulphate added to spinal anaesthesia	No morphine sulphate added to spinal anaesthesia	No difference in WOMAC pain between groups at 6 months. No adverse events noted

Myofascial trigger point dry needling 2.

Author	Indication	Common pain manageme	nt	Follow up
Country Recruitment dates Setting	Number randomised intervention; control Age % female	Group 1 (intervention)	Group C (control)	Losses to follow up intervention; control Risk of bias issues Key results
Mayoral et al. 2013[118] Spain 2007-2008 Single centre	Unilateral TKR for osteoarthritis 20; 20 Mean 71.7 (SD 6.1); 72.9 (7.9) 72.5%	General or spinal anaesthes After anaesthesia and surgery started, dry needling applied 20 times to all myofascial trigger points by a trained and experienced physical therapist.	ia If spinal anaesthesia used, dry needling simulated behind screen	6 months 4; 5 High risk of bias due to large losses to follow up WOMAC pain at 6 months: mean 3.24 (SD 3.03); 3.13 (2.72). Difference not statistically significant. No difference between groups in VAS pain (p=0.725) or proportion of patients reporting significant VAS pain at 6 months.

	No complications related to the dry needling intervention. Other adverse events not collected.
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3. Tourniquet

Author	Indication Number randomised intervention; control Age % female	Common blood conservation	Follow up	
Country Recruitment dates Setting		Group 1 (intervention)	Group C (control)	Losses to follow up intervention; control Risk of bias issues Key results
Ejaz et al. 2014[54] Denmark 2011-2012 1 centre	Primary unilateral TKR for osteoarthritis 35; 35 (33; 31 received intervention) Mean 68 (SD 8.0); 68 (7.8) 45.5%; 45.2%	Before surgery, oral tranexar (0.5g) 3 hours after surgery a postoperatively. Appropriately sized thigh tourniquet applied. Limb exsanguination by elevation for 2 minutes and cuff inflated to 250mm Hg.	nic acid (1g). Tranexamic acid and 6 and 12 hours Appropriately sized thigh tourniquet applied but not inflated. Served as safety device in case of uncontrollable bleeding.	6 and 12 months 0; 0 of those who received intervention Low risk of bias Statistically significant difference in KOOS pain intensity at 2 months favouring TKR without a tourniquet (p < 0.001). Small difference between groups not statistically significant at 6 and 12 months. Small number of adverse events did not suggest extra risk in the group with no tourniquet.
Liu et al. 2014[56] Australia Before 2014 1 surgeon	Unilateral TKR for osteoarthritis 10; 10 Mean 67.0; 70.0 30%; 10%	PCA. No CPM Tourniquet inflated to 300 mmHg before skin incision. Tourniquet deflated after wound closure and dressing.	Tourniquet placed but not inflated	6 and 12 months 0; 0 Low risk of bias No separate pain measure. Total OKS not significantly different at 6 and 12 months Blood transfusions: 3; 0.
Mittal et al. 2012[57] Australia 2008-2010	Primary unilateral TKR 31; 34	Autologous blood re-infused Short duration. Tourniquet set at 300mm Hg inflated	if required Long-duration. Tourniquet set at 300mm Hg inflated before	1 year 5; 2

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1 centre	Mean 67.5 (SD 8.9); 66.6 (8.4) 81%:74%	prior to cement application and deflated when cement hardened		skin incision and deflated when cement hardened		Low risk of bias. However, RCT terminated early due to increased need for blood transfusion in short
	r _c					duration tourniquet group. No separate pain outcome. Total OKS (0-48) at 52 weeks higher in long-duration group reflecting better recovery than short duration group but not significantly (p=0.12). Mean difference approximately 5 which is greater than MCID of 4[78]. Transfusions: 10; 2. Patient reported
						adverse event: 26; 12
Abdel-Salam and	Primary unilateral	Tourniquet placed around thigh			1 and 2 years	
Eyres 1995[119]	TKR of which 91% osteoarthritis 40; 40 Mean 72 (range 65-80); 74 (64- 82) 57.5%; 62.5%	Limb exsanguinated for 2 minutes and tourniquet inflated to twice systolic blood pressure		Tourniquet not inflated		0; 0
UK Date not stated 1 surgeon						Unclear risk of bias due to limited reporting of methods. No pain measure or PROM
						Surgeon recorded HSS score at 1 year 90 (78-97); 91 (80-97). Not significantly different at 1 or 2 years.
						Blood loss similar between groups. Wound infections: 5;0. DVT: 4;0
Şükür et	TKR, in women bl with osteoarthritis K 30; 30; 30; 30 flat Mean 67.0 (SD tc 7.0); 66.9 (8.5); da 68.4 (6.9); 68.4 w	Pneumatic tourniquet inflated to 125mm Hg above systolic			6 months	
al.2016[120]		blood pressure				0;0;0;0
Turkey 2015 1 surgeon		flexion and flexion flexion	wound	Knee in full extension and	n extension and et tourniquet inflated during wound	High risk of bias. KSS outcome noted in methods but not presented in results.
Tsurgeon				tourniquet deflated during wound		KSS results not reported at 6 months but no significant differences between groups at 3 months.
			ciosure	closure		Surgical and wound complications similar between groups. No infections, fractures or instability requiring revision within 6 months
		Blood transfusion if required				3-22 months, mean 12;13 months

Zhang et al.2016	Primary TKR for	Tourniquet		No tourni	quet	Not clear
[121]	osteoarthritis					High risk of bias. Variable follow up.
China	84; 82					HSS outcome noted in methods but not presented in results.
2014-2015	Not reported					HSS not reported.
1 hospital	Not reported					Transfusion rates similar between
	A.	6				groups. At mean follow up of 12 -13 months, patients operated on without a tourniquet had a lower rate of DVT (2.4%) compared with those with a tourniquet (10.7%).
Zhang et al.	Primary unilateral	Tourniquet inflated to 300-337mm Hg. Tranexamic acid not				6 months
2017[58]	cemented TKR	generally used	r		1	0; 0; 0
China	for osteoarthritis	entire operation remov	Tourniqu	d before first bone	Tourniquet from	Low risk of bias
2008-2011 1 surgeon	50; 50; 50 Mean 70.3 (SD 6.6); 71 (10.2); 68.2 (6.8) 54%; 60%; 50%		wound closure		osteotomy until	No separate pain outcome. HSS similar between groups at 6 months (p=0.839).
			10			At 2 weeks DVT: 0; 0; 1. Intramuscular vein thrombosis: 4; 3; 3. Transfusions: 30%; 26%; 10%
Huang et al.	Primary unilateral	Tranexamic acid			6 months	
2017[55]	TKR for	Tourniquet		No tourniquet		0; 0
China	2015 50; 50					Low risk of bias
2015 1 centre						VAS pain similar between groups at months (p=0.728). Mean HSS score 90.3 (SD 3.2); 91.2 (2.5). P=0.151
						DVT: 0; 0. PE: 0; 0. Intramuscular venous thrombosis: 6; 4. Superficial infection: 1; 0. Wound secretion: 6; 0 No significant difference in blood los between groups.

4. Compression bandage

Author	Indication	Common treatments	Follow up

Country Recruitment dates Setting	Number randomised intervention; control	Intervention	Control	Losses to follow up intervention; control Risk of bias issues Key results
	Age % female			Reyresuits
Brock et al. 2017[122] UK 2013-2014 1 hospital	Primary unilateral TKR for osteoarthritis 25; 25 (24 received intervention) Mean 67.3 (SD 8.2); 69.5 (6.8) 66.7%; 64.0%	Hydrocolloid dressing left in p 10-14 Soft inner layer with compressive outer layer bandage. Removed after 24 hours.	lace until clips removed on day Standard bandaging with soft inner layer and crepe bandage outer layer. Removed after 24 hours and cryocuff used.	6 months 0; 0 of patients receiving intervention Low risk of bias No separate pain outcome. Mean OKS similar between groups at 6 months: 35.8 (SD 7.7); 34.3 (10.6). P=0.58 No infections or thromboembolic events in either group
Pland concor	wation			
Blood conser Author	vation Indication	Common blood conservation	n strategies	Follow up
		Common blood conservation	n strategies Control	Follow up Losses to follow up intervention; control Risk of bias issues Key results
Author Country Recruitment dates	Indication Number randomised intervention; control Age			Losses to follow up intervention; control Risk of bias issues
Author Country Recruitment dates Setting Tranexamic acid Sa-Ngasoongsong	Indication Number randomised intervention; control Age % female	Intervention Drain and compressive dress	Control	Losses to follow up intervention; control Risk of bias issues Key results 6 months
Author Country Recruitment dates Setting <i>Tranexamic acid</i>	Indication Number randomised intervention; control Age % female	Intervention	Control	Losses to follow up intervention; control Risk of bias issues Key results

						wound complications or infection reported in either group
Kim et al. 2014[61] Korea 2009-2011 1 hospital Sa-Ngasoongsong et al. 2013[65] Thailand 2010-2011 1 hospital	Primary unilateral TKR for osteoarthritis 90; 90 Mean 73.5 (SD 5.5); 71.9 (SD 5.9) 88%; 87% Primary unilateral cemented TKR for osteoarthritis 45; 45; 45 Mean 68.1 (SD 6.2); 67.6 (8.7); 66.2 (7.3) 88.9%; 93.3%; 95.6%	Tourniquet, drain, con transfusion and intrav required 10 mg/kg body weight tranexamic acid in 100 normal saline given as intravenous injection 3 before tourniquet defla and the same amount hours later. Drain and compressiv 25ml saline solution containing 500mg tranexamic acid injected into knee joint after fascial closure via drain tube.	enous irc t 0 mL of s slow 30 min ation, t 3 25ml sa solution containi tranexar injected joint afte	n and eryth No tranexa placebo		 1 year 0; 0 Low risk of bias WOMAC pain mean 3.2 (2.6); 2.8 (2.3). Difference not statistically significant Lower blood loss and need for allogenic transfusion in tranexamic acid group. No DVT. 1 PE in control group. 1 year 0; 0; 0 Low risk of bias No separate pain outcome but WOMAC mean 14.5 (7.1); 15.1 (6.2); 15.5 (6.6). P=0.42 Total blood and Hb loss lower in intervention groups than control. Fewer transfusions in 500mg (0) than 250mg tranexamic acid group (6) and control group (10). 2 DVT in 500mg group. 1 DVT in 250mg group. 1 PE and 3 DVT in control group. No infections.
Hourlier et al. 2015[60] France 2009-2010 1 hospital	Primary unilateral TKR for osteoarthritis 52; 54 74 (SD 6); 72 (7) 62%; 63%	Tourniquet, electrocau drain. No blood salvag 10 mg/kg intra-operat tranexamic infusion. A hours, continuous infu tranexamic acid 2 mg, for 20 hours via electr syringe	ge syster ive After 2 usion of /kg/hr	n. single bolu tranexami intraopera 2 hours, p	us of 30 mg/kg c acid as an tive infusion. After lacebo saline s infusion via	6 months 0; 0 Low risk of bias. No separate pain score but KSS clinical score mean 90 (SD 6); 90 (13). P=0.90 No difference between groups in total blood loss. 1 MUA in single treatment

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Huang et al. 2017[55] China 2015 1 centre	Primary unilateral TKR for osteoarthritis 50; 50 Mean 66.2 (SD 8.3); 65.8 (6.3) 64%; 70%	Tourniquet inflated to 100mm I and deflated after wound closu Intravenous tranexamic acid 20mg/kg before incision and tranexamic acid 10mg/kg at 3, 6, 12 and 24 hours. 1g tranexamic acid in 50ml saline irrigated into wound during operation		group. No deep infections or revisions. 6 months 0; 0 Low risk of bias VAS pain similar between groups at months (p=0.728). Mean HSS score (0-100) better in tranexamic acid group than controls: 90.3 (SD 3.2); 88.9 (3.0). P<0.001. Mean difference 1.4 lower than MCID of 8.29[81] Greater blood loss in control group than tranexamic group (p<0.001). DVT: 0; 0. PE: 0; 0. Intramuscular venous thrombosis: 6; 3. Superficial
Thrombin infusio	<u> </u>			infection: 1; 3. Wound secretion: 6;
Kusuma et al. 2013[62] USA Not stated 1 hospital	Primary unilateral TKR for osteoarthritis 40; 40 Mean 64.6 (SD 10.2); 64.5 (7.3) 82.5%; 67.5%	Tourniquet, drain, Esmarch ba 20,000 IU thrombin infusion (1,000 IU/mL) through fascial defect	ndage, electrocautery Closure and drain placement protocol without the thrombin infusion.	1 year (6 months and 2 years also reported) 0; 0 Low risk of bias No separate pain outcome. KSS mean 95.5; 96.0. p=0.45 Lower drop in Hb in thrombin group Blood transfusion in 4 intervention and 7 control patients. 1 control patient had haematoma. No hospita readmissions
Flexion vs extens	-			
Napier et al. 2014[63] UK 2003-2004 1 hospital	Primary unilateral TKR of which 89% for osteoarthritis 90; 90	No drains or tranexamic acid Flexion. Operated knee kept in passive flexion (120°) post-operatively for 6 hours using a jig. Wound redressed and placed in flexion over a	Extension. Operated knee kept in full passive extension	1 year 5; 1 (12 did not attend follow up) Low risk of bias. No separate pain outcome. OKS mean 20.5 (SD9.0); 22.1 (9.7). P=0.27

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Recruitment dates Setting	randomised intervention;		-	control Risk of bias issues
Country	Number	Group 1 (intervention)	Group C (control)	Losses to follow up intervention;
Author	Indication	Common blood conservat	ion strategies	Follow up
. Platelet rich p	blasma			groups.
				7% of auto-transfusion group required allogenic transfusion compared with 28% in control group. Fewer infections, readmissions and GP visits in auto-transfusion group. No significant differences in other serious adverse events or mortality between
1 hospital	70.0 (40-88) 62%; 53%	washed and re-suspended before re-infusion using a centrifugal cell washing machine		No separate pain outcome. No significant difference in EQ-5D between groups.
Not stated	Mean 69.3 (range 32-95);	post-operative. Blood		Unclear risk of bias due to limited details of methods and follow up.
2001[123] UK	115; 116	Auto-transfusion of wound drainage if volume >125ml	Wound drainage discarded	Losses to follow up not reported
Thomas et al.	Unilateral TKR	Allogenic transfusion if Hb fe	ell below 9g/dl	6 months
Auto-transfusion of	washed blood			
	74%; 64%	morning.		infection and 1 extension group. More transfusions in extension group (p=0.002)
	Mean 70.4 (SD 9.9) 71.0 (7.6)	single pillow until POD1 morning.		1 MI and 1 DVT in each group. 1 haematoma in flexion group. 1 deep

Platelet rich plasma 6.

Author	Indication	Common blood conservation	Follow up	
Country Recruitment dates Setting	Number randomised intervention; control Age % female	Group 1 (intervention)	Group C (control)	Losses to follow up intervention; control Risk of bias issues Key results
Aggarwal et al. 2014[124]	Primary unilateral surgery or first surgery of staged	Tourniquet. No tranexamic acid or suction drain. Blood transfusion if necessary due to intraoperative blood loss or postoperative haemoglobin <8g/dl.		6 months No losses to follow up reported

India 2010-2011 1 surgeon	bilateral TKR for osteoarthritis 7; 14 Mean 56.43 (SD 7.59); 53.79 (9.75) Sex not stated	8 ml PRP, prepared from patient's blood. Calcium chloride for activation given in a separate syringe in 4:1 ratio. PRP and calcium chloride injected into the posterior recess, gutters and capsule, and repaired extensor mechanism and prepatellar fat.		High risk of bias due to unexplained differences in numbers of patients in randomised groups. No separate pain outcome. WOMAC total at 6 months PRP mean 7.14 (S 0.69), controls 7.86 (1.23), p=0.173 PRP group had lower fall in haemoglobin and need for blood transfusion
Cryotherapy	Ċ			<u> </u>
Author Country Recruitment dates Setting	Indication Number randomised intervention; control	Common treatment Group 1 (intervention)	Group 1 (intervention)	Follow up Losses to follow up intervention; control Risk of bias issues
	Age % female	1		Key results
Wang 2017[125] China 2013-2015	Unilateral TKR for osteoarthritis 53; 53 Mean 65.23 (SD 5.41); 64.97(5.36) 62.3%; 58.5%	CPM for 2 weeks Compression cold therapy for 48 hours	No compression cold therapy	 6 months 0; 0 Unclear risk of bias due to limited reporting No separate pain outcome. At 6 months 87% of cryotherapy patients had excellent or good knee function compared with 69% of controls (p=0.032). No adverse events reported in either group during functional

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8. Denusomab

Author	Indication	Common treatment		Follow up
Country Recruitment dates Setting	Number randomised intervention; control Age % female	Group 1 (intervention)	Group 1 (intervention)	Losses to follow up intervention; control Risk of bias issues Key results
Ledin et al. 2017[66] Sweden 2012-2014 2 centres	Elective cemented primary unilateral TKR for osteoarthritis 25; 25 Mean 66 (SD 6.3); 64 (5.5) 60%; 60%	Injection of 60mg denusomab 1 day after surgery and after 6 months	Injection of placebo 1 day after surgery and after 6 months	 12, 24 months 0; 2 Low risk of bias No significant differences in KOOS pain or other KOOS domains between groups 12 12 of 24 months No suspected unexpected adverse reactions in either group
). Continuous p Author	bassive motion	Common treatment	10	Follow up

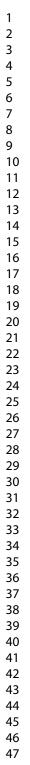
Continuous passive motion 9.

Author	Indication Common treatment			nt Follow up		Follow up	
Country Recruitment dates Setting	Number randomised intervention; control Age % female	Group 1 (intervention)	Group 2 (interventi	ion)	Group C (control)	Losses to follow up intervention; control Risk of bias issues Key results	
Leach et al. 2006[126] UK Before 2005 1 hospital	Unilateral cruciate retaining rotating platform TKR for osteoarthritis 85 overall Mean 71.2 (range 53-84); 72.9 (52- 89)	Physiotherapy protocol from POD1 including s exercises to improve ROM and quadriceps str exercises. CPM commenced on first postoperative day set at a range 0–30 and used for 1 hour twice per day. Each day,				6 and 12 months 25 patients lost to follow up High risk of bias due to large loss to follow up and use of date of birth randomisation No difference in mean VAS pain at 1 year, CPM 0.6; control 0.9. p=0.49	

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	50%; 54%	range was increased with discharge at POI			Adverse events not reported
Sahin et al. 2006[127] Turkey Before 2006 1 hospital Pope et al. 1997[128] Australia 1988-1999 1 hospital	Primary unilateral TKR for osteoarthritis 15; 16 Mean 61 (SD 6.0); 61.6 (7.5) 86%; 86% Primary unilateral or bilateral TKR of which 86% for osteoarthritis 62 (70 knees). Authors excluded those not followed up so groups were 18; 20; 19	with discharge at POE Standard physiothera From POD 1, CPM 2. 2x/day. Initially 0-40° and increased by 10° until POD 7 Physiotherapy comme Patients had an initial CPM range of 0-40° increased by 10° twice, on day after surgery and day 2, so that 0-60° flexion achieved before removal of	py 5 hours No C flexion each day each day enced on postope Patients had an initial CPM rang 0-70° increased 10° twice, on da after surgery and day 2, so that 0- flexion achieved before removal of	erative day 1 Knee placed e of extension sp by the recovery y d 90°	lint in death room High risk of bias due to losses to follow up and limited reporting o methods No separate pain outcome. However, "pain disability"
were 18; 20; 19 Mean 72.5 (95% CI 64.4, 74.98); 72.7 (70.4, 75.0); 69.4 (64.4, 74.98) 64.7%; 50%; 72.2%	machine at 48 hours	machine at 48 hours	NO,	contributed up to 50 points out of a total of 70-point functional score (70 best outcome). No difference between groups in functional score: CPM 0-40 median 56 (range 20, 70); CPM 0-70 52 (1 70); no CPM 52 (25, 70). p=0.8 CPM groups had greater blood loss than controls, p=0.008). 1 manipulation under anaesthesia in no CPM group, 2 revisions du to patellar dislocation in the 0-4 CPM group, 1 PE death in the 0 70 CPM group.	
Beaupré etal. 2001[129]	Primary unilateral TKR of which	Standardised exercise a slider board session		admission which in	cluded 6 months

Canada	92% for	3 sessions (2	-	of two 10-	No intervention	6; 8; 6
1997-1998 1 hospital	osteoarthritis 40; 40; 40 Mean 68 (SD 9); 68 (9); 69 (8) 52.5%; 50%; 30%	hours) with CPM machine per day from POD2. Range increased from starting range 0-30 degrees as tolerated.	minute sli therapy se per day in to one in t standardis exercise. knee flexi extension and lying performed independe tolerated.	essions a addition the sed Active on and in sitting positions	further than standardised exercise.	Unclear risk of bias due to losses to follow up Mean WOMAC pain at 6 months 76 (15); 85 (15); 79 (16). No difference over time between groups, p=0.62. Long-term adverse events. Need for MUA: 1; 1; 0. DVT: 0; 1; 0. Cellulitis: 0; 0; 1. Infection 0; 0; 1
Kumar et al. 1996[130] USA Before 1996 1 hospital	Primary unilateral TKR for osteoarthritis 40 (46 knees); 33 (37) Mean 69 (range 52-86); 68 (42-88) 58%; 67%	Standard physiothera CPM from POD 0. Ini hours/ day 0-90° unti discharge	apy itially 10	movemen to 90° 2x/	Passive range of t ("drop and dangle") day initially for 20 ater 30-45 minutes.	6 months 15; 13 lost to follow up High risk of bias due to large losses to follow up No separate pain outcome. KSS CPM 82.7; Drop and dangle 80. p=0.78 Haematoma 3;1. Closed
Worland et al. 1998[131] USA 1996 1 hospital	Unilateral or bilateral TKR for osteoarthritis. 91 patients (114 knees randomised). After post- randomisation exclusions: 37 (49 knees); 43 (54 knees) Mean 70.2 (range 44-84) 66.25%	CPM and physiothera At home after dischar machine 3 hours per replaced knee for I0 o	rge, CPM day on	Physical t	herapist home visit 1 e times per week for	manipulation 1;3. DVT 0;0. PE 0 6 months 11 patients (11 knees) Unclear risk of bias due to post- operative exclusions not reporte separately for groups and limited reporting of methods. No separate pain outcome. At 6 months, mean HSS score CPM 95.3 (SD 2.8); physiotherapy 95 (3.0). P=0.49. Adverse events not reported.



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MacDonald et al. 2000[132]	Primary unilateral TKR for	Active ROM, passive using walker or crutcl	ROM exercises, mobi nes.	6 and 12 months Not reported	
Canada Before 2000 1 hospital	osteoarthritis 40; 40; 40 Age and sex not reported	CPM commenced POD 0. Initially 0- 50 degrees. Provided for 18-24 hour/ day. Increased by 10 degrees/ hour as tolerated. Continued until POD 1	CPM commenced POD 0. Initially 70- 110 degrees. Provided for 18-24 hr/ day. Not increased. Continued until POD 1	No CPM	Unclear risk of bias due to limited and selective reporting. No separate pain outcome. No statistical differences between groups for KSS at 6 and 12 months. Adverse events not reported
Bennett et al. 2005[67] Australia 1997-2000 1 hospital	Primary unilateral TKR for osteoarthritis 47; 48; 52 70.7; 71.4; 71.7 72.3%; 64.6%; 67.3%	Standard in hospital p Standard CPM from 0° to 40° for 2x3 hours on POD 1 increased by 10° per day until POD 6. Extension splint applied overnight	bhysiotherapy program Early flexion CPM commenced in recovery room from 90° to 50° knee flexion. Increased gradually to CPM 90° to 0° for 2x3 hours in day 4-6.	No CPM	12 months1 patient excluded due to inabilityto achieve 90° flexionLow risk of biasNo separate pain outcome. No significant difference in KSS between groups at 1 year.No difference in wound healing between groups
Ersözlü et al. 2009[68] Turkey 2003-2004	Primary unilateral TKR for osteoarthritis 30; 30; 30 Mean 65 (range 54-73); 61 (49- 80); 62 (52-78) 66%; 55%; 57%	Conventional physica CPM set at 30-40° from POD1. Increased as tolerated to POD7. 1 hour CPM 3x/day.	I therapy CPM set at 60-70° from POD3. Increased by 10°/ day to POD7. 1 hour CPM 3x/day.	No CPM	2 years 1; 1; 2 Low risk of bias No separate pain outcome. KSS scores 98; 95; 92. No significant difference between groups p=0.67. Infection 0; 0; 1. Arrhythmia 0; 1; 0. No difference in complications between groups

10. Electrical stimulation

Author	Indication	Common rehabilitation strategies	
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Country Recruitment dates Setting	Number randomised intervention; control Age % female	Intervention	Intervention	Common rehabilitation strategies
Avramidis et al. 2011[69] Greece 2005-2006 1 hospital	Elective primary unilateral TKR for osteoarthritis 38; 38 Mean 70.54 (SD 4.68); 70.66 (3.73) 80%; 82.9%	Standard physiotherapy for 6 we Transcutaneous electric muscle stimulation of the vastus medialis muscle from POD2 2x/ day for 2 hours for 6 weeks.	eeks. No CPM No intervention	1 year 3 (intervention intolerance); 3 Low risk of bias Improved SF-36 bodily pain at 1 year in intervention group compared with control, mean 92 (SD 10.57); 79.48 (12.72). P<0.001. Difference of 12.52 close to MCID of 16.86[82]. No difference in OKS or American KSS Adverse events not reported
Stevens-Lapsley et al. 2012[133] USA 2006-2010 1 hospital	Primary unilateral TKR for osteoarthritis 35; 31 Mean 66.2 (SD 9.1); 64.8 (7.7) 57.1%; 51.6%	Standard inpatient rehabilitation, therapy Neuromuscular electrical stimulation commenced on POD2 for 6 weeks 2x/ day.	home and outpatient physical No intervention	6 months and 1 year 5; 6 Unclear risk of bias due to baseline differences in WOMAC No difference in resting pain (points) at 1 year intervention mean 0.6 (SD 1.4); control 0.4 (1.5). Also similar at 6 months. Mean WOMAC total score better at 1 year in intervention group compared with control, 5.7 (5.9); 10.0 (12.2) and at 6 months. However, probably explained by baseline differences. Authors state no differences for change in WOMAC. DVT 1; 0. Unspecified complication 1; 0. Infection 0; 2. Revision 0; 1

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Levine et al.	Elective unilateral	2 sessions of ROM exercise		6 months
2013[134] USA Before 2013 1 surgeon	TKR for osteoarthritis 35; 35 Mean 68.1; 65.1 76%; 62%	Neuromuscular electrical stimulation commenced 14 days pre-operatively until 1 day before surgery. Recommenced at POD1 for 60 days. After hospital discharge no direct contact with a physical therapist	Formal physical therapy programme with progressive resistive exercises and strengthening in hospital and after discharge supervised by physical therapist.	5; 9 Unclear risk of bias due to larg uneven losses to follow up KSS pain favoured interventio 6 months but not significantly 79.08 (SD 10.97); 75.5 (14.77) 95%CI for difference -3.78, 10 Similar for WOMAC total score 95%CI for difference -3.19, 14 Confusion 2; 0
Moretti et al.	Primary unilateral	Rehabilitation protocol including	CPM	6 and 12 months
2012[70] Italy 2008-2010 1 hospital	TKR for osteoarthritis 15; 15 Mean 70.0 (SD 10.6); 70.5 (8.1) Not reported	Pulsed electromagnetic fields (I-ONE therapy) from POD7, 4 hours/ day for 60 days	No intervention	No losses to follow up Low risk of bias Mean VAS pain (10-point scale lower at 12 months in intervent group compared with control, 0 (SD 1.3); 3.6 (3.9). p< 0.05. Me difference of 2.1 (10-point scal greater than MCID of 16.1 (100 point scale)[83] Difference also at 6 months. More swelling of the knee in intervention patients than controls, statistically significant 1 and 2 months
Adravanti et al. 2014[135] Italy 1 hospital	Primary unilateral TKR for osteoarthritis 16; 17 Mean 66 (SD 13); 73 (5) 62.5%; 52.9%	Standard rehabilitation protocol: Pulsed electromagnetic fields (I-ONE therapy) by POD7 for 4 hours/ day for 60 days	active and passive mobilisation No intervention	 6 months 4; 3 High risk of bias: small study, proportionately high losses to follow up At 6 months, mean VAS pain in intervention group lower than in controls (p<0.05). At 3 years, 1 intervention patients and 4/12 controls reported severe pain

	No difference between groups in swelling at 6 months.
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11. Rehabilitation

Author	Indication	Common rehabilitation stra	ategies	Follow up
Country Recruitment dates Setting	Number randomised intervention; control Age % female	Intervention Control		Losses to follow up intervention; control Risk of bias issues Key results
Walking guidance a	nd training	No	•	1
Li et al. 2017[71] China 2015-2016 1 hospital	Primary unilateral TKR for osteoarthritis 43; 43 Mean 76.33 (SD 5.28); 78.47 (5.50) 55.8%; 51.2%	muscle strength, use of aids, methods and precautions. Knee passive flexion and ext muscle strength training com straight leg raising exercises increased joint activities and	ce on joint activities, quadriceps diet guidance, correct walking mension to 90° and quadriceps menced on POD 1. POD 3-7, . 2 weeks after replacement, muscle strength training, centre nb weight training, and walking No additional rehabilitation	6 months 0; 0 Low risk of bias Mean VAS pain at 6 months: 0.51 (SD 0.74); 2.83 (0.88) favouring walking intervention group, p<0.01. Difference of 2.42 (10 point scale) greater than the MCID of 16.1 (100- point scale)[83]. HSS scores at 6 months favoured intervention, p<0.01. No infection, allergic reaction or immune reaction in either group. Intervention not associated with swelling, pain, prosthesis loosening, thrombosis, or delayed wound healing
Aquatic therapy			and the second strength of the second strength of the	
Liebs et al. 2012[72] Germany 2003-2004 4 hospitals	Elective primary unilateral TKR for osteoarthritis 87;98	suction drains. Programme o motion activities; exercises for	nce, coordination and gait; and	6, 12 and 24 months 13.8%; 19.4% excluding deaths and unexplained reasons Low risk of bias

	Mean 68.5 (SD 8.6); 70.9 (7.5) 70.1%;73.5%	Aquatic therapy for 30 minutes 3 times a week up to postoperative week 5. Pool exercises aimed at training of proprioception, coordination and strengthening with aid of float cuffs, training kickboards and bar floats.			WOMAC pain at 12 months: early aquatic mean 13.2 (SD 15.0); late aquatic 17.4 (22.4) p=0.22. No difference at 6 and 24 months.	
	A.	Aquatic therapy beg on the 6th postopera day with the wound covered with a wate adhesive dressing.	ative	exercise a	erapy as pool fter the completion nealing on the 14th tive day	5 early aquatic therapy patients and late aquatic therapy patient readmitted to hospital within 3 months. 2 early aquatic patients and 1 late aquatic patient readmission directly or indirectly related to the intervention.
Rahmann et al. 2009[136]	Unilateral primary TKR or THR for	Standard ward-base physiotherapy treatr with an occlusive, w	nent per (day. Surgica	al wounds covered	6 months 4;2;0 for combined THR and TKR
Australia 2003-2005 1 hospital with 2 surgeons	osteoarthritis (50% TKR) 18;19;17 (11 had been excluded post- randomisation due to complications in hospital Mean 69.4 (SD 6.5); 69.0 (8.9); 70.4 (9.2) 44.4%; 63.2%; 70.6%	From day 4, 1 to 1 individual physiotherapy. Aquatic physiotherapy programme to maximize function and strength. 40 mins/ day. Fast pace metronome 80-88 bpm	From da individu, physioth Water e program general not targ specific retrainin aquatic environ	ay 4, 1 to 1 al herapy. exercises eted at functional og in the ment. Slow etronome	From day 4, 1 to 1 individual ward- based physiotherapy. 40 mins/ day	 Unclear risk of bias as TKR patients more likely to receive ward-based control intervention. THR and TKR analysed together No difference in overall WOMAC outcome at 6 months in THR and TKR patients combined between aquatic at fast pace and ward-based (p=0.929) and aquatic at 2 paces (p=0.872). No adverse events reported after intervention commenced.
Supported early d						
Mahomed et al. 2008[137] Canada 2000-2002 2 centres	Primary unilateral TKR or THR for osteoarthritis (approximately 50% TKR) 119;115 68	Inpatient physiothera Discharged home w to independently tra supine to sitting and standing, walk 30 m climb stairs if necess Physiotherapist hom within 48 hours and	hen able nsfer sitting to etres and sary.	rehabilita day stay.	to independent ation centre for 14	12 months No losses to follow up Low risk of bias (analysis by actual treatment received showed similar results) WOMAC pain at 12 months marginally favoured home-based

Hill et al. 2000[138] UK 1997-1998 1 centre	About 67% women Unilateral, primary TKR, irrespective of diagnosis or concomitant disease 70 randomised, with 32;28 eligible for trial at day 5	subsequent management along a multidisciplinary clinical pathway (4-16 visits). Then outpatient physiotherapy or self- directed programme. Care pathway for medical, nurs from admission until day 5 Outreach team domiciliary visit prior to admission with assessment of home environment. At days 5–7, patients assessed to ensure discharge safe. Outreach team visit on day of discharge with further visits as required. 1+ physiotherapist visit linked with nurses to monitor knee performance. Discharge when skin clips removed, wound healed and specialist	sing and physiotherapy care Inpatient care until removal of skin clips and wound healing.	rehabilitation mean 87 (SD 16); 83 SD (20), p=0.08 but this was not statistically significant. Mean difference of 4 less than MCID of 8- 9[77]. Results did not differ between TKR and THR patients. Similar rates of dislocation, DVT and readmissions between groups. 2% inpatient group developed infections compared with 0 in home group 1 year No losses to follow up reported after commencement of intervention Unclear risk of bias due to limited reporting of methods. No pain outcome or patient reported outcome. Control group had better mean KSS scores, but this did not reach statistical significance at 1 year or earlier. 1;1 serious infection, other wound infections 1;6, painful joints 9;4, other minor complications similar between groups
Flexion or extension	during knee closu	orthopaedic assistance not required, usually day 10–12		
				6 months
Wang et al. 2014[74] China 2009-2010 1 centre	Primary unilateral TKR for osteoarthritis 40; 40 Mean 68.34 (SD 7.09), 67.87 (6.47) 17.5%; 22.5%	No patellar replacement or late Articular capsule, soft tissue and skin enclosed in 90° flexion which was maintained for 1-2 min after wound closure.	ral retinacular release Wound closure performed in full extension	6 months No losses to follow up Low risk of bias Mean VAS pain in flexion group 1.15 (SD 0.73); extension group 1.12 (0.68), p=0.64

		fractu	vound complications, patella ure or infection requiring surgery her group
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12. Wound management

Author	Indication	Common wound manageme	nt strategies	Follow up
Country Recruitment dates Setting	Number randomised intervention; control Age % female	Intervention	Control	Losses to follow up intervention; control Risk of bias issues Key results
Kong et al. 2014[75] South Korea 2011 1 surgeon	Primary cemented unilateral TKR for osteoarthritis 50; 50 Mean 69.0 (SD 7.7); 68.0 (4.8) 89.6%; 87.5%	Skin staples removed on day applied for 5 days After removal of wound closure strip, patients managed operation scars with application of silicone gel for 1 month after stitches removed	10 and wound closure strip After removal of wound closure strip, patients managed operation scars with application of petroleum gel for 1 month after stitches removed	6 and 12 months 2; 2 lost to follow up Low risk of bias At 12 months, VAS pain in silicone gel group mean 2.50 (SD 1.16); control 2.92 (1.90). P=0.201. No difference at 6 months, p=0.886. No wound dehiscence or infection associated with application of silicone gel or petroleum
3. Anabolic sterc	bids Indication	Common rehabilitation strat	regies	Follow up

13. Anabolic steroids

Author	Indication	Common rehabilitation strat	egies	Follow up
Country Recruitment dates Setting	Number randomised intervention; control Age % female	Intervention	Control	Losses to follow up intervention; control Risk of bias issues Key results
		Cold compression and CPM	·	6, 9 and 12 months

Hohmann et al.	Primary unilateral	On day 5, intramuscular	On day 5, intramuscular	0; 0 lost to follow up
2010[76] Australia Before 2010 1 surgeon	TKR for osteoarthritis 5; 5 Mean 66.2 (range 58, 72); 65.2 (59, 72) 20%; 40%	injection of 50 mg Nandrolone decanoate solution. Patients visited every 2 weeks and injections continued for 6 months.	injection of saline. Patients visited every 2 weeks and injections continued for 6 months.	Low risk of bias (but small feasibility study) No separate pain outcome. KSS at 12 months in intervention group mean 91.4 (SD 3.5); control 81.2 (SD 7.1). p=0.03. Difference also at 6 months (p=0.04), marginal at 9 months (p=0.06). Difference in means at 12 months of 10.2 close to MCID of 12.3[79].
		D _O		Intervention group had smaller decrease in bone mineral density at 6 months than controls but not significant

Guided imagery 14.

4. Guided image Author	ery Indication	Common rehabilitation strat	egies	Follow up
Country Recruitment dates Setting	Number randomised intervention; control Age % female	Intervention	Control	Losses to follow up intervention; control Risk of bias issues Key results
Jacobson et al. 2016[139] USA 2011-2012 1 surgeon	Primary unilateral TKR for osteoarthritis 42; 40 (41; 39 received treatment) Mean 65.0 SD 8.6) 62.2%	Participants listened to a 19- 21-minute CD each day for 2 weeks before and 3 weeks after surgery. Content covered concerns and hopes about TKR with aim to facilitate mind–body connections to promote optimal TKR outcomes.	Participants listened to a 17- 21-minute CD each day for 2 weeks before and 3 weeks after surgery. Content comprised poetry, short stories and essays	6 months 12; 10 of patients receiving treatments High risk of bias due to large losses to follow up Mean WOMAC pain 2.7 (SD 3.1); 3.4 (SD 3.3). P<0.001 Adverse events not reported

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CD compact disc; CPM Continuous passive motion; DN4 Douleur Neuropathique 4; FNB Femoral nerve block; HSS Hospital for Special Surgery; i.v. intravenous; KOOS Knee injury and Osteoarthritis Outcome Score; KSS Knee Society Score; LIA local infiltration analgesia; NRS Numerical rating scale; OKS Oxford Knee Score; ONB obturator nerve block; PCA Patient controlled analgesia; PNB psoas nerve block; SF-36 Short Form 36 Health Survey; S-LANSS Leeds assessment of Neuropathic Symptoms and Signs Pain Scale; SNB Sciatic nerve block; TKR Total knee replacement; VAS Visual analogue scale; VTE Venous thromboembolism; WOMAC Western Ontario and McMaster Universities Osteoarthritis Index.

ITT, ITT CC, POD, MI, PE

Supplementary material. Risk of bias assessment

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blind outcome assessment	Incomplete outcome data	Selective reporting	Other bias	Summary
Pain manageme	ent							
Albrecht et al. 2014[34]	Computer generated	Anaesthetist blind to allocation	Physiotherapists, surgeons, research assistants collecting data, and members of the Acute Pain Service were kept blinded to group allocation.	Physiotherapists, surgeons, research assistants collecting data, and members of the Acute Pain Service were kept blinded to group allocation.	ITT analysis low losses to follow up	No but not checked protocol	Study was terminated early with 61% of planned recruitment completed due to change in standard anaesthesia at hospital	Low
Anastase et al. 2014[113]	Method of the Ulm Institute of Statistics	Method of the Ulm Institute of Statistics	No	No	15:14 lost to follow up	No but not checked protocol	ASA comorbidities differed between groups	High
Aveline et al. 2014[52]	Computer generated	opaque sealed envelopes	Blinded syringes prepared by nurse not involved in study	Yes	Low losses to follow up	Consistent with short term follow up paper	No	Low
Bergeron et al. 2009[105]	Blocks of different sizes according to list preprepared by study epidemiologist	Not described	Anaesthetist not blind. Patients blind	Nurse observers collecting data blind to allocation	32/59 lost to follow up	No but not checked protocol	No	High
Buvanendran et al. 2010[53]	computer generated	Yes, physicians and nurses blind	Yes	Yes	ITT	Protocol not checked	No	Low

Choy et al. 2011[35]	Computer generated	sealed envelope	No, the catheter was removed at either day 3 or 7	Patient reported outcome. Other outcomes by blinded independent physician	Low losses to follow up	Protocol not checked but reasonable range of outcomes	No	Low
Davidson et al. 2016[111]	Computer generated	Sealed opaque envelopes	Subjects and investigators were not masked to treatment group	Subjects and investigators were not masked to treatment group. PROM	31; 29 lost to follow up	None apparent but protocol not checked	Combined data from 2 RCTs	High
Fan et al. 2016[36]	No details	sealed opaque envelopes	Patients and assessors blind to randomisation	Patients and assessors blind to randomisation	2% protocol violation	No but not checked protocol	No	Low
Foadi et al. 2017[117]	Computer generated	Not described	Not described	Patient reported outcome	>70% questionnaire return	None apparent but protocol not checked	Described as pilot study	Unclea
Gao et al. 2017[37]	Random number table	Not described	Blind to patients	Blind to observers	2; 1; 0	None apparent but protocol not checked	Groups similar at baseline	Low
llfeld et al. 2009[108]	Computer generated	Investigators, patients, and all clinical staff were unaware of treatment group assignments	Investigators, patients, and all clinical staff were unaware of treatment group assignments	Investigators, patients, and all clinical staff were unaware of treatment group assignments	4:1 lost to follow up	No but not checked protocol	Basal infusion halved on POD1 in 10 intervention patients compared with 3 controls	High
llfeld et al. 2011[109]	Computer generated tables	Solutions prepared by investigational pharmacist	Yes. Intervention and control solutions indistinguishable	Patient reported outcomes. Staff masked to treatment group	11;12 did not have 4 measures out	Protocol not checked	WOMAC and WOMAC domain scores	High

				assignment performed all measures and assessments	of 6 up to 12 months	but seems reasonable	somewhat lower pre- intervention in extended infusion group. Authors report change scores	
Macrinici et al. 2017[38]	Computer generated	Staff performing injections blind	Anaesthesiologist, surgeons, patients and physical therapists blind to allocation	Yes	3; 4 lost to follow up. 6; 3 complications	None apparent but protocol not checked	Groups similar at baseline	Low
McDonald et al. 2016[45]	Computerised blocked	Study coordinator independent of care and surgery	Patients blind. Surgeon aware of study	Outcome assessment blind to allocation	1; 4 unexplained	None apparent, protocol not checked	Groups similar at baseline	Low
Meunier et al. 2007[51]	Computer generated	Sealed envelope	Randomisation code broken after 1 year	Yes	ITT reported except for 12 month pain outcome	No but not checked protocol	M/F ratio differed	Low
Morin et al. 2005[110]	Allocated randomly	Sealed envelope	All patients received some form of nerve block. Anaesthesiologist not blind to intervention	Observers not blinded	Per protocol analysis	No but not checked protocol	Difference between groups in anesthetist's opinion of difficulty of catheter placement. BMI differed between groups	High
Motififard et al. 2017[46]	Computer generated	Study coordinator independent of care and surgery	Patients blind. Surgeon aware of study	Outcome assessment blind to allocation	3; 7 (1; 4 unexplained)	None apparent, protocol not checked	Groups similar at baseline	Low

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Nader et al. 2012[39]	Computer generated	Opaque envelope	No	Patient reported outcome	1:1 lost to follow up	Protocol not checked but reasonable range of outcomes	FNB group somewhat higher BMI	Low
Niemeläinen et al. 2014[47]	No details	Opaque sealed envelopes	Only research nurse preparing infiltrate aware of randomisation. All other personnel unaware until after 1 year follow up	Only research nurse preparing infiltrate aware of randomisation. All other personnel unaware until after 1 year follow up	All patients who received intervention completed follow up	No but not checked protocol	No	Low
Peng et al. 2014[40]	Computer generated	Not possible	Not possible	Patient reported outcome	31:38 lost at 12 months but ITT and per- protocol analysis	No but not checked protocol	No	Lov
Perrin and Purcell 2009[107]	No details	Sealed syringe code stored in pharmacy department	yes	Yes	4 failed to complete protocol	No but not checked protocol	Pilot investigation. High risk of bias due to recruitment difficulties leading to small trial	Hig
Reinhardt et al. 2014[41]	Computer generated	Maintained by pharmacy department for blinding	Patients blind to intervention	Blinded research assistant and partially physical therapist	0 reported lost to follow up of those who received interventions	No but not checked protocol	No	Low
Seah et al. 2011[48]	Randomisation tables	Sealed envelopes. Anaesthetist and surgeon blind before opening of	Blinding of patients not stated	Blind outcome assessors and PROMs	No losses to follow up reported	No but not checked protocol	No	Low

		sealed envelope						
Shum et al. 2009[106]	No details	No details	Anaesthetist performing the blocks was not involved in the postoperative follow-up and data collection	Patient reported	14% and 20%	No but not checked protocol	Mean patient weight lower in no FNB group. More favourable mean OKS in no FNB group. Two groups combined for 2 year outcome but not for earlier	High
Spreng et al. 2012[115], Spreng et al. 2010[116]	Hospital pharmacy	Epidural catheter or sham set-up taped along the back of the patient and connected to an infusion pump covered in an opaque bag. Also sham knee catheter	Patients blind	Blind outcome assessment	13%	Limited reporting in conference abstract	Conference abstract only so limited information additional to early follow up paper	Unclear
Wang et al. 2015[112]	No details	No details	Not stated	Not stated	2:4 lost to follow up	No but not checked protocol	No	Unclear
Wegener et al. 2013[42]	No details	Opaque envelope	Patients, surgeons and researchers not blind to intervention	Patients not blinded	2:7:5 lost to follow up	No. Protocol checked	no	Low
Widmer et al. 2012[43]	Coded envelope	Coded envelope	Except for anaesthetist and surgeon	Both the investigators and patients were blinded	None reported as incomplete	No but protocol not checked	No	Low

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Williams et al. 2013[49]	Computer generated	Not stated	Patients and assessors blind	Patients and assessors blind	3:1 of those who received treatment	No but not checked protocol	No	Low
Wu and Wong 2014[44]	Computer	Sealed envelopes	No	No	Available cases	No but not checked protocol	No	Low
Wylde et al. 2015[50]	Trials unit	Trials unit	Surgeon and anaesthetist not blind to allocation, Patients blind	Patients and research nurses blind to allocation	ITT with imputed data	No as per protocol	No	Low
Yue et al. 2013[114]	No details	No details	Surgeons and patients were double-blinded to the injection administered	surgeons and patients were double-blinded to the injection administered	Losses to follow up not reported	Limited reporting	No	Unclea
	ger point dry ne		ſ	1			1	
Mayoral et al. 2013[118]	Computerised	Not described	Patient and other researchers apart from physical therapist blind	Patient outcomes	4: 5 loss to follow up	None apparent but protocol not checked	No	High
Tourniquet		•						
Abdel-Salam and Eyres 1995[119]	Card system	Not described	No	No	No losses to follow up	None apparent but protocol not checked	No	Unclea
Ejaz et al. 2014[54]	Block randomised	Sealed envelopes	Patients unaware	PROM	No losses to follow up of those who received treatments	None apparent but protocol not checked	No	Low
Huang et al. 2017[55]	Computer generated	Sealed opaque envelopes	Surgeons not blind. Patients blind to allocation	Data collector blind to allocation	No losses to follow up reported	None apparent but protocol	Groups similar at baseline	Low

						not checked		
Liu et al. 2014[56]	Excel	Not described	Patients blind	PROM	No losses	None apparent but protocol not checked.	No	Low
Mittal et al. 2012[57]	Computer generated	Sealed opaque envelopes	Patient blind	Outcome assessors blind. PROM	5:2	None apparent but protocol not checked	Study stopped because of high risk of transfusion in short tourniquet duration group	Low
Şükür et al.2016[120]	Computer generated	Not described	Possibly patients	Outcome assessors blind	No losses to follow up	KSS outcome noted in methods but not presented in results	No	High
Zhang et al. 2017[58]	Excel	Randomisation by blinded researcher.	Patients and nurses on ward blind	Not clear	No losses reported	None apparent but protocol not checked	Groups similar at baseline	Low
Zhang et al.2016[121]	Randomly allocated	Not clear	Not clear	Not clear	Not clear	HSS outcome noted in methods but not presented in results	No	High

Brock et al. 2017[122]	Web-based	Not specified	Not possible	No but PROMs	4; 2 of those receiving intervention	None apparent but protocol not checked	Groups similar at baseline	Low
Blood conserva Hourlier et al. 2015[60]	ation Computer generated	Opaque envelopes	Anaethsetist, surgeon and patient blind to treatment allocation	Assessors blind	No missing data	None apparent but protocol not checked	No	Low
	Computer generated	Sealed opaque envelopes	Surgeons not blind. Patients blind to allocation	Data collector blind to allocation	No losses to follow up reported	None apparent but protocol not checked	Groups similar at baseline	Low
Kim et al. 2014[61]	Computer generated	Not stated	patients blind to allocation	Clinical investigator blind to allocation	No missing data	None apparent but protocol not checked	No	Low
Kusuma et al. 2013[62]	Computer generated	Sealed envelopes	Surgeon and patient blind	Outcome assessor blind	No missing data	None apparent but protocol not checked	No	Low
Napier et al. 2014[63]	Computer generated	Sealed envelopes	Unlikely	Not stated but PROM	low losses to follow up	None apparent but protocol not checked	No	Low
Sa- Ngasoongsong et al. 2011[64]	Computer generated	Sealed envelopes	Surgeon and patient blind	Outcome assessor blind	No missing data	None apparent but	No	Lov

<i>Cryotherapy</i> Wang 2017[125]	No details	No details	No details	No details	No losses to follow up	None apparent	Groups similar at	Unclear
						not checked		
Aggarwai et al. 2014[124]	Not described	envelopes	Patients blind	examiners blind	follow up reported	apparent but protocol	in groups from randomisation	Hign
Platelet rich pla Aggarwal et al.	asma Not described	Opaque	Patients blind	Patients and	No losses to	not checked	Odd numbers	High
Thomas et al. 2001[123]	Not described	not stated	Not reported	Not reported but PROM	Not reported but ITT	None apparent but protocol	No	Unclear
et al. 2013[65]			Not report	Not you and the	Notareation	protocol not checked	between groups in pre- operative Hb	110-1
Sa- Ngasoongsong et al. 2013[65]	Computer generated	Sealed envelopes	Surgeon and patient blind	Outcome assessor blind	No missing data	not checked None apparent but	Some difference between	Low

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					forward for missing data		reassigned to CPM	
Bennett et al. 2005[67]	Block	Not stated	Operating surgeon blind. Patient not	Independent assessor blind	1 not included in analyses as not able to achieve 90 degree flexion	No	No	Low
Ersözlü et al. 2009[68]	Divided into groups by random selection	Not described	No	Surgeon score	A diabetic patient from the control group was excluded because of a superficial wound infection, a patient with a cardiac problem in group II due to dysrhythmia, and two patients due to insufficient follow-up.	Not apparent	No differences baseline	Unclea
Kumar et al. 1996[130]	Random number generator	Not stated	No	Not described	Large loss to follow up	Not all data clearly reported	No	High
Leach et al. 2006[126]	Allocation by date of birth	No	No	Blinded evaluation	Large loss to follow up	No	No	High
MacDonald et al. 2000[132]	Computer generated	Allocation concealed	No	Not described	Not reported	Yes, not all outcomes reported in full	No	Unclea
Pope et al. 1997[128]	Not described	Not described	Not described	Not described	No separate reporting. 8 patients (12 knees)	None apparent but protocol	No	High

					excluding 1 death	not checked		
Sahin et al. 2006[127]	Not described	Not stated	No	Followed up by treating physician	Low loss to follow up	No	No	Unclea
Worland et al. 1998[131]	Not described	Not described	No	Researcher blind	Not reported separately	None apparent but protocol not checked	No	Unclea
Electrical stime								
Adravanti et al. 2014[135]	Computer generated	Not described	Research assistant not involved in patient assessment	Principal investigator and all physicians in charge of clinical controls were blinded to patient allocation	78% retained at 6 months	Not apparent but protocol not checked	No	High
Avramidis et al. 2011[69]	Computer generated	Not described	No	Independent assessors blind	3 (intolerance of intervention); 3	Not apparent	Baseline similar	Low
Levine et al. 2013[134]	Drawing papers from hat	Not described	No	Not described. WOMAC PROM	5:9 for KSS pain and WOMAC	Not apparent but protocol not checked	No	Unclea
Moretti et al. 2012[70]	Computer generated	Not described	Physicians, as well as medical assessors, were blinded to the allocation of patients in the study groups	Physicians, as well as medical assessors, were blinded to the allocation of patients in the study groups	No losses reported	Not apparent but protocol not checked	No	Low
Stevens- Lapsley et al. 2012[133]	Stratified	Concealed	No	no but standardised scripts used	5; 6	Not apparent but protocol	WOMAC, BMI unequal at baseline	Unclea

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9 10 11 12 13 14 15 16 17	
18 19 20 21 22 23 24 25	
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						not checked		
Rehabilitation				4	•	1		
Hill et al. 2000[138]	Not described	Not stated	Not possible	Not described	No losses to follow up after initial 23222	No but protocol not checked	No	Unclea
Li et al. 2017[71]	Random number table	Not stated	Not possible	Not described but PROM	No losses to follow up	No but protocol not checked	Groups similar at baseline	Low
Liebs et al. 2012[72]	Computer generated	Allocation concealed	Not possible	No but PROM	Low losses to follow up (<20% if deaths and other explained reasons not counted)	No but protocol not checked	No	Low
Mahomed et al. 2008[137]	Block randomisation	Not stated	Not possible	PROM	No loss	No but protocol not checked	ITT gave similar results to analysis according to actual discharge destination (20 inpatient group received home based)	Low
Rahmann et al. 2009[136]	Not described	Sealed numbered envelopes	Not possible	Assessor blind to intervention. Patient reported outcome	Low losses to follow up	No but protocol not checked	TKR patients more likely to receive ward- based control intervention. THR and TKR analysed together	Unclea
Wang et al. 2014[74]	Computer generated	Surgeons did not participate	Surgery was performed by the	Postoperative evaluation was	No loss to follow up	None apparent	No baseline differences	Low

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		in pre- operative grouping	physicians who did not participate in the preoperative grouping and postoperative evaluation	conducted by the physicians who were unaware of the grouping.		but protocol not checked		
Wound manag Kong et al.	Not described	Not described	Placebo used	Patient outcome	Low loss to	None	Similar at	Low
2014[75]		Not described	Flacebo useu		follow up	apparent but protocol not checked	baseline	LOW
Anabolic stero								1 -
Hohmann et al. 2010[76]	Internet based	Not reported	Placebo trial	Double-blind design minimized systemic error and eliminated observer and experimenter's bias	0 loss to follow up	None apparent	None apparent but small study	Low
Guided imager	v	1			1			
Jacobson et al. 2016[139]	Permuted blocks	Opaque CD holders	Personnel yes, participants no	Yes	12; 10 of patients receiving treatment	None apparent but protocol not checked	No	High

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Reporting checklist for systematic review and meta-analysis.

Based on the PRISMA guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

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		Reporting Item	Page Number
	#1	Identify the report as a systematic review, meta-analysis, or both.	1
Structured summary	#2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number	2-3,5
Rationale	#3	Describe the rationale for the review in the context of what is already known.	4-5
Objectives	#4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5-6
Protocol and registration	#5 For p	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address) and, if available, provide registration information including the registration number. beer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	5

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1 2 3 4 5	Eligibility criteria	#6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rational	5-6
6 7 8 9 10 11 12 13 14 15	Information sources	#7	Describe all information sources in the search (e.g., databases with dates of coverage, contact with study authors to identify additional studies) and date last searched.	6
	Search	#8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	See note 1
16 17 18 19 20 21	Study selection	#9	State the process for selecting studies (i.e., for screening, for determining eligibility, for inclusion in the systematic review, and, if applicable, for inclusion in the meta-analysis).	5,6
22 23 24 25 26	Data collection process	#10	Describe the method of data extraction from reports (e.g., piloted forms, independently by two reviewers) and any processes for obtaining and confirming data from investigators.	6
27 28 29 30 31 32 33 34 35 36 37 38	Data items	#11	List and define all variables for which data were sought (e.g., PICOS, funding sources), and any assumptions and simplifications made.	5/6
	Risk of bias in individual studies	#12	Describe methods used for assessing risk of bias in individual studies (including specification of whether this was done at the study or outcome level, or both), and how this information is to be used in any data synthesis.	6
39 40 41 42	Summary measures	#13	State the principal summary measures (e.g., risk ratio, difference in means).	7
43 44 45 46 47	Planned methods of analyis	#14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I2) for each meta-analysis.	7
48 49 50 51 52 53 54 55 56 57 58	Risk of bias across studies	#15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6
	Additional analyses	#16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	7
59 60		For p	eer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	

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1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20	Study selection	#17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	See note 2
	Study characteristics	#18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citation.	See note 3
	Risk of bias within studies	#19	Present data on risk of bias of each study and, if available, any outcome-level assessment (see Item 12).	See note 4
	Results of individual studies	#20	For all outcomes considered (benefits and harms), present, for each study: (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot.	See note 5
21 22 23 24 25 26	Synthesis of results	#21	Present the main results of the review. If meta-analyses are done, include for each, confidence intervals and measures of consistency.	16-23
27 28 29 30 31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46	Risk of bias across studies	#22	Present results of any assessment of risk of bias across studies (see Item 15).	See note 6
	Additional analysis	#23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	16-23
	Summary of Evidence	#24	Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., health care providers, users, and policy makers	16-23
	Limitations	#25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias).	24-25
47 48 49 50	Conclusions	#26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	23-25
50 51 52 53 54 55 56	Funding	#27	Describe sources of funding or other support (e.g., supply of data) for the systematic review; role of funders for the systematic review.	26
56 57	Author notes			

Author notes

- 1. 5, Supplemetary material
- ²₃ 2. 7, Figure 1
- 4
 5 3. 8-15, Table1, Supplementary material
 - 4. 7, Supplementary material
- 5. 8-15, Table1, Supplementary material

1112 6. 8-15, Supplementary material13

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Are peri-operative interventions effective in preventing chronic pain after primary total knee replacement? A systematic review

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Are peri-operative interventions effective in preventing chronic pain after primary total knee replacement? A systematic review

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ABSTRACT

Objectives

For many people with advanced osteoarthritis, total knee replacement (TKR) is an effective treatment for relieving pain and improving function. Features of peri-operative care may be associated with the adverse event of chronic pain six months or longer after surgery; effects may be direct, e.g. through nerve damage or surgical complications, or indirect through adverse events. This systematic review aims to evaluate whether non-surgical peri-operative interventions prevent long-term pain after TKR.

Methods

We conducted a systematic review of peri-operative interventions for adults with osteoarthritis receiving primary TKR evaluated in a randomised controlled trial (RCT). We searched *The Cochrane Library*, MEDLINE, Embase, PsycINFO and CINAHL to February 2018. After screening, two reviewers evaluated articles. Studies at low risk of bias according to the Cochrane tool were included.

Interventions

Peri-operative non-surgical interventions; control receiving no intervention or alternative treatment.

Primary and secondary outcome measures

Pain or score with pain component assessed at six months or longer post-operative.

Results

44 RCTs at low risk of bias assessed long-term pain. Intervention heterogeneity precluded meta-analysis and definitive statements on effectiveness. Good-quality research provided generally weak evidence for small reductions in long-term pain with local infiltration analgesia (3 studies), ketamine infusion (1 study), pregabalin (1 study) and supported early discharge (1 study) compared with no intervention. For electric muscle stimulation (2 studies), anabolic steroids (1 study) and walking training (1 study) there was a suggestion of more clinically important benefit. No concerns relating to long-term adverse events were reported. For a range of treatments there was no evidence linking them with unfavourable pain outcomes.

Conclusions

To prevent chronic pain after TKR, several peri-operative interventions show benefits and merit further research. Good quality studies assessing long-term pain after peri-operative interventions are feasible and necessary to ensure that patients with osteoarthritis achieve good long-term outcomes after TKR.

STRENGTHS AND LIMITATIONS

• For the first time, this systematic review brings together contemporary evidence on aspects of peri-operative care for people with total knee replacement and their effects on long-term pain.

- Only studies assessed to be at low risk of bias were included in the narrative synthesis.
- Intervention and outcome heterogeneity precluded meta-analysis.

KEYWORDS

Total knee replacement; Systematic review; Randomised controlled trial; Peri-operative care; Long-term pain

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BACKGROUND

In the US about 13% of men and 19% of women will be diagnosed with knee osteoarthritis and over half will receive a total knee replacement (TKR)[1]. For people with advanced osteoarthritis unresponsive to pharmacological or conservative treatments, TKR aims to relieve pain and improve function. In the UK nearly 100,000 primary TKRs were performed in 2017[2,3] and in the USA in 2010, an estimated 4.7 million people were living with a TKR[4]. Despite good outcomes for many, some people report long-term pain and are disappointed with their surgery[5,6]. After TKR, pain levels plateau from about 6 months[7,8] after which persistent pain is considered "chronic"[9] and is reported by 10-34% of patients[10].

The mechanisms that influence the development of chronic pain after total knee replacement may be biological, mechanical and psychosocial. Biological explanations include the sensitising impact of long-term pain from osteoarthritis[11,12], inflammation, infection and localised nerve injury[13]. Mechanical explanations include altered gait, prosthesis loosening, and effects on ligaments[14,15]. Psychological factors including depression and catastrophizing may also influence outcomes[16-19]. Much research has focused on pre-operative predictors of outcomes and these include pain intensity, presence of widespread pain, anxiety, depression and catastrophizing.[10,20] However, attempts to target or modify pre-operative care have, as yet, shown no benefit regarding chronic pain or other long-term patient outcomes[10,21-23].

Peri-operative risk factors suggest that appropriate interventions may reduce long-term pain. For example, acute post-operative pain, which may be a direct consequence of the operation, anaesthetic protocol and subsequent analgesia, or related to particular aspects of care, is an acknowledged risk factor for chronic post-surgical pain[24].

In the peri-operative period from hospital admission to the early stages of recovery, care focuses on acute pain management, prevention of adverse events, facilitation of early mobilisation and timely discharge. However, for people with osteoarthritis the key aim of TKR is the achievement of a long-term painless and well-functioning knee with no adverse events. All aspects of peri-operative care should work together to achieve this.

Any treatment in the peri-operative period including pain management, blood conservation, deep vein thrombosis (DVT) and infection prevention, and inpatient rehabilitation could potentially affect patient recovery and chronic pain, either directly or indirectly. Direct mechanisms may be through prevention of nerve damage[25], post-thrombotic syndrome[26], reperfusion injury[27] and articular bleeding[28]. For other treatments, pathways leading to long-

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term pain may be indirect, possibly being mediated through increased risks of adverse events[29]. Irrespective of mechanism, chronic pain is a highly prevalent adverse event after TKR and should be considered along with infection, DVT and other complications in the safety profile of interventions.

Our systematic review of randomised controlled trials (RCTs) aims to evaluate the effectiveness of treatments in the peri-operative period in preventing long-term pain after TKR. By focusing on studies with low risk of bias we aim to identify interventions with robust evidence of long-term effectiveness and identify gaps in the research base.

METHODS

The systematic review protocol was registered (PROSPERO CRD42017041382) and PRISMA reporting guidelines used[30]. A checklist is included as Supplementary material.

Patient and public involvement

As part of the STAR programme of research (NIHR RP-PG-0613-20001), this review benefited from extensive patient and public involvement. Advice was sought from patients and stakeholders at a group discussion in March 2016 with decisions made on inclusion criteria and outcomes. Our patient advisory group comprises five patients with experience of long-term pain after TKR, supported by a dedicated co-ordinator. This group will advise on dissemination of the study results to a general audience including plain language summaries.

Eligibility criteria

Studies were eligible if they satisfied PICOS criteria defined in the protocol. Participants were adults receiving unilateral primary TKR with osteoarthritis in at least 75% of patients. Pharmacological or non-pharmacological interventions commenced in the peri-operative setting with "peri-operative" reflecting the time from hospital admission to immediately post-discharge. Interventions relating to implant designs and surgical procedures were excluded. The comparator was usual care, placebo or an alternative intervention. Outcomes were, in preference, patient-reported joint-specific pain intensity measured by tools such as the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) or Oxford Knee Score (OKS). If joint-specific measures were unavailable, pain dimensions from quality of life measures were used or pain rated on a visual analogue scale (VAS) or numerical rating scale (NRS). We also considered composite patient-reported outcome measures and surgeon scores which included a pain intensity component, such as the American Knee Society Score (KSS) and Hospital for Special Surgery (HSS) score. Measures specifically of neuropathic pain were also used. The occurrence of adverse events was summarised. The studies included were RCTs with follow up at ≥6 months after surgery and a pain outcome or score including pain. Authors of studies were contacted regarding incomplete pain outcome data.

Database searches

We established an Endnote database of all RCTs in TKR. On 14th February 2018, a search from database inception was conducted in: *The Cochrane Library*; MEDLINE, Embase and PsycINFO on Ovid; and CINAHL on EBSCOhost. The MEDLINE search strategy is included as supplementary material. Citations of key articles were tracked in Web of Science. No language restrictions were applied, and translations made. Studies reported as abstracts or unobtainable using inter-library loans and author contact were excluded.

Screening and data extraction

We imported records into Endnote X7 (Thomson Reuters). An initial screen by one reviewer excluded clearly irrelevant articles. Subsequently, abstracts and full articles were screened independently by two reviewers and reasons for exclusion recorded.

Data were extracted onto piloted forms and an Excel spreadsheet by one reviewer, specifically: country; dates; participants (indication, age, sex); inclusion and exclusion criteria; intervention and control content; setting, timing, duration and intensity of intervention; follow up intervals; losses to follow up; pain outcome data; and serious adverse events. Data was checked against source material by a second reviewer.

Authors were contacted for missing data, and data provided for previous reviews was used[10,31].

Quality assessment

Potential sources of bias were assessed by two experienced reviewers using the Cochrane risk of bias tool[32], specifically: the randomisation process; deviations from intended interventions; missing outcome data (>20%), measurement of the outcome; and selection of the reported result. Studies with serious concerns relating to risk of bias were considered high risk and those with limited reporting unclear risk. Studies with high or unclear risk of bias were excluded from the narrative synthesis but are included in supplementary summary tables with reasons for exclusion.

Data analysis

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Insufficient studies with similar interventions and outcomes were identified for meta-analysis, and a narrative synthesis is presented. Results reported with p-values ≤0.001 were considered "strong" evidence of effectiveness[33], p-values 0.001-0.05 "some" evidence, and p-values 0.05-0.1 "weak" evidence. When authors reported results "statistically significant" with no p-value, this was noted. Where possible, effect sizes were compared with published minimal clinically important differences (MCID). Concerns relating to adverse events were summarised.

RESULTS

Figure 1 shows review progress and reasons for exclusion. Of 1515 RCTs of interventions in the peri-operative setting, 1385 had no long-term follow up. Peri-operative interventions with follow up of \geq six months were evaluated in 130 RCTs of which 76 reported a pain outcome or score with a pain component. Detailed intervention and study characteristics and risk of bias assessments are provided as supplementary material. Studies excluded had concerns for risk of bias pertaining to at least one of: large baseline differences in group characteristics or numbers in groups (n=4); incomplete outcome data (n=15); limited or selective reporting (n=12); or unblinded surgeon follow up (n=1).

Details of 44 studies assessed to be at low risk of bias are summarised in Table 1. In 34 studies, patients received TKR exclusively for osteoarthritis and in three, 75% or more patients had osteoarthritis. In seven studies there was no information on reason for surgery but there was no suggestion that patients had an indication other than osteoarthritis. Interventions focused on pain management (n=20), tourniquets (n=5), compression bandages (n=1), blood conservation (n=7), denusomab (n=1), continuous passive motion (n=2), electrical stimulation (n=2), rehabilitation (n=4), wound management (n=1) and anabolic steroids (n=1). Primary pain outcome measures reported were VAS or NRS pain (n=12), WOMAC pain (n=7), KOOS pain (n=3), Leeds assessment of Neuropathic Symptoms and Signs Pain Scale (S-LANSS) (n=1), SF-36 bodily pain (n=1), or composite scores including a pain measure, OKS or WOMAC (n=10), KSS or HSS (n=10). Latest outcomes were recorded at 6 months (n=12), 12 months (n=26) and 24 months (n=6). Reporting of adverse events covered the entire follow up period in 27 studies, short-term after surgery in 15 studies, but were not reported in two studies.

Table 1. Perioperative interventions with follow up for pain or score at6 months or later and assessed to be at low risk of bias

Study	Treatment common to		Number patients	Follow up Group difference
	randomised		patiente	
Pain management: nerve	blocks			
Albrecht et al. 2014[34]	SNB	1. FNB continuous high	99	1 year
Canada, 2009-2011,		2. FNB continuous low		WOMAC score: no difference
1 hospital		3. FNB single		(p=0.68)
Choy et al. 2011[35]	PCA	1. FNB continuous long	61	1 year
Korea, 2006-2007,		2. FNB continuous short		WOMAC pain: no difference
1 surgeon				(p=0.2)
Fan et al. 2016[36]	PCA	1. FNB single	157	1 year
China, 2012-2014,		2. LIA		KSS: no difference (p=0.51)
2 surgeons				
Gao et al. 2017[37]	LIA	1. General anaesthesia	150	6 months
China, 2014-2015,		2. FNB single		HSS score: no significant
1 centre		3. FNB/ SNB single		difference (p> 0.05)
Macrinici et al. 2017[38]	LIA	1. ACB single	98	6 months
USA, Before 2017		2. FNB single		VAS pain: no difference
1 centre				
Nader et al. 2012[39]	PCA	1. FNB continuous	62	1 year
USA, 2007-2008,		2. Oral opioid		NRS pain stair: some evidence
1 surgeon				favouring opioid (p=0.01) but not consistent. Overall NRS pain: no difference (p=1.0)
				VTE: concern opioid
Peng et al. 2014[40]		1. FNB continuous	280	6 months and 1 year
China, Before 2014,		2. PCA		NRS pain: some evidence favouring FNB at 6 months
		8		

1 centre				(p=0.021); no difference at 1 year (p=0.273)
Reinhardt et al. 2014[41]		1. FNB single/ epidural	94	1 year
USA, 2010-2012,		2. LIA 48 hours		VAS pain: no difference
2 surgeons				
Wegener et al. 2013[42]	FNB	1. SNB single	89	1 year
The Netherlands, 2008-2010,		2. SNB continuous		WOMAC pain: no difference
1 centre		3. PCA		(p=0.81)
Widmer et al. 2012[43]	LIA, PCA	1. FNB single	55	1 year
Australia, before 2012,		2. Control no FNB		WOMAC pain: no difference (p=0.74)
2 surgeons		1. FNB continuous	60	C months
Wu and Wong 2014[44]			60	6 months
China, 2009-2011,		2. PCA		KSS: no difference (p=0.513)
1 centre		6		
Pain management: LIA				
McDonald et al. 2016[45]		1. LIA	222	1 year
UK, 2010-2011		2. PCA		OKS: no difference (p=0.915)
1 hospital				
Motififard et al. 2017[46]		1. LIA pre-emptive	120	6 months
Iran, 2014-2015		-		KSS: weak evidence favouring
1 hospital		2. Control saline with epinephrine		LIA (p=0.07). Difference between groups (14.2/200) less than MCID (12.3/200).
Niemeläinen et al. 2014[47]	PCA	1. LIA	56	1 year
Finland, 2011-2012		2. Control saline		OKS: weak evidence from
1 hospital				means and confidence intervals favouring LIA. Difference (2.7/48) less than MCID (4.0/48)
Seah et al. 2011[48]	PCA	1. LIA with corticosteroid	100	6 months and 2 years
Singapore, 2004-2005		2. LIA no corticosteroid		OKS: no difference

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1 hospital				
Williams et al. 2013[49]	LIA, PCA	1. LIA 48 hours	51	6 months and 1 year
Canada, Before 2013		2. Control saline		VAS pain: no difference (6 months p=0.836, 1 year
2 surgeons				p=0.767)
Wylde et al. 2015[50]	FNB, PCA	1. LIA	280	6 months and 1 year
UK, 2009-2012		2. Control no LIA		WOMAC pain: weak evidence favouring LIA at 6 months
1 centre				p=0.063; 1 year p=0.107. Mean difference at 1 year (3.8/100) lower than MCID (8– 9/100)
Pain management: Celeco.	xib			
Meunier et al. 2007[51]	PCA	1. Celecoxib	44	1 year
Sweden, 2004-2005		2. Control placebo		KOOS/VAS pain: no difference
1 centre				
Pain management: Ketami	ne/ Nefopam	0,		
Aveline et al. 2014[52]	PCA	1. Ketamine infusion	75	6 months and 1 year
France, 2005		2. Nefopam infusion		DN4/VAS pain: some evidence favouring ketamine (for DN4
1 centre		3. Control saline		p=0.02). Few patients had neuropathic pain at 12 months
Pain management: Pregab	alin	(9	
Buvanendran et al. 2010[53]	LIA, PCA	1. Pregabalin	240	6 months
USA, 2006-2007		2. Control placebo		NRS pain: some evidence favouring pregabalin at 6
Single centre				months (p=0.0176)
				S-LANSS pain: no neuropathi pain reported in pregabalin group compared with 5.2% of patients in control group
				(p=0.014) Sedation and confusion day 0
				and day 1: concern pregabalin

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Tourniquet				
Ejaz et al. 2014[54]	Tranexamic	1. Tourniquet	64	6 months and 1 year
Denmark, 2011-2012	acid	2. Tourniquet not inflated		KOOS pain: no significant
1 centre				difference
Huang et al. 2017[55]	Tranexamic	1. Tourniquet	100	6 months
China, 2015	acid	2. No tourniquet		VAS pain: no difference (p=0.728)
1 centre				Wound: concern tourniquet
Liu et al. 2014[56]	0,	1. Tourniquet	20	6 months and 1 year
Australia, Before 2014		2. Tourniquet not inflated		OKS: no significant differenc
1 surgeon				Transfusion: concern tourniquet
Mittal et al. 2012[57]		1. Tourniquet short	65	1 year
Australia, 2008-2010		duration		OKS: weak evidence from
1 centre		2. Tourniquet long duration		means and Cis on graph favouring long duration at 1 year. Mean difference (5) greater than MCID (4)
				Transfusions/ adverse events
Zhang et al. 2017[58]		1. Tourniquet for entire	150	6 months
China, 2008-2011		operation		HSS score: no difference
1 surgeon		2. Tourniquet removed before wound closure		(p=0.839)
		3. Tourniquet from first		Transfusions: concern late tourniquet start in groups 1
		bone osteotomy until closure		and 2
Compression bandage				
Brock et al. 2017[59]	Hydrocolloid	1. Compression bandage	49	6 months
UK, 2013-2014	dressing	2. Standard crepe		OKS: no difference (p=0.58)
1 hospital		bandage		
Blood conservation				
		11		

1 2 3 4 5 6 7 8 9 10 1 12 13 14 15 16 17 8 19 20 21 22 32 4 5 26 7 8 9 10 1 12 13 14 15 16 17 8 19 20 21 22 32 4 5 26 7 8 9 30 3 12 33 4 35 36 7 8 9 40 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4 4	
44 45 46 47 48	

tourniquet, electrocautery Tourniquet	tranexamic acid 2. Control saline 1. Intravenous and topical tranexamic acid 2. No tranexamic acid	100	KSS: no difference (p=0.90) 6 months VAS pain: no difference (p=0.728)
Tourniquet	1. Intravenous and topical tranexamic acid	100	VAS pain: no difference
Tourniquet	tranexamic acid	100	VAS pain: no difference
			•
	2. No tranexamic acid		(p=0.728)
			HSS score: strong evidence favouring tranexamic acid (p<0.001). Mean difference (1.4/100) lower than MCID (8.3/100)
			Blood loss: control concern
Tourniquet,	1. Tranexamic acid	180	1 year
compressive	2. No tranexamic acid		WOMAC pain: no significant difference
aressing			
			Transfusion: control concern
Tourniquet, Esmarch	1. Thrombin infusion	80	6 months, 1 and 2 years
bandage,	2. No thrombin infusion		KSS: no difference (p=0.45)
electrocautery			
	1. Passive flexion	180	1 year
	2. Passive extension		OKS: no difference (p=0.27)
			Transfusion: extension concern
Drain and	1. Tranexamic acid	48	6 months
compressive dressing	2. Control saline		WOMAC score: no difference (p=0.282)
			Transfusion: control concern
Drain and	1. Tranexamic acid	135	1 year
dressing	2. Tranexamic acid		WOMAC score: no difference (p=0.42)
	250mg 3. Control saline		Transfusions: control and 250mg group concerns
	drain, compressive dressing Tourniquet, Esmarch bandage, electrocautery Drain and compressive dressing Drain and compressive	drain, compressive dressing2. No tranexamic acidTourniquet, Esmarch bandage, electrocautery1. Thrombin infusion 2. No thrombin infusion1. Passive flexion 2. Passive extensionDrain and compressive dressing1. Tranexamic acid 2. Control salineDrain and compressive dressing1. Tranexamic acid 500mg 2. Tranexamic acid 250mg	drain, compressive dressing2. No tranexamic acidTourniquet, Esmarch bandage, electrocautery1. Thrombin infusion802. No thrombin infusion electrocautery2. No thrombin infusion801. Passive flexion 2. Passive extension180Drain and compressive dressing1. Tranexamic acid482. Control saline1. Tranexamic acid135Drain and compressive dressing1. Tranexamic acid135Drain and compressive dressing1. Tranexamic acid135Drain and compressive dressing1. Tranexamic acid135Drain and compressive dressing1. Tranexamic acid135Jong dressing3. Control saline135

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Denusomab				
Ledin et al. 2017[66]		1. Denusomab	50	1 and 2 years
Sweden, 2012-2014		2. Placebo		KOOS pain: no significant
2 centres				difference
Continuous passive motio	n			
Bennett et al. 2005[67]	Physiotherapy	1. Standard CPM	147	1 year
Australia, 1997-2000		2. Early flexion CPM		KSS: no significant difference
1 hospital		3. No CPM		
Ersözlü et al. 2009[68]	Physiotherapy	1. CPM low and	90	2 years
Turkey, 2003-2004		increasing		KSS: no difference (p=0.67)
1 hospital		2. CPM high and increasing		
		3. No CPM		
Electrical stimulation				
Avramidis et al. 2011[69]	Physiotherapy	1. Transcutaneous	76	1 year
Greece, 2005-2006		electric muscle stimulation		SF-36 bodily pain: strong
1 hospital		2. No treatment		evidence favouring electrical stimulation (p<0.001). Mean difference (12.5/100) close to
				MCID (16.9/100). OKS/ KSS: no difference
Moretti et al. 2012[70]	Rehabilitation	1. Pulsed electromagnetic	30	6 months and 1 year
Italy, 2008-2010	protocol	fields		VAS pain: some evidence
-		2. No treatment		favouring electrical stimulation
1 hospital				(p<0.05). Mean difference (2.1/10) greater than MCID
				(16.1/100)
				Knee swelling: electrical stimulation concern
Rehabilitation				
Li et al. 2017[71]	Standard	1. Walking guidance and	86	6 months
China, 2015-2016	rehabilitation	training		
		13		

1 hospital		2. No treatment		VAS pain/ HSS score: some evidence favouring walking (both p<0.01). Mean VAS pair difference (2.4/100) greater than MCID (16.1/100)
Liebs et al. 2012[72]	CPM,	1. Early aquatic therapy	185	6 months, 1 and 2 years
Germany, 2003-2004	physiotherapy, post-discharge aquatic	2. Delayed aquatic therapy		WOMAC pain: no difference (p=0.22 at 12 months)
4 hospitals	therapy			(p)
Mahomed et al. 2008[73]	Physiotherapy	1. Multidisciplinary	234 hip	1 year
Canada, 2000-2002		and home physiotherapy	or knee replace	WOMAC pain: weak evidence favouring supported discharge
2 centres		2. Transfer to rehabilitation centre	ment	(p=0.08). Mean difference (4) less than MCID (8-9)
Wang et al. 2014[74]		1. Wound closure in	80	6 months
China, 2009-2010		flexion 2. Wound closure in		VAS pain: no difference (p=0.64)
1 centre		extension		(p=0.64)
Wound management		()		
Kong et al. 2014[75]	Skin staples	1. Silicone gel	100	6 months and 1 year
South Korea, 2011	and closure strip	2. Petroleum gel		VAS pain: no difference (6 months p=0.886, 1 year
1 surgeon				p=0.201)
Anabolic steroids		C		
Hohmann et al. 2010[76]	CPM. Cold compression,	1. Intramuscular nandrolone injections	10	6 and 9 months, 1 year
Australia, Before 2010		2. Saline injections		KSS: some evidence favourin nandrolone (6 months p=0.04
1 surgeon				9 months p=0.06, 12 months p=0.03). Difference at 12 months (10.2) close to MCID (12.3)
				Bone mineral density: weak evidence favouring nandrolon
ACB adductor canal blo	ock; CPM Continuou	us passive motion; DN4 Doule	eur Neurop	athique 4; FNB
Femoral nerve block; H	ISS Hospital for Spe	ecial Surgery; KOOS Knee inj	ury and Os	steoarthritis Outcome
Score; KSS Knee Socie	ety Score; LIA local	infiltration analgesia; MCID n	ninimal clin	ically important
		14		

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difference; NRS Numerical rating scale; OKS Oxford Knee Score; PCA Patient controlled analgesia; SF-36 Short Form 36 Health Survey; S-LANSS Leeds assessment of Neuropathic Symptoms and Signs Pain Scale; SNB Sciatic nerve block; VAS Visual analogue scale; VTE Venous thromboembolism; WOMAC Western Ontario and McMaster Universities Osteoarthritis Index.

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Pain management

We identified 20 RCTs with 2393 participants evaluating components of multi-modal pain management. Four studies each were from China and the USA, two each from Canada and the UK and one each from Australia, Finland, France, Iran, Singapore, South Korea, Sweden and The Netherlands. All were conducted at a single centre and, in those with dates, participants were recruited between 2004 and 2015. Sample sizes ranged from 44 to 280 participants, with a median of 96. Four studies had three trial arms and 16 had two. The range of mean or median ages of participants in randomised groups was 61 to 73 years and, in 17/19 studies with data, a majority of participants were women.

Femoral nerve block

Femoral nerve blocks (FNB) were studied in 10 RCTs.

Three RCTs compared FNB with no FNB. In one study with 55 patients, WOMAC pain scores at one year were similar in patients receiving single-shot FNB and untreated controls[43]. All patients received local anaesthetic infiltration (LIA) and patient-controlled analgesia (PCA). In another study with all participants receiving LIA, 150 were randomised to receive single-shot FNB with or without sciatic nerve block (SNB), or general anaesthesia[37]. There were no differences in HSS scores between groups at six months. Continuous FNB was compared with oral hydrocodone opioid in 62 patients receiving PCA[39]. There was some evidence for 'pain using stairs' favouring hydrocodone (p=0.01) but no difference in overall NRS-rated pain at one year and concern over venous thromboembolism in 4/31 participants treated with hydrocodone.

In two RCTs, continuous FNB was compared with PCA. In one study with 60 participants, the KSS at six months was similar between groups[44]. In another study with 280 participants, there was some evidence for higher incidence of NRS-rated pain at six months in the PCA group than the FNB group (p=0.021) but not at 12 months (p=0.273).[40]

Two RCTs compared FNB with LIA. In one study, all 157 participants also received PCA[36]. At one year, KSS values were similar in single-shot FNB and LIA groups. In the other study, 94 participants were randomised to receive single-shot FNB with continuous epidural infusion or LIA through an intra-articular catheter[41]. VAS-rated pain was similar between groups at one year.

In two RCTs, FNB procedures were compared. In one study with 99 patients randomised to two FNB concentrations, there was no difference in WOMAC score between groups at 12 months[34]. In another study with 61 participants allocated to two different durations of FNB,

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there was no difference in WOMAC pain scores at one year[35]. In these studies, all participants received either SNB[34] or PCA[35].

Single-shot FNB was compared with single adductor canal block in one RCT with 98 participants, all receiving LIA[38]. At six months there was no difference in VAS-rated pain.

Sciatic nerve block

In one study, 89 patients were randomised to single-shot SNB, continuous SNB, or PCA[42]. All patients received FNB. At 12 months, there were no differences in pain for single-shot SNB and continuous SNB on the WOMAC pain scale or VAS-rated pain at rest or during mobilisation. Similarly, there were no differences between single-shot SNB and PCA in WOMAC pain scale or VAS-rated pain at rest or during mobilisation, or between continuous SNB and PCA.

Local anaesthetic infiltration

In six RCTs, treatment with LIA was investigated.

Three RCTs compared intra-operative LIA with placebo or no intervention. In one study, all 280 participants received FNB and PCA[50]. There was weak evidence that WOMAC pain scores were better in the LIA group at six (p=0.063) but not at 12 months (p=0.107) when the difference in means of 3.8/100 was lower than the MCID of 8-9/100 reported by Ehrich and colleagues[77]. In another study, 56 patients received LIA including ketorolac, or saline placebo, and all received PCA[47]. At one year, mean differences and confidence intervals provided weak evidence that OKS scores were better in the LIA group but the difference in means of 2.7/48 was less than the MCID of 4/48 reported by Beard and colleagues[78]. LIA before surgical incision was compared with placebo in one study with 120 participants[46]. None received FNB or PCA. There was weak evidence for a better KSS (function and knee score components) at six months in those receiving LIA (p=0.07) with a difference in means of 14.2/200 exceeding the MCID of 12.3/200 reported by Lee and colleagues[79].

In one study, 51 participants received LIA intra-operatively, followed by PCA[49]. Those randomised to further post-operative catheter-delivered LIA with ketorolac, or saline placebo had similar VAS-rated pain at six and 12 months.

LIA delivered as an injection and post-operative infusion was compared with epidural PCA in one study with 222 patients[45]. There was no difference between groups in OKS at 12 months. In one study of 100 participants, LIA with or without corticosteroid were compared[48]. All patients received PCA. At two years there was no difference in OKS between groups.

Oral celecoxib

In one RCT, 44 participants received oral celecoxib or placebo[51], as well as PCA. There were no differences between groups in KOOS or VAS-rated pain at 12 months.

Ketamine or nefopam infusion

In one RCT, ketamine infusion, nefopam infusion and saline placebo were compared in 75 patients, all of whom received PCA[52]. VAS-rated pain on movement did not differ between groups at 12 months. For the Douleur Neuropathique 4 (DN4) measure of neuropathic pain, there was some evidence favouring ketamine over placebo at six and 12 months (p=0.02), but overall, few patients reported neuropathic pain at 12 months.

Pregabalin

Oral pregabalin was compared with placebo in one RCT with 240 participants[53]. All received LIA and PCA. At six months, there was some evidence for better NRS pain in patients receiving pregabalin compared with placebo (p=0.0176) but the difference in means of 0.54/10 was less than the MCID of 1/10 reported by Salaffi and colleagues[80]. No participants receiving pregabalin reported neuropathic pain when assessed using the S-LANSS, compared with 5.2% of those receiving placebo (p=0.014). Patients receiving pregabalin were more likely to be sedated and confused in the first two days after surgery.

Tourniquet

Five studies with 399 participants explored tourniquet use to provide a bloodless field. Two studies each were from Australia and China, and one from Denmark. All were conducted at a single centre with participants recruited between 2008 and 2015. Sample sizes ranged from 20 to 150 participants, with a median of 65. The range of mean ages of participants in randomised groups was 66 to 71 years and in 3/5 studies, a majority of participants were women.

In three RCTs, participants received TKR with or without a tourniquet. In one study with 64 patients, a difference in KOOS pain favouring tourniquet use was not significant at six or 12 months[54]. In another study with 20 patients, the OKS was not significantly different between groups at six or 12 months[56]. There were three blood transfusions in the tourniquet group, compared with none in the 'no tourniquet' group. In the third study with 100 participants, VAS-rated pain and HSS scores were similar between groups at 6 months[55]. Six cases of wound ooze occurred in the tourniquet group.

In two RCTs, short and long-duration tourniquet use were compared. In one study with 65 participants, there was weak evidence based on graphical representation of means and confidence intervals for improved OKS at 12 months in the long-duration group and the difference in means of 5/48[57] was greater than the MCID of 4/48. Adverse events were reported by 62% of participants receiving short-duration tourniquet compared with 38% in the long-duration group. The study was terminated early as 10 blood transfusions were required in the short-duration group compared with three in the long-duration group. In the second study with 150 participants, tourniquets were used in three different periods during surgery[58]. At six months, there were no differences between groups in HSS scores.

Blood conservation

Seven studies with 829 participants evaluated strategies to limit blood loss after TKR. Two studies were from Thailand, and one each from China, France, South Korea, the UK and the USA. All were conducted at a single centre with participants recruited between 2003 and 2015 when stated. Sample sizes ranged from 48 to 180 participants, with a median of 106. One study had three trial arms. The range of mean ages of participants in randomised groups was 65 to 74 years and in all studies, a majority of participants were women.

Tranexamic acid

Five RCTs evaluated tranexamic acid.

Tranexamic acid injections or infusions were compared with saline placebo or untreated control in four RCTs[55,61,64,65]. In all studies, control patients required more blood transfusions. In one study including 180 participants comparing intravenous tranexamic acid with untreated controls, there was no significant difference in WOMAC pain scores at one year[61]. In another study with 48 participants comparing intra-articular tranexamic acid injection with saline placebo, there was no significant difference in WOMAC scores at six months[64]. One study with 135 participants compared two intra-articular tranexamic acid doses and saline control[65]. There were no significant differences in WOMAC scores at one year. Intravenous and intra-articular tranexamic was compared with untreated controls in one study with 100 participants[55]. VAS-rated pain at six months was similar between groups, but there was strong evidence favouring tranexamic acid for HSS scores (p<0.001) although the difference in means of 1.4/100 was lower than the MCID of 8.3/100 reported by Singh and colleagues[81].

In one study, continuous tranexamic acid infusion was compared with a single bolus in 106 patients[60]. There was no difference between groups in KSS at six months or blood loss.

Thrombin infusion

In one RCT with 80 participants, thrombin infusion was compared with untreated control[62]. At one year there was no difference between groups in pain measured on the KSS.

Flexion or extension

For blood management, operated knees were kept in passive flexion or passive extension after surgery in one RCT with 180 patients[63]. At one year, OKS was similar between groups. Transfusion requirement was greater in patients with passive extension.

Compression bandage

One RCT conducted at a single UK centre with 49 participants recruited between 2013 and 2014 compared compression bandaging to reduce post-operative knee swelling with standard bandaging. The mean age of participants was about 69 years and a majority were women. OKS was similar in randomised groups at six months[59].

Wound management

One RCT with recruitment in 2011 at a single centre in South Korea evaluated a wound care strategy to limit post-operative scar pain. The mean age of participants was about 69 years and a majority were women. Investigators compared silicone gel application to the surgical scar with placebo in 100 participants[75]. There were no significant differences in VAS-rated pain at six and 12 months.

Denusomab

One RCT evaluated use of the antiresorptive monoclonal antibody Denusomab to promote bone healing. The study was conducted in two centres in Sweden with recruitment of 50 participants between 2012 and 2014. The mean age of participants was about 65 years and a majority were women. At 12 and 24 months there were no significant differences between groups in KOOS pain[66].

Continuous passive motion

Two RCTs with 237 participants evaluated use of continuous passive motion (CPM) to minimise joint stiffness and improve range of movement. Studies were conducted in single centres in Australia and Turkey with participant recruitment between 1997 and 2004 and both had three trial arms. Sample sizes were 90 and 147 participants. The mean ages of participants in studies were about 63 and 72 years and a majority of participants were women. In one study, 90

participants were randomised to no CPM, CPM at low flexion from post-operative day 1–7, or CPM at high flexion from post-operative day 3–7[68]. There was no significant difference between groups in KSS at two years. In the other study, 147 participants were randomised to CPM with increasing range of movement from day 1–6, early flexion CPM from day 0–6, or no CPM[67]. There were no significant differences between groups in KSS at 12 months.

Electrical stimulation

Two RCTs with 106 participants conducted in single centres in Greece and Italy evaluated electrical stimulation which is believed to have anti-inflammatory activity and limit muscle atrophy. Studies included 76 and 30 participants recruited between 2005 and 2010. The mean ages of participants were 71 and 70 years and in one study that reported it, a majority of participants were female.

In one study with 76 participants receiving transcutaneous electric muscle stimulation from postoperative day two for six weeks or no intervention, Short Form 36 bodily pain showed strong evidence for greater improvement at one year in the intervention group compared to control (p<0.001)[69]. The difference in means of 12.5/100 was close to the MCID of 16.9/100 reported by Escobar and colleagues[82]. There were no differences in OKS or KSS scores. In another study with 30 participants, pulsed electromagnetic fields from post-operative day 7 were compared with untreated control[70]. At 12 months, there was some evidence that VAS-rated pain was lower in intervention patients compared with controls (p<0.05). The difference in means of 2.1/10 was greater than the MCID of 16.1/100 reported by Danoff and colleagues[83]. Knee swelling was common during the intervention.

Rehabilitation

Four RCTs with 585 participants recruited between 2000 and 2016 evaluated features of early rehabilitation focusing on regaining range of movement, functional independence and improving mobility. Two studies were conducted at single centres in China and at two and four centres in Canada and Germany respectively. Sample sizes ranged from 80 to 234 participants, with a median of 136. The range of mean ages of participants in randomised groups was 68 to 78 years and in 3/4 studies, a majority of participants were women.

Walking guidance and training

In one study, 86 participants were randomised to walking guidance and training from postoperative day two or no intervention further to standard rehabilitation[71]. At six months, there was some evidence that those receiving intervention had lower VAS-rated pain (p<0.01) and

HSS score (p<0.01) than controls. The difference in mean VAS-rated pain of 2.4/10 was greater than the MCID of 16.1/100.

Flexion or extension during knee closure

Targeting improved functional recovery, wound closure performed in 90° flexion was compared with wound closure in full extension in one study with 80 participants[74]. There was no difference between groups in VAS-rated pain at six months.

Aquatic therapy

In one study with 185 participants, aquatic therapy commencing on post-operative day six was compared with aquatic therapy commencing on day 14[72]. Patients reported similar WOMAC pain at 12 and 24 months.

Supported early discharge

In one study, early discharge supported by physiotherapist home visits and outpatient or selfdirected physiotherapy was compared with two weeks of rehabilitation centre-based usual care[73]. The study included 234 individuals receiving TKR or total hip replacement. Compared with usual care, there was weak evidence that patients with early discharge had lower WOMAC pain scores at 12 months (p=0.08). The difference in means of 4 was less than the MCID of 8-9/100. Results were not presented separately but did not differ between patients with TKR or total hip replacement.

Anabolic steroids

Searches identified one study of anabolic steroids to improve post-operative muscle strength conducted in one centre in Australia with recruitment of 10 participants before 2010. The mean age of participants was about 66 years and a minority were women. Participants received intramuscular nandrolone injections or saline from post-operative day five for six months. KSS results indicated some evidence for improvement in the intervention group compared with controls at 12 months (p=0.03)[76]. The difference in means of 10.2/200 was close to the MCID of 12.3/200.

DISCUSSION

Much research in TKR aims to identify treatments that facilitate a speedy recovery with minimal short-term pain. However, patients choose to have joint replacement for long-term pain relief and reduction in functional limitations. Thus, changes to peri-operative care, supported by short-

term RCT evidence, should be backed up with evidence about long-term effectiveness for reducing pain and reassurance that there are no long-term unfavourable consequences. To this end, we synthesised evidence from RCTs evaluating peri-operative interventions which have considered their long-term effects on pain outcomes.

Consistent with its status as a key peri-operative risk factor, a major focus of research into improving long-term pain after TKR has been through prevention of acute post-operative pain using multimodal analgesia. Our review provides good quality evidence for a small benefit for intra-articular LIA injections, as previously shown in short-term studies[31,84], oral pregabalin, oral opioids, and in relation to neuropathic pain, ketamine infusion. As well as potential benefits for reduced long-term pain, future studies will need to consider concerns associated with these interventions which may not have been identified in small studies including infection[31], venous thromboembolism[39] and sedation[53].

Nerve blocks are effective for managing peri-operative pain[85] but we identified no long-term benefit. In single studies, there was no benefit for nefopam infusion, oral celecoxib or LIA with additional corticosteroid. Regarding future studies, standardisation of the multi-modal regimen will allow evaluation of extra or alternative components in multiple studies in different settings. With such an approach, convincing evidence will accrue to guide multimodal pain management.

Some interventions targeted the prevention of adverse events and facilitation of early mobilisation. Tranexamic acid is highly effective in reducing blood transfusions during TKR[86] and we found no evidence that tranexamic acid affects long-term pain or, consistent with registry studies[87,88], adverse events. Single RCTs of thrombin infusion and maintenance of knee in flexion to prevent blood loss showed no effect on long-term pain. Tourniquets improve intraoperative visualisation of the joint, reduce blood loss and facilitate cement fixation but are associated with nerve damage, delayed recovery, acute pain and need for analgesics[89,90]. The RCTs we identified showed no effects of tourniquet use on long-term pain.

As shown in a previous review[91], there was no suggestion that CPM affects long-term pain. There was good quality evidence for a small benefit for reduced long-term pain in patients receiving walking training, anabolic steroid injection, electrical stimulation and supported discharge.

For some interventions a direct mechanism is clear, but for others, reasons for long-term impact are less obvious. This may explain why, for example, no studies evaluated DVT prophylaxis with long-term follow up excepting a small number reporting adverse events. However, treatments to

prevent symptomatic DVTs which occur in about 1% of treated patients[92] also reduce the incidence of asymptomatic DVT observed in about 28% of treated patients[93] and this may have long-term benefits. Conversely, new anticoagulants are associated with bleeding[94], which may increase the risk of wound complications[95] and joint infection[96] which are associated with long-term pain[97,98]. More peri-operative interventions with no information on long-term pain outcomes from RCTs are shown in Figure 1.

Our study is limited by the lack of meta-analysis which was not appropriate due to intervention and outcome heterogeneity. In the context of perioperative pain management, this was noted previously[84]. Our approach to assessing the evidence was a narrative synthesis of studies with low risk of bias. While this may seem overly restrictive, Cochrane risk of bias assessment allows us to screen out studies with important issues that may affect the validity of results. The main potential source of bias was incomplete outcome assessment. Although studies with longterm follow up are naturally at higher risk of missing data, we maintained a standard in this domain as it is recognised that research participants who do not complete follow up assessments differ in outcomes from those with follow up data and their inclusion could change the interpretation of results[99].

Another limitation is that pain assessed with questionnaires does not take into account the effect of pain medications and assistive aids. About 58% of women and 40% of men report taking pain medications after TKR because of pain in the operated knee[100] and we must recognise that pain levels at follow up without this treatment might be considerably higher. Even with treatment, around 20% of patients report chronic pain after TKR[10] and in the context of a blinded RCT we should expect to be able to identify effects of peri-operative treatments.

We summarised p-values to assess the strength of evidence but, as statistically strong evidence may not reflect clinically important results[101], where possible we also compared effect sizes with MCIDs. Our review considered a diverse range of interventions at a specific time in the TKR pathway and, as we were unable to make clinical practice recommendations, we did not adopt the GRADE system[102] for this review.

An alternative approach to the prevention of chronic pain after TKR is the individualisation of care based on pain phenotype, genetic, psychosocial and other factors[103]. An example of this might be the peri-operative treatment only of individuals with neuropathic pain with pregabalin, as opposed to the non-stratified provision in the RCT of Buvanendran and colleagues[53]. In an RCT with pregabalin provided to patients with painful HIV-neuropathy, while no overall benefit was seen, a group with hyperalgesia responded to pregabalin treatment[104].

Our systematic review of peri-operative interventions brings together evidence on interventions in the peri-operative phase of the TKR pathway. There was good quality evidence for some interventions of a small benefit for reduced long-term pain, and whilst not supportive of the inclusion of specific interventions in clinical practice, there are clearly areas that merit research. High quality studies assessing long-term pain after peri-operative interventions are feasible and necessary to ensure that patients with osteoarthritis achieve good long-term outcomes after TKR.

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AUTHOR CONTRIBUTIONS

All authors, ADB, JD, RG-H and AWB, contributed to the conception and design of the study. ADB, JD and VW undertook the systematic review. ADB and JD carried out the risk of bias assessments. ADB drafted the article with revisions by JD, VW, RG-H and AWB. All authors approved the final version for publication.

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COMPETING INTERESTS STATEMENT

The authors report no competing interests.

DATA STATEMENT

All data relevant to the study are included in the article or uploaded as supplementary information.

Legend

Figure 1. Systematic review flow diagram

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dentification	Articles identified in searches of <i>The Cochrane Library</i> , MEDLINE, Embase, PsycINFO and CINAHL from inception to February 2018 (n = 9697)									
				•						
Screening		Artic	les scree	ened (n = 90	697)		No re	levance	(n = 736	64)
				+						
Eligibility				Pote	ntially rele	vant (n =	2333)			
				•						
Intervention	N	In: low risk of bias	No pain/ score outcome	High/ unclear risk of bias	No long- term follow up	Abstract only	Additional publication	Protocol	Review	Ret
Adenosine triphosphate	2	0	0	0	1 1	0	0	0	1	
Alternative medicine	4	0	0	0	4	0	0	0	0	
Anabolic steroids	2	1	0	0	0	0	0	0	1	
Antibiotic prophylaxis	43	0	16	0	13	0	0	1	13	
Assistive devices	2	0	0	0	2	0	0	0	0	
Bisphosphonates	17	0	6	0	0	0	2	0	9	
Blood management	355	7	10	1	209	0	0	4	124	
Brain stimulation	3	0	0	0	3	0	0	0	0	
Calcium supplement	1	0	0	0	1	0	0	0	0	
Cardiovascular drugs	4	0	0	0	2	0	0	0	2	
Chinese medicine	2 30	0	0	0	2 24	0	0	0	0	
Cold therapy	30	0	0	1	24	0	0	0	5 0	
Colloids and crystalloids Comorbidity management	1	0	0	0	1	0	0	0	0	
Compression	8	1	0	0	6	0	0	0	0	
Constipation treatment	2	0	0	0	2	0	0	0	0	
Continuous passive motion	56	2	8	7	23	1	0	1	14	
Creatine monohydrate	1	0	0	0	1	0	0	0	0	
Delirium prevention	4	0	0	0	3	0	0	0	1	
Denusomab	1	1	0	0	0	0	0	0	0	
Dexmedetomidine	1	0	0	0	1	0	0	0	0	
Deep vein thrombosis prophylaxis	474	0	5	0	143	0	4	8	314	
Electrical stimulation	37	2	0	3	20	0	2	0	10	
Glucocorticoid	2	0	0	0	0	0	0	0	2	
Glucose infusion	1	0	0	0	1	0	0	0	0	
Guided imagery	5	0	0	1	4	0	0	0	0	
Iron	7	0	0	0	6	0	0	0	1	
Laser therapy	1	0	0	0	1	0	0	0	0	
Methylprednisolone	3	0	0	0	3	0	0	0	0	
Music therapy	9	0	0	0	9	0	0	0	0	
Nausea prevention	11	0	0	0	9	0	2	0	0	
Nutritional supplements	4 987	0 20	0	0 12	4 711	0	0 20	0 9	0 207	
Pain management Physiological	26	20	5 0	0	23	0	20	9	207	
Platelet rich plasma	12	0	0	1	6	0	0	0	5	
Rehabilitation	67	4	0	2	43	0	0	0	17	
Remote ischaemic pre-conditioning	5	0	0	0	43	0	0	0	0	
Sleep treatment	3	0	0	0	2	0	1	0	0	
Teriparatide	1	0	1	0	0	0	0	0	0	
Therapy dogs	1	0	0	0	1	0	0	0	0	1
Tourniquet use	100	5	3	3	67	0	2	1	19	1
Trigger point needling	1	0	0	1	0	0	0	0	0	
Warming	19	0 0	0	0	16	0	0	0	3	
Wound management	17	1	0	0	12	0	0	1	3	
Total	2333	44	54	32	1385	2	33	28	753	

Reporting checklist for systematic review and meta-analysis.

Based on the PRISMA guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the PRISMA reporting guidelines, and cite them as:

Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement

0 1				Page
2 3			Reporting Item	Number
4 5 6 7		#1	Identify the report as a systematic review, meta-analysis, or both.	1
8 9 1 2 3 4 5	Structured summary	#2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number	2-3,5
6 7 8 9	Rationale	#3	Describe the rationale for the review in the context of what is already known.	4-5
0 1 2 3 4	Objectives	#4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5-6
5 6 7 8 9 0	Protocol and registration	#5 For p	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address) and, if available, provide registration information including the registration number. beer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	5

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1 2 3 4 5	Eligibility criteria	#6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rational	5-6
6 7 8 9 10	Information sources	#7	Describe all information sources in the search (e.g., databases with dates of coverage, contact with study authors to identify additional studies) and date last searched.	6
11 12 13 14 15 16	Search	#8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	See note 1
17 18 19 20 21	Study selection	#9	State the process for selecting studies (i.e., for screening, for determining eligibility, for inclusion in the systematic review, and, if applicable, for inclusion in the meta-analysis).	5,6
22 23 24 25 26	Data collection process	#10	Describe the method of data extraction from reports (e.g., piloted forms, independently by two reviewers) and any processes for obtaining and confirming data from investigators.	6
27 28 29 30 31	Data items	#11	List and define all variables for which data were sought (e.g., PICOS, funding sources), and any assumptions and simplifications made.	5/6
32 33 34 35 36 37 38	Risk of bias in individual studies	#12	Describe methods used for assessing risk of bias in individual studies (including specification of whether this was done at the study or outcome level, or both), and how this information is to be used in any data synthesis.	6
39 40 41 42	Summary measures	#13	State the principal summary measures (e.g., risk ratio, difference in means).	7
43 44 45 46 47	Planned methods of analyis	#14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I2) for each meta-analysis.	7
48 49 50 51 52 53	Risk of bias across studies	#15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6
53 54 55 56 57 58	Additional analyses	#16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	7
59 60		For p	eer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml	

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1 2 3 4 5	Study selection	#17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	See note 2
6 7 8 9 10	Study characteristics	#18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citation.	See note 3
11 12 13 14	Risk of bias within studies	#19	Present data on risk of bias of each study and, if available, any outcome-level assessment (see Item 12).	See note 4
15 16 17 18 19 20 21	Results of individual studies	#20	For all outcomes considered (benefits and harms), present, for each study: (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot.	See note 5
22 23 24 25 26	Synthesis of results	#21	Present the main results of the review. If meta-analyses are done, include for each, confidence intervals and measures of consistency.	16-23
27 28 29 30	Risk of bias across studies	#22	Present results of any assessment of risk of bias across studies (see Item 15).	See note 6
31 32 33 34	Additional analysis	#23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	16-23
35 36 37 38 39 40 41	Summary of Evidence	#24	Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., health care providers, users, and policy makers	16-23
41 42 43 44 45 46	Limitations	#25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias).	24-25
47 48 49 50	Conclusions	#26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	23-25
50 51 52 53 54 55 56	Funding	#27	Describe sources of funding or other support (e.g., supply of data) for the systematic review; role of funders for the systematic review.	26
56 57	Author notes			

Author notes

- 1. 5, Supplemetary material
- ²₃ 2. 7, Figure 1
- 4
 5 3. 8-15, Table1, Supplementary material
 - 4. 7, Supplementary material
- 5. 8-15, Table1, Supplementary material

1112 6. 8-15, Supplementary material13

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 tool made by the <u>EQUATOR Network</u> in collaboration with <u>Penelope.ai</u>

Supplementary material. Search strategy as applied in MEDLINE on Ovid

- 1 randomized controlled trial/ or randomized controlled trial.pt.
- 2 controlled clinical trial.pt.
- 3 randomized.ab.
- 4 placebo.ab.
- 5 randomly.ab
- 6 trial.ab
- 7 randomised.tw
- 8 1 or 2 or 3 or 4 or 5 or 6 or 7

9 review/

- 10 'systematic review\$'.mp
- 11 9 or 10
- 12 8 or 11
- 13 Arthroplasty, Replacement, Knee/
- 14 Knee Prosthesis/

15 (arthoplast\$ adj3 knee\$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

16 (knee\$ adj3 replac\$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

17 (knee adj3 implant\$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]

18 13 or 14 or 15 or 16 or 17

19 12 and 18

Supplementary material. All peri-operative interventions with long-term pain or score follow up

1. Pain management

Author	Indication	Common anaesth	esia			Follow up	
Country Recruitment dates Setting Number randomised intervention; control Age % female		Group 1 (intervention)	Group 2 (interve		Group C (control)	Losses to follow up intervention; control Risk of bias issues Key results	
FNB single vs No F	NB	6					
Widmer et al. 2012[43] Australia Before 2012 2 surgeons	Elective primary unilateral TKR 27; 28 Median 72.1 (IQR 64.4, 76.5); 69.4 (63.4, 75.5) 44.4%; 44.4%	Premedication 1-3mg i.v. midazolam. Propofol induction and sevoflurane general anaesthetic.LIA with 200mg ropivacaine and 0.5mg adrenaline in 100ml saline.PCA 20µg fentanyl at 5-minute intervals on demand until morning POD2. Then, oral oxycodone SR 10mg every 12 hours. Daily COX II inhibitor and paracetamol 1g every 6 hours as tolerated. For breakthrough pain, 5-10mg oxycodone immediate release every 3 hours as needed.Ultrasound guided FNB with 100mg ropivacaine in 30ml salineSham setup for FNB. No identification or injection of femoral sheath			1 year No losses to follow up reported Low risk of bias WOMAC pain (high score favourable) at 1 year: FNB and LIA median 2.0 (IQR 0, 2.8); LIA no FNB 1.0 (0, 2.0). p=0.74 No adverse events occurred in either group		
FNB single vs ONB							
Bergeron et al. 2009[105] Canada 2005-2006 1 centre	Elective primary unilateral TKR 19; 20; 20 Mean 65.1 (SE 2.0); 72 (1.8); 67 (1.3) 79%; 80%; 75%	Intraoperative sedation with iv propofol at discretion of anaesthesiologist. Lumbar spinal anaesthesia with 12mg 0.5% bupivacaine. Postoperative i.v. PCA with fentanyl 50µg/ml set to deliver 25µg every 5 min as needed. Celecoxib 100mg and acetaminophen 650mg on arrival in recovery room and every 12 and 6 hrs respectively. Breakthrough medication with intramuscular ketorolac 10 mg every 4 hrs.		1 year Overall 32 lost to follow up High risk of bias: only 27/59 patients followed up due to resource limitations. No difference in HSS pain at rest or during activity at 1 year between the study groups.			

		FNB with stimulator. 20ml 0.5% bupivacaine with 1/200,000 epinephrine.	ONB with stimulator. 20ml 0.5% bupivacaine with 1/200,000 epinephrine.	No injection but inguinal area prepared, and sham block performed behind drapes.	No long-term complications attributable to anaesthetic regimen
FNB continuous lo	w dose vs FNB continu	ious high dose vs No	5 FNB		
Shum et al. 2009[106] Singapore Before 2009 1 hospital	Unilateral TKR for osteoarthritis 20 (17 received treatment); 20 (18 received treatment); 20 Mean 66.7 (SD 8.4); 65.4 (8.4); 67.8 (5.5) 88%; 72%; 80%	bupivacaine. Intraop increments of 0.5mg Intravenous PCA mo doses of 1 mg with 5 mg/hr) Low dose continuous FNB at conclusion of TKR with ropivacaine 0.15% (10 ml/hr in the first 24 hours, followed by 5ml/hr in the next 24 hours)	orphine (1mg/ml, on-co minute lockout, max	midazolam in demand bolus	2 years 16.4% of patients who received intervention lost to follow up Unclear risk of bias due to differences in OKS and weight at baseline, and limited methodologica details. No separate pain outcome but mean OKS slightly more favourable in group with no FNB, 18.2 (SD 3.7) compared with combined FNB groups, 19.8 (5.4) but this was not significant. No complications attributable to use of FNB
SNB injection vs S	NB continuous vs con	rol		0	
Wegener et al. 2013[42] The Netherlands 2008-2010 1 centre	Unilateral TKR 29; 30; 30 (90 randomised) Median 65 (range 43-81); 66 (43-83); 62 (50-79) 62%; 70%; 73%	Lorazepam 1mg 2 hours and acetaminophen 2g 1 hour before surgery. FNB with stimulating catheter: loading dose 20 ml levobupivacaine 0.375% and after 45 minutes a continuous infusion of levobupivacaine 0.125% 10 ml/hr. General anaesthesia induced with 3-5 µg/ml propofol infusion and remifentanil 0.5 µg/kg/min and maintained with 2-3 µg/ml at 0.1-0.25 µg/kg/min. Postoperatively, FNB changed to patient controlled FNB, 5ml bolus, 30-minute lockout; basal rate 6 ml/hr. i.v. morphine administered if needed. Postoperative analgesia with acetaminophen 1g 4 times daily. Diclofenac 50mg or tramadol 50mg 3 times daily. Tramadol 100mg before removal of nerve catheters. Morphine pain relief as required.			12 months 2;7;5 lost to follow up Low risk of bias Median WOMAC pain scores at 12 months: SNB injection 80 (range 25- 100), SNB continuous 90 (55-100) and PCA only 90 (35-100), p=0.81. No difference between groups in VAS pain at rest (p=0.90) or during mobilisation (p=0.43). No information on adverse events.

Comerci errecetive s	a vs FNB single vs FN	Group Fs: SNB single injection. SNB loading dose of 20 ml levobupivacaine 0.375%.	Group FCS: SNB continuous infusion. SNB loading dose of 20 ml levobupivacaine 0.375%. Continuous infusion of levobupivacaine 0.125% 10 ml/hr started 45 mins after catheter placement. SNB maintained for 36 hours postoperatively (10 ml/hr).	Group F: No SNB. PCA via femoral nerve catheter	
Gao et al. 2017[37] China 2014-2015 1 centre	Primary unilateral TKR for osteoarthritis 50; 50; 50 Mean 65.8 (SD 6.7); 66.4 (7.4); 67.6 (6.3) 81%; 80%; 76%	Pre-operative and p daily.	oost-operative celecox ve LIA with ropivacain g. Ultrasound guided FNB 5g/l ropivacaine 20ml plus 0.1mg epinephrine	-	6 months 2; 1; 0 Low risk of bias Mean HSS at 6 months: 87.1 (SD 6.9); 87.4 (7.3); 88.5 (6.7). No significant difference. Nausea and vomiting: 4; 2; 1, urinary retention: 3; 1; 2.
<i>LIA no corticostero</i> Wylde et al. 2015 [50] UK	<i>id vs No LIA/ placebo</i> Primary unilateral TKR for osteoarthritis	FNB with nerve stimulator and/ or ultrasound guidance (20ml 0.25% bupivacaine). Spinal or general anaesthetic. Intra-operative analgesia provided by titration of i.v. fentanyl initially and morphine if necessary. 1g intravenous			6 and 12 months 24;19 at 12 months (including those who did not receive treatment)

2009-2012	157; 159 (143; 137	paracetamol 30 minutes before the end of operation.	Low risk of bias
1 centre	received treatment) Mean 69.5 (SD 9.4); 68.7 (7.9) 52%; 54%	Immediately post-operative 400mg oral ibuprofen. PCA with morphine 1mg/ml, 1 mg bolus dose and a 5- minute lock-out. If necessary morphine bolus up to 0.2mg/kg as rescue analgesia. During hospital stay, visit from pain specialist nurse. Oral or i.v. paracetamol every 6 hours and ibuprofen 400mg every 8 hours. When PCA no longer needed, oral codeine phosphate 30-60mg every 6 hours, tramadol 50-100mg every 6 hours and oramorph 10-20mg as rescue analgesia. 60ml intra-operative LIA with 0.25% bupivacaine and 1/200,000 adrenaline injected into the posterior capsule, medial and lateral capsule, fascia and muscle, and subcutaneous tissues.	At 12 months WOMAC pain score (0 100) in LIA group median 90 (IQR 30), Control 85 (35); ITT-CC linear regression coefficient 3.83 (95%CI -
Williams et al. 2013[49] Canada Before 2013 1 centre, 2 surgeons	Primary unilateral TKR for osteoarthritis 35; 32 (26; 25 received treatment) Mean 66 (SD 9.7); 67 (12.5) 58%; 60%	Sedation with i.v. midazolam and propofol. Intraoperative LIA loading dose of 20ml 0.25% bupivacaine/ epinephrine injection, 10ml into medial and lateral subcutaneous tissue around the incision and 10ml intra-articular after closure. Infiltrate delivered by pain pump into lateral recess of intra articular space. Spinal anaesthetic with 10-15 mg of 0.75% or 0.5% plain bupivacaine and 20µg fentanyl. Postoperative morphine PCA. 7.5mg i.v ketorolac preoperatively plus 15mg every 6 hours postoperatively for 48 hours, then oral ketorolac 10mg every 6 hours for 2 days. Gabapentin 600mg given preoperatively plus 300mg twice daily for 48 hours postoperatively. Oxycodone 10mg twice daily for 48 hours postoperative. Oral paracetamol 650mg every 4 hours for 72 hours. Infusion of 0.5% bupivacaine at 2ml/hr for 48 hrs	 Low risk of blas Mean VAS pain score at 6 months 1.2 (SD 1.3); 1.2 (1.2). p=0.836. At 12 months 0.9 (1.2); 1.0 (1.1). p=0.767 No short-term differences in adverse events except control patients more likely to be drowsy at 48 hrs. Long- term adverse events not reported.
Niemeläinen et al. 2014[47] Finland 2011-2012	Primary unilateral TKR for osteoarthritis 30; 30 (27; 29 received treatment)	Oral paracetamol 1g given 1 hour before surgery. Spinal anaesthesia with 15mg bupivacaine in 3ml. After surgery oral paracetamol 1g every 6 hours and oral meloxicam (15mg) every 24 hours. PCA with oxycodone 2mg, lock-out time 8 min.	12 months 1; 4 Low risk of bias No pain measure separate from OKS Weak evidence of more favourable

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1 hospital	Mean 65 (SD 4.9); 64 (6.7)	Rescue levobupivacaine medic epidural catheter	ation through a lumbar	OKS (0-48) in the LIA group at 12 months, mean difference -2.7 (95%
56%; 48%	56%; 48%	Intra-operative periarticular LIA of 100ml saline with levobupivacaine (150mg) mixed with ketorolac (30mg) and adrenaline (0.5mg).	Intra-operative periarticular LIA of 100ml saline	CI -5.48, 0.07). Difference lower than MCID of 4.0[78]. Infection: 0; 0. Severe pain treated with epidural analgesia: 0; 3. Nausea 1; 1
Motififard et al. 2017[46]Primary unilateral TKR for osteoarthritis 60; 601 hospitalMean 66.4 (6.4); 64.5 (6.0) 86.0%; 94.3%	Spinal anaesthesia. No FNB or SNB. Pain medication provided as re meloxicam (15 mg daily), celec acetaminophen (1g every 8 hou 8 hours), ketorolac (30 mg slow dose max), and morphine (5–1	6 months 3; 7 Low risk of bias No separate pain measure. Weak evidence for improved KSS (0-200) i LIA group at 6 months, mean 115.55 (SD 15.506); 101.40 (16.117).		
		Peri-articular injection, 15 minutes before incision, of 100ml saline containing 50 mg bupivacaine hydrochloride 0.5%, 1 ml morphine sulphate 10 mg/ml, 300 µg epinephrine (1:1000) and 30 mg ketorolac	100ml saline containing 300 μg epinephrine (1:1000)	P=0.07. Difference of 14.15 greate than MCID of 12.3[79]. Difference was significant at 6 weeks, p<0.00 No complications related to TKR of LIA. Low back pain (1; 2), stroke (1), CHF (1; 0)
McDonald et al. 2016[45] UK 2010-2011 1 hospital	Primary unilateral TKR for osteoarthritis 113; 109 received common spinal anaesthesia (121; 121 randomised) Median 68 (IQR 62, 72); 67 (62, 73) 59%; 55%	Oral premedication with 10-20r ranatidine, 10mg dexamethaso paracetamol. Spinal anaesthesia Intra-articular and subcutaneous infiltration during surgery of 200 ml of 2mg/ml ropivacaine without adrenalin or additives. Catheter inserted, and 20 ml infiltrate injected following wound closure. Further boluses of 40 ml 2 mg/ml ropivacaine via infusion pump 4 hours after leaving theatre and morning of POD1. Two		12 months 9; 11 of those receiving treatments Low risk of bias No separate pain outcome. Mean OKS at 12 months: median 41 (IQR 35, 44); 41 (34;44). P=0.915 Suspected infection 2; 1. MI 0; 1. GI bleed 1; 0. renal failure 1; 0. Died 2; 0)

		additional top ups of 40 ml 2mg/ml ropivacaine were prescribed if required.		
Celecoxib vs placeb	0			
Meunier et al. 2007[51] Sweden 2004-2005 1 centre	Elective primary unilateral TKR for osteoarthritis 25; 25 (24; 20 received treatment) Mean 68 (SD 6.3); 69 (7.7) 71%; 40%	Spinal anaesthesia with bupiva midazolam or propofol sedation preoperatively and then with tra day during hospital stay. Ketob subcutaneous) on demand. Pa used as required after discharg Oral celecoxib 200mg 1 hour preoperatively and twice daily for 3 weeks	n if needed. Paracetamol 1 g amadol 50-100 mg 4 times a emidone (2.5-5mg i.v. or racetamol and tramadol	12 months No losses to follow up after surgery reported Low risk of bias No effect of celecoxib on VAS or KOOS pain at 1 year. DVT: 0; 1. Deep infection: 0; 0.
Ketamine vs placeb	0			
Perrin and Purcell2009 [107] Australia Before 2009 1 centre (pilot study)	Elective unilateral TKR 16 (5; 7 completed study per protocol) Mean 65.6 (SD 10.2); 60.3 (11.9) 40%; 43%	Intrathecal injection of 15mg bupivacaine and 100µg morphine. General anaesthesia. After surgery 1.5g paracetamol and then 750mg every 4 hours; PCA with morphine 2mg boluses with 10-minute lockout; morphine rescue 2.5mg intravenously as required; and rescue oral ibuprofen 800mg.Ketamine 0.5mg/kg bolus followed by 4µg/kg/min infusion. Commenced before surgical incision and continued until wound bandaged or syringe empty.Saline infusion. Commenced before surgical incision and continued until wound bandaged or syringe empty.		6 months 3 protocol breaches and 1 patient with uncontrolled pain. High risk of bias due to non-ITT reporting and recruitment difficulties 2/5 ketamine group had mild/moderate pain on the WOMAC pain scale at 26 weeks or failed to improve compared with 5/7 controls. 1 adverse psycho-mimetic effect not attributed to intervention or control treatment
Ketamine vs Nefopa	m vs placebo			
Aveline et al. 2014[52] France 2005 1 centre	Elective primary unilateral TKR for osteoarthritis 25; 25; 25 Mean 73 (SD 9); 72 (9); 70 (7) 67%; 60%; 63%	General anaesthesia induced v 1µ/kg remifentanil and a single 0.15mg/kg. Remifentanil infusio closure. Anaesthesia maintaine 1.2% with 50% nitrogen in oxyg closure, 0.15mg/kg i.v. morphine droperidol. PCA with morphine bolus with 7-min lockout. On ar i.v. morphine boluses at 5 minu	6 and 12 months 3; 1; 2 Low risk of bias Median DN4 at 12 months: 1 (IQR 1, 2); 1 (0, 1); 2 (1, 3). p=0.02 for difference between ketamine and placebo groups. Number of patients with VAS pain on movement score	

	6	0.2mg/kg nefopam administered over 20 min before incision; 2mg/ml nefopam continuous infusion at 120µg/kg/hr until end of surgery and 60µg/kg/hr for 48 hours	0.2mg/kg ketamine administered ove 20 min before incision; 2mg/ml ketamine continuous infusion at 120µg/kg/hr unti end of surgery and 60µg/kg/hr for 48 hours	incision; saline continuous infusion until second post- operative day	≥40mm at 12 months by group: nefopam (3/22, 13.7%), ketamine (3/24, 12.5%), and placebo group (6/23, 26.1%). Ketamine reduced DN4 pain (p=0.02) compared with placebo. At 12 months only 7/69 patients had DN4≥4 indicative of neuropathic pain. Infection: 0; 0; 0. Revision: 0; 0; 0.
Pregabalin vs place					
Buvanendran et al. 2010[53] USA 2006-2007 Single centre	Primary unilateral TKR for osteoarthritis. 120; 120 (9; 2 did not receive post- operative treatment but ITT analysis) Mean 64.0 (SD 8.3); 63.3 (8.9) 76%; 70%	Sedation with mid spinal-epidural an bupivacaine with 2 Catheter inserted LIA 60 ml 0.25% k into the wound at surgery until 32-42 of fentanyl (5µg/m using continuous PCA bolus doses to oral opioid (mod as required. All pa celecoxib 400mg twice daily for 3 da	aesthetic. 1.5ml 0 25µg fentanyl inje- for epidural drug a oupivacaine with e capsule closure. F 2 hours post-oper 1) and bupivacain basal infusion of 6 (maximum 10ml/h rphine, oxycodone atients received pr 1–2 hours before	6 months 7; 5 Low risk of bias Mean VRS pain score at 6 months: pregabalin 0.41 (SD 1.20); control 0.95 (1.80). p=0.0084. Distributions skewed but nonparametric Wilcoxo significant (p=0.0176). Difference of 0.54 less than MCID of 1.0. In the pregabalin group the incident of neuropathic pain measured using S-LANSS was 0% (0/113) and 5.29 (6/115) in the placebo group	
		Oral pregabalin 30 h before surgery, twice daily for the postoperative day twice daily on day 12, and 50mg twice days 13 and 14	r, 150mgsurgery, twice daily for the first 10 postoperative days, twice daily on days 11 and 12, and twice daily on days		 (p=0.014). No clinically significant adverse events up to 6 months and no falls. Sedation, confusion and dry mouth more frequent in pregabalin than placebo group on day of surgery ar first postoperative day.

llfeld et al. 2009[108]	Primary unilateral TKR for	Femoral catheter inserted using 0.2% ropivacaine infusion (8m)		6 and 12 months
USA	osteoarthritis	controlled bolus; 30-minute loc		4; 1 lost to follow up
	25; 25	POD1.		High risk of bias: uneven loss to
2005-2007 2 centres	Median 66 (IQR 60, 70); 64 (60, 69) 56%; 60%	1 week oral acetaminophen (97 sustained release oral opioid (0 hours), and either oral aspirin ((200mg every 12 hours). Oral o or i.v. morphine sulfate 2-4 mg	follow up between groups; muscle weakness resulted in lower dose of infusion on POD1 (10 continuous; saline) Groups had similar WOMAC pain scores at 6 and 12 months	
		At 6 a.m. POD1, infusion pump replaced with infusion pump with 0.2% ropivacaine.At 6 a.m. POD1, infusion pump replaced but saline substituted.		(p>0.05). MI: 1; 0. PE: 1; 0. Fall: 1; 0. Catheter leak, dislodged: 1; 2
		At 6 p.m. POD2 pump replaced with portable infusion pump (400ml 0.2% ropivacaine). Catheter removed evening of POD4.	At 6 p.m. POD2 pump replaced with portable infusion pump (saline). Catheter removed evening of POD4	
llfeld et al. 2011[109] USA	Primary unilateral cemented TKR for osteoarthritis	Femoral catheter inserted using 0.2% ropivacaine infusion (6m controlled bolus; 30-min lockou	12 months 11; 12 incomplete follow up High risk of bias: 11;12 did not hav	
2007-2009 2 centres	40; 40 (39; 38 included in RCT) Median 61 (IQR 58, 67); 66 (60, 70) 67%; 66%	1 week oral acetaminophen (97 sustained release oral opioid (0 hours), and either oral aspirin (1 (200mg every 12 hours). Oral (tablets) and/ or i.v. opioids (mo breakthrough pain.	4 measures out of 6 up to 12 months; graph suggests WOMAC pain lower pre-intervention in continuous infusion group. No difference in WOMAC pain scores between randomised group	
		At 6 a.m. POD2, infusion pump replaced and 0.2% ropivacaine continued.	At 6 a.m. POD2, infusion pump replaced but saline substituted.	(p>0.05). Falls: 4; 0
		At 6 p.m. POD2 pump replaced with portable infusion pump (400ml 0.2% ropivacaine). Catheter removed evening of POD4	At 6 p.m. POD2 pump replaced with portable infusion pump (saline). Catheter removed evening of POD4	
Choy et al. 2011[35] Korea 2006-2007	Primary unilateral TKR for osteoarthritis	Spinal anaesthesia. Continuous POD3. Catheter inserted with u Analgesia induced with 20ml of 2% lidocaine with 1:200,000 ep	2 years 4; 3 lost to follow up	

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1 surgeon 33; 30 (2 patients received GA and excluded) Mean 66.7 (SD 10); 67.5 (11) 97%; 93%		infusion with 0.125% bu (butorphanol 4mg, keto programmed to deliver maximum dose 6mg/hr oral ibuprofen 600mg 3	Low risk of bias for 2 year outcome measures. At 2 years, intervention WOMAC pain mean 7.2 (SD 2), control 6.3 (SD 1); p=0.2		
		Continuous femoral ner block via catheter contin from POD3 to POD7		uous femoral nerve liscontinued on	Superficial infection: 1; 1
	high concentration vs F		•		-
Albrecht et al. 2014[34] Canada 2009-2011 1 hospital	Scheduled primary unilateral TKR 32; 32; 35 Mean 61 (Cl 57, 64); 63 (60, 67);63 (60, 66) 46%; 44%; 52%	Stimulating catheter ins Immediately after catheter was injected through the ropivacaine 0.2%. Spin- isobaric bupivacaine 0.3 Bolus of 20ml ropivacaine 0.2% with epinephrine 1:400,000 into the femoral catheter followed by ropivacaine 0.2% at a rate of 5 ml/hr with patient-controlled boluses of 5ml available every 30minutes.	ter placement, 10 e catheter. SNB ι al anaesthesia wi	ml mepivacaine 2% ising 30 ml th 2.5 to 3.0 ml rathecal morphine. Bolus of 30ml ropivacaine 0.375% with epinephrine 1:400,000 into the femoral catheter followed by normal saline at a rate of 1 ml/hr with patient-controlled boluses of 1mL	12 months 4;0;2 lost to follow up Low risk of bias. No separate pain outcome. Mean WOMAC score at 12 months: high concentration FNB 17 (95% CI 7, 27); 22 (14, 30); 18 (8, 27). P=0.60 Falls: 0; 0; 1
	vs Psoas compartment l		•	•	0. 12 months
Morin et al. 2005[110] Germany Before 2005 1 centre	Elective unilateral TKR 30; 30; 30	Oral pre-medication with 20mg chlorazepate. General anaesthesia with intravenous propofol and 4–8µg/kg i.v. fentanyl and desflurane in N2O. 100mg diclofenac suppository after anaesthesia induction and 2.5g intravenous metamizole before end of surgery. Post- operative 3 daily doses of oral diclofenac 50mg. i.v. PCA			9–12 months7; 6; 5High risk of bias due to large losse to follow up, non-blinded outcome collection, and differences betwee

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	Median 68 (IQR 62, 74); 71 (63, 74); 65 (53, 73) 50%; 70%; 59%		olus 2mg as needed wit urs.	groups in BMI and anaesthetist's opinion of difficulty of catheter placement. No difference between groups in level of pain at the knee joint during	
	6	Continuous FNB Stimulating catheter used. Initial bolus of prilocaine 1% and ropivacaine 0.75%. 300mg prilocaine 1% (30ml) and 150mg ropivacaine 0.75% (20ml). During first 48hrs post- operative ropivacaine 0.2% infusion 14ml/hr.	Continuous FNB and continuous SNB Stimulating catheter used. Initial bolus of prilocaine 1% and ropivacaine 0.75%. In each catheter: 200mg prilocaine 1% (20ml) and 75mg ropivacaine 0.75% (10ml). During first 48hrs post-operative infusion through each catheter of 0.2% ropivacaine 7ml/hr.	Continuous psoas compartment block Stimulating catheter used. Initial bolus of prilocaine 1% and ropivacaine 0.75%. 300mg prilocaine 1% (30ml) and 150mg ropivacaine 0.75% (20ml). During first 48hrs post- operative ropivacaine 0.2% infusion 14ml/hr.	level of pain at the knee joint during past 4 weeks: FNB median 2.5 (IQR 1, 4), FNB and SNB 2 (1, 4), Psoas block 2 (IQR 1, 4), p=0.44 No early complications but longer term adverse events not reported.
ACB continuous vs	FNB continuous				
Davidson et al. 2016[111] USA 2013-2014 2 studies combined from 1 centre	Primary, unilateral TKR or unicompartmental 54 (39 TKR, 16 UKR); 56 (41 TKR, 15 UKR) TKR mean 67 (SD 8); 66 (7). UKR 70 (10); 68 (12)	hydromorphone, a LIA with 30 ml rop epinephrine (5 µg/ Post-operative: or celecoxib (200 mg oxycodone (10 mg infusion pump bol titrated to pain sev	ivacaine (0.5%), ketoro	blac (30 mg), and o mg every 6 hr), tained release akthrough pain, out). Rescue opioid 2%) bolus was	12 months 31; 29 High risk of bias due to partial follow up TKR and UKR combined. Pain score (0-10) at 12 months median 0.0 (IQR 0.0, 3.0); 0.5 (0.0, 2.0). P=0.80). Pain score >0: 35%; 32%. P=0.65. No difference at 4 months when follow up more complete (51;

	TKR 59%; 66%. UKR 47%; 47%	Ultrasound guided ACB. Ropivacaine 0.2% at basal rate of 6 ml/hr, a 4-ml bolus, and a lockout of 30 minutes	Ultrasound guided continuous FNB. Ropivacaine 0.2% at basal rate of 6 ml/hr, a 4-ml bolus, and a lockout of 30 minutes	52) in pain score (p=0.80) or pain score >0 (p=0.48). Falls in hospital: 2; 5
ACB single vs FNE Macrinici et al. 2017[38] USA Before 2017	Primary unilateral TKR, indication not specified (selected by the surgeon for	Multimodal regimen including analgesics, opioids. LIA 40ml All patients received an ultrase into ACB and FNB sites.	Marcaine 0.25%.	6 months 3; 4 lost to follow up. 6; 3 complications Low risk of bias
1 centre	TKA) 49; 49 Mean 67 (SD 8); 67 (8) 61%; 63%	Immediately after surgery, 30ml solution with 100mlImmediately after surgery 30ml solution with 100ml		VAS pain similar between groups a 6 months. No difference in functional outcomes Medical complications: 3; 0. Surgical complication: 0; 1. Temporary foot drop: 3; 2.
<i>FNB continuous vs</i> Nader et al. 2012[39] USA 2007-2008 1 surgeon	S oral opioid Elective unilateral TKR 31; 31 Median (IQR) 65 (60, 76); 64 (60, 71) 58%; 77%	Before surgery, patients received 1–2mg midazolam as needed. Epidural with 10mg 0.5% isobaric bupivacaine injected intrathecally. Intraoperative sedation with propofol infusion of 25-75mcg/kg/minute. In post-anesthesia recovery area, PCA epidural with basal infusion of 3 ml/hr (1 mg/ml bupivacaine and 10 mg/ml hydromorphone) with patient- activated boluses of 3 ml with a lockout interval of 15 minutes and per hour maximum of 15 ml. Infusion discontinued and epidural catheter removed on morning of POD 1. All subjects received 5 mg warfarin on evening of surgery and 40 mg enoxaparin starting on POD 1Continuous FNB inserted with use of stimulator. After discontinuation of epidural anaesthesia on the morning of POD1 10mL bolus of ropivacaine 0.25% followed by 5ml/h infusion of 0.1%10 mg oral hydrocodone plus 325mg acetaminophen every 4-6 hours administered for pain as needed. Sustained release oxycodone 10mg for 12 hours with oral hydromorphone 2 mg over		6 and 12 months 1; 1 lost to follow up at 12 months Low risk of bias No difference in overall median NRS pain score at 6 months and 1 months: 0 (IQR 0, 1); 0 (0, 1). p=1.0. At 12 months, some evidence favouring hydrocodone for pain ascending/ descending stairs 1 (0, 2); 0 (0, 0). p=0.01. Also, suggestion of reduced pain in hydrocodone group at night in bed (p=0.06) and sitting/ lying (p=0.07) standing upright (p=0.10). No difference walking on flat surface (p=0.41). Falls in month after surgery: 1;0. Positive joint aspirate: 3; 0. VTE: 0

		discontinued. Femoral catheter removed 24 hours after previous dose of enoxaparin.	4 hours for breakthrough pain	
FNB continuous vs Wang et al. 2015[112] China 2012-2013 3 centres	PCA Elective unilateral TKR 82; 86 No significant differences in age or sex	General anaesthesia with mida fentanyl (1µg/kg), propofol (1-2 (0.15mg/kg). Anaesthesia main during surgery. Intramuscular in metoclopramide and 2.5mg dro surgery. Post-surgery, celocoxi patients with severe pain, and i Continuous FNB with ultrasound stimulator. After surgery, 0.2% ropivacaine (20ml) injected through	6 and 12 months 2; 4 lost to follow up at 12 months Unclear risk of bias: limited reporting of randomisation method No differences were observed between groups at 6 or 12 months for any HSS domain including pain No nerve injuries	
Peng et al. 2014[40] China Before 2014 1 centre (2 surgical teams with 4 surgeons and 2 anaesthesiologists)	Primary unilateral TKR 140;140 Mean: 66.8 (SD 9.4); 68.0 (SD 11.2) 73%; 65%	catheter. Then an analgesia pump was attached delivering 0.2% ropivacaine 8ml/hr. General intravenous and inhala midazolam 0.1-0.15mg/kg (eton patients >65 years), propofol 2. 0.3-1.0µg/kg, and vecuronium of anaesthesia. Maintenance w sevoflurane and continuous intr remifentanil 7-8µg/kg/hr and pr wound closure, 5-10µg intraver dose of PCA injected. i.v. inject FNB with ultrasound guidance. Initial dose of 10ml 2% lidocaine and 10ml 1% ropivacaine. 30 minutes before end of operation, catheter connected to PCA pump; patients received loading dose of 5ml of 0.15% ropivacaine followed by infusion of 0.15% ropivacaine at 5ml/hr, with bolus of 5mL	6 and 12 months 31; 38 at 12 months Low risk of bias Chronic post-operative pain (NRS 1+) in 38.5% of PCA group at 6 months compared with 25.7% in FNB group (p=0.021). No difference at 12 months (p=0.273). Authors only reported short term adverse events associated with us of PCA.	

China osteoarthritis 40; 39 (30; 30 after post randomisation exclusions) Catheter inserted under nerve timulation and ultrasound guidance. Standardised bolus of 15 mL 0.5% Intravenous PCA morphine after the operation exclusions Mean 68.8 (SD 6.4); 68.9 (7.5) 73%; 73% Catheter inserted under nerve post randomisation exclusions) Intravenous PCA morphine after the operation fifter the operation fifter the operation 73%; 73% Mean 68.8 (SD 6.4); 68.9 (7.5) 73%; 73% O.08% levobupivacaine postpartively until POD 3 Intravenous PCA morphine after the operation fifter the operation fifter the operation operative was FNB 48.73 at 44.7 (p=0.513) 73%; 73% 0.08% levobupivacaine postpartively until POD 3 Including patients not follow Deaths: 0; 0. Infection: 1; 1.3. Shock: 3; 2. Transfusion: from excluded cases. Atria fibrillation and confusion: 0 0, 0, 1. Sepsis: 1; 0. ICU admi shock: 1; 0. FNB and SNB continuous vs epidural PCA Primary unilateral Germany Primary unilateral Premedication with 10 mg oral clorazepate. Spinal anaesthesia installed, SNB and FNB catheters inserted with ultrasound guidance. 5 ml bolus 0.2% ropivacaine. 50; 69% fight anaesthesia installed, SNB and FNB catheters inserted with ultrasound guidance. 5 ml bolus 0.2% ropivacaine. 5 ml, bolus administration of 5 ml, bolus administra			and lock time of 30 min. Preoperatively, a loading dose of 30ml was injected for intraoperative analgesia.		
Anastase et al. 2014[113]Primary unilateral TKR 55; 50 Mean 68.2 (SD 9.2); 69.7 (SD 8.7)Premedication with 10 mg oral clorazepate. Spinal anaesthesia with light sedation: 12.5mg 0.5% bupivacaine. Supplemental postoperative analgesia available with i.v. piritramid6 and 12 months1 centre55; 50 Mean 68.2 (SD 	2014[44] TKF China oste 2009-2011 40; 1 centre exc Mea 6.4)	nilateral elective KR, 98% for steoarthritisParacetamol, sustained release diclofenate, opioid (codeine or morphine). Spinal anaesthesia0; 39 (30; 30 after ost randomisation (clusions) ean 68.8 (SD 4); 68.9 (7.5)Catheter inserted under nerve stimulation and ultrasound guidance. Standardised bolus of 15 mL 0.5% levobupivacaine. Continuous infusion of 8 to 12 mL/h 0.08% levobupivacaine postoperatively until POD 3Intravenous PCA in after the operation		anaesthesia Intravenous PCA morphine after the operation	2; 2 not pre- and peri-operative exclusions Low risk of bias No separate pain outcome but improvement of KSS from pre- operative was FNB 48.73 and PC/ 44.7 (p=0.513) Including patients not followed up. Deaths: 0; 0. Infection: 1;1. DVT: 2 3. Shock: 3;2. Transfusion: 2;3. All from excluded cases. Atrial fibrillation and confusion: 0; 1. PE: 0; 1. Sepsis: 1;0. ICU admission for
2014[113]TKRanaesthesia with light sedation: 12.5mg 0.5% bupivacaine. Supplemental postoperative analgesia available with i.v. piritramid15; 14Germany 2010-2011Mean 68.2 (SD 9.2); 69.7 (SD 8.7) 65%; 69%After spinal anaesthesia installed, SNB and FNB catheters inserted with ultrasound guidance. 5 ml bolus 0.2% ropivacaine. FNB with an hourly rate of 5 ml, bolus administration of 5 ml by the patient and the lock-out interval of 20 mins.Epidural catheter installed at the same time as spinal catheter. 5ml 0.2% ropivacaine and PCA performed through the epidural catheter. Hourly rate 3 ml, bolus administration of 5 ml, and lock-out period of 30 minutes.15; 14High risk of bias due to large follow upPain during previous 4 wee pain, 2 very little, 3 little, 4 moderate, 5 loud, 6 very lo (translation from German). difference at 6 months p=0 12 months, FNB/SNB med (1.00, 2.00), PCA 2.00 (2.00) p=0.004 favouring FNB/SNB	FNB and SNB continuou	s vs epidural PC	A		
	2014[113] TKF Germany 55; 2010-2011 Mea 1 centre 9.2)	R 50 an 68.2 (SD); 69.7 (SD 8.7)	anaesthesia with light sedation Supplemental postoperative a piritramid After spinal anaesthesia installed, SNB and FNB catheters inserted with ultrasound guidance. 5 ml bolus 0.2% ropivacaine. FNB with an hourly rate of 5 ml, bolus administration of 5 ml by the patient and the lock-out interval of 20 mins. SNB 5 ml/h to a maximum	n: 12.5mg 0.5% bupivacaine. nalgesia available with i.v. Epidural catheter installed at the same time as spinal catheter. 5ml 0.2% ropivacaine and PCA performed through the epidural catheter. Hourly rate 3 ml, bolus administration of 5 ml, and lock-out period of	15; 14 High risk of bias due to large loss follow up Pain during previous 4 weeks: 1 n

		and lock-out interval of 20 minutes.		
FNB single vs LIA				
Fan et al. 2016[36] China 2012-2014 Single hospital, 2 surgeons	Primary unilateral TKR (75% osteoarthritis; 25% rheumatoid arthritis) 80; 80 (78; 79 in analysis) Mean 68.4 (SD 8.8); 67.6 (6.3) 79%; 86%	General anaesthesia in all but surgery, i.v. morphine, PCA ar FNB performed pre- operatively with 20ml ropivacaine 0.5%. After cementing prostheses, 50ml of saline injected into periarticular soft tissue.		1 year 3 protocol violations Low risk of bias No separate pain outcome. Mean KSS at 1 year similar between groups: 94.2 (SD 2.6); LIA 93.9 (3.1). p=0.51 Infection: 0; 0. DVT: 1; 1. Femoral nerve injury: 1; 0.
FNB single and epic Reinhardt et al. 2014[41] USA 2010-2012 Single hospital, 2 surgeons	Elective unilateral TKR for osteoarthritis 51; 51 (49; 45 received allocated intervention) Mean 67.9 (SD 10.9); 66.6 (10.1) 59.2%; 57.8%	Spinal anaesthetic (2.5ml 0.5% daily. Oral Perocet or Vicodin Dilaudid for severe breakthrou Combined spinal-epidural (500ml hydromorphone 10µg/ml and bupivacaine HCl 0.06%). Single intra-operative FNB injection (30ml 0.25% bupivacaine). Continuous 48-hour epidural infusion (4ml/hr with 4ml per demand dose, locked out every 10 minutes with an hourly limit of 20ml). Epidural infusion weaned to 2ml/hr on POD1 and to 0 ml/hr at 5 p.m. on POD1. Demand dose with	as required. Subcutaneous	1 year 0: 0 of patients who received allocated intervention Low risk of bias VAS pain at 1 year similar betweer groups (noted in text and shown graphically) No wound-related complications or infections. 1 DVT and 1 DVT plus PE in epidural group. Arthrofibrosis 2; 1

LIA with corticostere	oid vs LIA with no a	lockout parameters continued for 48 hours. Placebo intraarticular knee catheter placed intra- operatively with continuous saline 7ml/hr infusion until POD2. corticosteroid		
Seah et al. 2011[48] Singapore 2004-2005 1 hospital	TKR 50; 50 Mean 65.4; 67.9 Sex not stated	General or spinal anaesthesia. and PCA (with morphine bolus of minutes, and maximum dose 8 Intraoperative periarticular injection of 0.5ml/kg 1:200,000 epinephrine and 0.5% bupivacaine diluted with 30ml of normal saline. 40mg of corticosteroid (triamcinolone acetonide) was added to half the mixture. The solution with the corticosteroid was injected into the deep tissues. The remaining solution was injected into the skin incision before closure.	of 1mg, lock-out time 5	6 months and 2 years No losses to follow up reported Low risk of bias No separate pain outcome but no statistically significant difference in OKS between groups at 2 years Deep infection: 1; 1
Yue et al. 2013[114] China 2011-2012 1 hospital	Unilateral TKR for osteoarthritis 36; 36 Mean 70.2 (SD 6.4); 69.3 (5.7) 89%; 89%	General anaesthesia. PCA (25) bolus, 6 minutes lock-out, and 5 hours after surgery. 5-10mg intr rescue. Celecoxib pre- and post Injections with local anaesthetic agent and adrenaline (0.75% ropivacaine 30ml, 1:1000 adrenaline 0.5ml, and isotonic sodium chloride solution 70ml) plus corticosteroid (1ml betamethasone).	5mg/hr maximum) for 72	6 and 12 months No loss to follow up reported Unclear risk of bias. No separate pain outcome. No difference in mean KSS between groups at 6 or 12 months No incision infection or tendon rupture complications

		Another 50ml syringes fluid without corticosteroid was infiltrated into the skin		Another 50ml syringes fluid without corticosteroid was infiltrated into the skin		
LIA including ketorolac vs epiduralSpreng et al. 2012[115], Spreng et al. 2010[116]Unilateral, non- cemented TKR with no patella resurfacingNorway 2007–2009 1 hospital34; 34; 34 66.5 (SD 11.); 67.2 (SD 8.9); 65.8 (SD 10.1) 61%;61%;67%	anaesthesia with 13-15 mg bupivacaine 5 mg/ml with 20µg fentanyl. If indicated, up to 10ml/hr 10mg/ml propofol for sedation. Acetaminophen 1g every 6 hours. i.v. PCA morphine for 48 hours after surgery (2mg bolus with 10 minutes lockout time). When PCA stopped, 10mg slow release oxycodone twice daily. 5 mg oxycodone as rescue analgesia.i.v. injection of ketorolac 1ml (30mg/ml) andi.v. injection of 6 ml saline. Infiltration with			12 months 13 did not provide complete data Unclear risk of bias due to limited reporting (long-term outcome only reported as conference abstract). Perioperative analgesic treatment did not have any significant influence on any KOOS outcomes. Infection: 0; 0; 1. No long-term advers events reported		
		 (sorng/ml) and morphine 5ml (1mg/ml). Infiltration with ropivacaine 150mg, epinephrine 0.5mg, ketorolac 30mg and morphine 5mg in 150ml saline. After closure, catheter placed into knee joint and 10ml infiltrate injected. 22-24 hours after surgery, 20ml injection through catheter of ropivacaine 19ml (7.5mg/ml) and ketorolac 1ml (30mg/ml). i.v. injection of 	Infiltration with ropivacaine 150mg, epinephrine 0.5mg, ketoro 30mg and morphine 5m 150ml saline. After closure, catheter place into knee join 10 ml infiltrate injected. 22-2 hours after surgery, 20m injection throu catheter of ropivacaine 1 (7.5mg/ml) ar saline 1ml. i.v injection of sa 1ml. Sham epidura catheter.	blac s g in o g in ir h ed 1 e 24 b l ugh 1 ir 9ml S nd c 7. ir aline	hinedately before spinal inaesthesia. Vhen spinal inaesthesia tarted to wear off, epidural offusion for 48 irs with 6-10 onl/hr fentanyl pug/ml, pupivacaine mg/ml. No knee offiltrations. Sham knee eatheter with no opjections	

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		ketorolac 1ml (30mg/ml).			
		Sham epidural catheter.			
Spinal with adde sulphate	d high dose morphine	e sulphate vs spinal	with added low dos	e morphine sulpha	ate vs spinal with no morphine
Foadi et al.	Unilateral TKR	3ml spinal anaesthe	esia with 0.5% bupiva	caine	6 months
2017[117]	or THR for	Post-operative 1 g r	metamizole (orally or	intravenously)	"only a few dropouts". >70%
Germany	osteoarthritis		morphine (intraveno	ous or	questionnaire return rate.
Before 2017	16; 16; 17	subcutaneous) as re	escue		Unclear risk of bias due to limited
1 centre	Mean 67.63 (SE	medication			reporting of pilot RCT.
	2.45); 67.33 (2.87); 63.71 (3.14) 56%; 44%; 65%	0.2mg morphine sulphate added to spinal anaesthesia	0.1mg morphine sulphate added to spinal anaesthesia	No morphine sulphate added to spinal anaesthesia	No difference in WOMAC pain betweer groups at 6 months. No adverse events noted

Myofascial trigger point dry needling 2.

Author	Indication	Common pain manageme	nt	Follow up
Country Recruitment dates Setting	Number randomised intervention; control Age % female	Group 1 (intervention)	Group C (control)	Losses to follow up intervention; control Risk of bias issues Key results
Mayoral et al. 2013[118] Spain 2007-2008 Single centre	Unilateral TKR for osteoarthritis 20; 20 Mean 71.7 (SD 6.1); 72.9 (7.9) 72.5%	General or spinal anaesthes After anaesthesia and surgery started, dry needling applied 20 times to all myofascial trigger points by a trained and experienced physical therapist.	ia If spinal anaesthesia used, dry needling simulated behind screen	6 months 4; 5 High risk of bias due to large losses to follow up WOMAC pain at 6 months: mean 3.24 (SD 3.03); 3.13 (2.72). Difference not statistically significant. No difference between groups in VAS pain (p=0.725) or proportion of patients reporting significant VAS pain at 6 months.

	No complications related to the dry needling intervention. Other adverse events not collected.
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3. Tourniquet

Author	Indication	Common blood conservation	on strategies	Follow up
Country Recruitment dates Setting	Number randomised intervention; control Age % female	Group 1 (intervention)	Group C (control)	Losses to follow up intervention; control Risk of bias issues Key results
Ejaz et al. 2014[54] Denmark 2011-2012 1 centre	Primary unilateral TKR for osteoarthritis 35; 35 (33; 31 received intervention) Mean 68 (SD 8.0); 68 (7.8) 45.5%; 45.2%	Before surgery, oral tranexan (0.5g) 3 hours after surgery a postoperatively. Appropriately sized thigh tourniquet applied. Limb exsanguination by elevation for 2 minutes and cuff inflated to 250mm Hg.	nic acid (1g). Tranexamic acid and 6 and 12 hours Appropriately sized thigh tourniquet applied but not inflated. Served as safety device in case of uncontrollable bleeding.	6 and 12 months 0; 0 of those who received intervention Low risk of bias Statistically significant difference in KOOS pain intensity at 2 months favouring TKR without a tourniquet (p < 0.001). Small difference between groups not statistically significant at 6 and 12 months. Small number of adverse events did not suggest extra risk in the group with no tourniquet.
Liu et al. 2014[56] Australia Before 2014 1 surgeon	Unilateral TKR for osteoarthritis 10; 10 Mean 67.0; 70.0 30%; 10%	PCA. No CPM Tourniquet inflated to 300 mmHg before skin incision. Tourniquet deflated after wound closure and dressing.	Tourniquet placed but not inflated	6 and 12 months 0; 0 Low risk of bias No separate pain measure. Total OKS not significantly different at 6 and 12 months Blood transfusions: 3; 0.
Mittal et al. 2012[57] Australia 2008-2010	Primary unilateral TKR 31; 34	Autologous blood re-infused Short duration. Tourniquet set at 300mm Hg inflated	if required Long-duration. Tourniquet set at 300mm Hg inflated before	1 year 5; 2

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1 centre	Mean 67.5 (SD 8.9); 66.6 (8.4) 81%:74%	prior to ceme and deflated hardened		skin incision an when cement h		Low risk of bias. However, RCT terminated early due to increased need for blood transfusion in short duration tourniquet group.
	×,					No separate pain outcome. Total OKS (0-48) at 52 weeks higher in long-duration group reflecting better recovery than short duration group but not significantly (p=0.12). Mean difference approximately 5 which is greater than MCID of 4[78]. Transfusions: 10; 2. Patient reported
		6				adverse event: 26; 12
Abdel-Salam and	Primary unilateral	Tourniquet pla	aced around thi	igh		1 and 2 years
Eyres 1995[119]	TKR of which	Limb exsangu		Tourniquet not	inflated	0; 0
UK 91% Date not stated 40; 40	minutes and tourniquet inflated to twice systolic blood pressure				Unclear risk of bias due to limited reporting of methods. No pain measure or PROM	
	Mean 72 (range 65-80); 74 (64- 82)			Via		Surgeon recorded HSS score at 1 year 90 (78-97); 91 (80-97). Not significantly different at 1 or 2 years.
	57.5%; 62.5%			- CV		Blood loss similar between groups. Wound infections: 5;0. DVT: 4;0
Şükür et	Primary unilateral			d to 125mm Hg a	bove systolic	6 months
al.2016[120]	TKR, in women with osteoarthritis	blood pressur				0;0;0;0
Turkey 2015 1 surgeon	30; 30; 30; 30 Mean 67.0 (SD	Knee in 90° flexion and tourniquet	Knee in 90° flexion and tourniquet	Knee in full extension and	Knee in full extension and	High risk of bias. KSS outcome noted in methods but not presented in results.
	7.0); 66.9 (8.5); 68.4 (6.9); 68.4 (6.8)	deflated during wound closure	inflated during wound closure	tourniquet deflated during wound	tourniquet inflated during wound	KSS results not reported at 6 months but no significant differences between groups at 3 months.
	100%	CIOSUIE	CIUSUIE	closure	closure	Surgical and wound complications similar between groups. No infections, fractures or instability requiring revision within 6 months
		Blood transfu	sion if required		1	3-22 months, mean 12;13 months

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Zhang et al.2016	Primary TKR for osteoarthritis	Tourniquet		No tourni	quet	Not clear
[121] China	84; 82					High risk of bias. Variable follow up. HSS outcome noted in methods but
2014-2015	Not reported					not presented in results.
1 hospital	Not reported					HSS not reported.
	~					Transfusion rates similar between groups. At mean follow up of 12 -13 months, patients operated on without a tourniquet had a lower rate of DVT (2.4%) compared with those with a tourniquet (10.7%).
Zhang et al.	Primary unilateral	Tourniquet inflated t	to 300-337	mm Hg. Tr	anexamic acid not	6 months
2017[58]	cemented TKR	generally used	1		1	0; 0; 0
China	for osteoarthritis	Tourniquet for	Tourniqu		Tourniquet from	Low risk of bias
2008-2011 1 surgeon	50; 50; 50 Mean 70.3 (SD 6.6); 71 (10.2);		removed wound cl		osteotomy until wound closure	No separate pain outcome. HSS similar between groups at 6 months (p=0.839).
	68.2 (6.8) 54%; 60%; 50%		16			At 2 weeks DVT: 0; 0; 1. Intramuscular vein thrombosis: 4; 3; 3. Transfusions: 30%; 26%; 10%
Huang et al.	Primary unilateral	Tranexamic acid				6 months
2017[55]	TKR for	Tourniquet		No tourni	quet	0; 0
China	osteoarthritis 50; 50					Low risk of bias
2015 1 centre	Mean 66.2 (SD 8.3); 65.1 (6.8)					VAS pain similar between groups at months (p=0.728). Mean HSS score 90.3 (SD 3.2); 91.2 (2.5). P=0.151
	64%; 68%					DVT: 0; 0. PE: 0; 0. Intramuscular venous thrombosis: 6; 4. Superficial infection: 1; 0. Wound secretion: 6; 0 No significant difference in blood los between groups.

4. Compression bandage

Author	Indication	Common treatments	Follow up

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Country Recruitment dates Setting	Number randomised intervention; control	Intervention	Control	Losses to follow up intervention; control Risk of bias issues Key results
	Age % female			
Brock et al. 2017[122] UK 2013-2014 1 hospital	Primary unilateral TKR for osteoarthritis 25; 25 (24 received intervention) Mean 67.3 (SD 8.2); 69.5 (6.8) 66.7%; 64.0%	Hydrocolloid dressing left in p 10-14 Soft inner layer with compressive outer layer bandage. Removed after 24 hours.	lace until clips removed on day Standard bandaging with soft inner layer and crepe bandage outer layer. Removed after 24 hours and cryocuff used.	6 months 0; 0 of patients receiving interventio Low risk of bias No separate pain outcome. Mean OKS similar between groups at 6 months: 35.8 (SD 7.7); 34.3 (10.6). P=0.58 No infections or thromboembolic events in either group
Blood conser Author Country Recruitment dates	Indication Number randomised	Common blood conservation	on strategies Control	control
Author Country	Indication Number randomised intervention; control Age			Losses to follow up intervention;
Author Country Recruitment dates Setting	Indication Number randomised intervention; control			Losses to follow up intervention; control Risk of bias issues
Author Country Recruitment dates Setting Tranexamic acid Sa-Ngasoongsong	Indication Number randomised intervention; control Age		Control	Losses to follow up intervention; control Risk of bias issues
Author Country Recruitment dates Setting <i>Tranexamic acid</i>	Indication Number randomised intervention; control Age % female	Intervention	Control	Losses to follow up intervention; control Risk of bias issues Key results

						wound complications or infection reported in either group
Kim et al. 2014[61] Korea 2009-2011 1 hospital Sa-Ngasoongsong et al. 2013[65] Thailand 2010-2011 1 hospital	Primary unilateral TKR for osteoarthritis 90; 90 Mean 73.5 (SD 5.5); 71.9 (SD 5.9) 88%; 87% Primary unilateral cemented TKR for osteoarthritis 45; 45; 45 Mean 68.1 (SD 6.2); 67.6 (8.7); 66.2 (7.3) 88.9%; 93.3%; 95.6%	containing 500mg tranexamic acid injected into knee joint after fascial closure via drain tube.	e dressir 25ml sal solution 25ml sal solution containin tranexar injected joint afte closure tube.	n and eryth No tranexa placebo	25ml saline solution injected into knee joint after fascial closure	 year 0; 0 Low risk of bias WOMAC pain mean 3.2 (2.6); 2.8 (2.3). Difference not statistically significant Lower blood loss and need for allogenic transfusion in tranexamic acid group. No DVT. 1 PE in control group. year 0; 0; 0 Low risk of bias No separate pain outcome but WOMAC mean 14.5 (7.1); 15.1 (6.2); 15.5 (6.6). P=0.42 Total blood and Hb loss lower in intervention groups than control. Fewer transfusions in 500mg (0) than 250mg tranexamic acid group (6) and control group (10). 2 DVT in 500mg group. 1 DVT in 250mg group. 1 PE and 3 DVT in control group. No infections.
Hourlier et al. 2015[60] France 2009-2010 1 hospital	Primary unilateral TKR for osteoarthritis 52; 54 74 (SD 6); 72 (7) 62%; 63%	Tourniquet, electrocau drain. No blood salvag 10 mg/kg intra-operativ tranexamic infusion. At hours, continuous infus tranexamic acid 2 mg/k for 20 hours via electric syringe	e systen ve fter 2 sion of kg/hr	n. single bolu tranexami intraopera 2 hours, p	us of 30 mg/kg c acid as an tive infusion. After lacebo saline s infusion via	6 months 0; 0 Low risk of bias. No separate pain score but KSS clinical score mean 90 (SD 6); 90 (13). P=0.90 No difference between groups in total blood loss. 1 MUA in single treatment

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				group. No deep infections or revisions.
Huang et al. 2017[55] China 2015 1 centre	Primary unilateral TKR for osteoarthritis 50; 50 Mean 66.2 (SD 8.3); 65.8 (6.3) 64%; 70%	Tourniquet inflated to 100mm and deflated after wound closu Intravenous tranexamic acid 20mg/kg before incision and tranexamic acid 10mg/kg at 3, 6, 12 and 24 hours. 1g tranexamic acid in 50ml saline irrigated into wound during operation		6 months 0; 0 Low risk of bias VAS pain similar between groups at months (p=0.728). Mean HSS score (0-100) better in tranexamic acid group than controls: 90.3 (SD 3.2); 88.9 (3.0). P<0.001. Mean difference 1.4 lower than MCID of 8.29[81] Greater blood loss in control group than tranexamic group (p<0.001). DVT: 0; 0. PE: 0; 0. Intramuscular venous thrombosis: 6; 3. Superficia infection: 1; 3. Wound secretion: 6;
Thrombin infusio	n			1
Kusuma et al. 2013[62] USA Not stated 1 hospital	Primary unilateral TKR for osteoarthritis 40; 40 Mean 64.6 (SD 10.2); 64.5 (7.3) 82.5%; 67.5%	Tourniquet, drain, Esmarch ba 20,000 IU thrombin infusion (1,000 IU/mL) through fascial defect	ndage, electrocautery Closure and drain placement protocol without the thrombin infusion.	 1 year (6 months and 2 years also reported) 0; 0 Low risk of bias No separate pain outcome. KSS mean 95.5; 96.0. p=0.45 Lower drop in Hb in thrombin group Blood transfusion in 4 intervention and 7 control patients. 1 control patient had haematoma. No hospita readmissions
Flexion vs extens				4
Napier et al. 2014[63] UK 2003-2004 1 hospital	Primary unilateral TKR of which 89% for osteoarthritis 90; 90	No drains or tranexamic acid Flexion. Operated knee kept in passive flexion (120°) post-operatively for 6 hours using a jig. Wound redressed and placed in flexion over a	Extension. Operated knee kept in full passive extension	1 year 5; 1 (12 did not attend follow up) Low risk of bias. No separate pain outcome. OKS mean 20.5 (SD9.0); 22.1 (9.7). P=0.27

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Country Recruitment dates	Number randomised	Group 1 (intervention)	Group C (control)	Losses to follow up intervention; control
Author	Indication	Common blood conservation	on strategies	Follow up
6. Platelet rich j	plasma		101	adverse events or mortality between groups.
			Li	7% of auto-transfusion group require allogenic transfusion compared with 28% in control group. Fewer infections, readmissions and GP visits in auto-transfusion group. No significant differences in other seriou
1 hospital	70.0 (40-88) 62%; 53%	before re-infusion using a centrifugal cell washing machine		No separate pain outcome. No significant difference in EQ-5D between groups.
UK Not stated	Mean 69.3 (range 32-95);	drainage if volume >125ml post-operative. Blood washed and re-suspended		Unclear risk of bias due to limited details of methods and follow up.
Thomas et al. 2001[123]	115; 116	Allogenic transfusion if Hb fel Auto-transfusion of wound	Wound drainage discarded	6 months Losses to follow up not reported
Auto-transfusion of	f washed blood			C months
	9.9) 71.0 (7.6) 74%; 64%	morning.		haematoma in flexion group. 1 deep infection and 1 extensor muscle weakness in extension group. More transfusions in extension group (p=0.002)
	Mean 70.4 (SD	single pillow until POD1		1 MI and 1 DVT in each group. 1

6. Platelet rich plasma

Author	Indication	Common blood conservation	Follow up	
Country Recruitment dates Setting	Number randomised intervention; control Age % female	Group 1 (intervention)	Group C (control)	Losses to follow up intervention; control Risk of bias issues Key results
Aggarwal et al. 2014[124]	Primary unilateral surgery or first surgery of staged	Tourniquet. No tranexamic acid or suction drain. Blood transfusion if necessary due to intraoperative blood loss or postoperative haemoglobin <8g/dl.		6 months No losses to follow up reported

India 2010-2011 1 surgeon	bilateral TKR for osteoarthritis 7; 14 Mean 56.43 (SD 7.59); 53.79 (9.75) Sex not stated	8 ml PRP, prepared from patient's blood. Calcium chloride for activation given in a separate syringe in 4:1 ratio. PRP and calcium chloride injected into the posterior recess, gutters and capsule, and repaired extensor mechanism and prepatellar fat.		High risk of bias due to unexplained differences in numbers of patients in randomised groups. No separate pain outcome. WOMAC total at 6 months PRP mean 7.14 (S 0.69), controls 7.86 (1.23), p=0.173 PRP group had lower fall in haemoglobin and need for blood transfusion
. Cryotherapy Author	Indication	Common treatment		Follow up
Country Recruitment dates	Number randomised intervention;	Group 1 (intervention)	Group 1 (intervention)	Losses to follow up intervention; control
Setting	control			Risk of bias issues Key results
	Age % female	6		Reyresuits
Wang 2017[125]	Unilateral TKR for	CPM for 2 weeks		6 months
China 2013-2015	osteoarthritis 53; 53 Mean 65.23 (SD 5.41); 64.97(5.36) 62.3%; 58.5%	Compression cold therapy for 48 hours	No compression cold therapy	0; 0 Unclear risk of bias due to limited reporting No separate pain outcome. At 6 months 87% of cryotherapy patients had excellent or good knee function compared with 699 of controls (p=0.032). No adverse events reported in

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8. Denusomab

Author	Indication	Common treatment		Follow up
Country Recruitment dates Setting	Number randomised intervention; control Age % female	Group 1 (intervention)	Group 1 (intervention)	Losses to follow up intervention; control Risk of bias issues Key results
Ledin et al. 2017[66] Sweden 2012-2014 2 centres	Elective cemented primary unilateral TKR for osteoarthritis 25; 25 Mean 66 (SD 6.3); 64 (5.5) 60%; 60%	Injection of 60mg denusomab 1 day after surgery and after 6 months	Injection of placebo 1 day after surgery and after 6 months	 12, 24 months 0; 2 Low risk of bias No significant differences in KOOS pain or other KOOS domains between groups 12 12 of 24 months No suspected unexpected adverse reactions in either group
). Continuous p Author	bassive motion	Common treatment	10	Follow up

9. Continuous passive motion

Author	Indication	Common treatment			cation Common treatment Follow up		Follow up
Country Recruitment dates Setting	Number randomised intervention; control Age % female	Group 1 (intervention)	Group 2 (interventi	ion)	Group C (control)	Losses to follow up intervention; control Risk of bias issues Key results	
Leach et al. 2006[126] UK Before 2005 1 hospital	Unilateral cruciate retaining rotating platform TKR for osteoarthritis 85 overall Mean 71.2 (range 53-84); 72.9 (52- 89)	Physiotherapy protoc exercises to improve exercises. CPM commenced on postoperative day se range 0–30 and used hour twice per day. E	ROM and q first t at a I for 1			6 and 12 months 25 patients lost to follow up High risk of bias due to large loss to follow up and use of date of birth randomisation No difference in mean VAS pain at 1 year, CPM 0.6; control 0.9. p=0.49	

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	50%; 54%	range was increased t with discharge at POD	by 10° 0 5-7.		Adverse events not reported
Sahin et al. 2006[127] Turkey Before 2006 1 hospital Pope et al. 1997[128] Australia 1988-1999 1 hospital	Primary unilateral TKR for osteoarthritis 15; 16 Mean 61 (SD 6.0); 61.6 (7.5) 86%; 86% Primary unilateral or bilateral TKR of which 86% for osteoarthritis 62 (70 knees). Authors excluded those not followed	Standard physiotherap From POD 1, CPM 2.5 2x/day. Initially 0-40° f and increased by 10° until POD 7 Physiotherapy comme Patients had an initial CPM range of 0-40° increased by 10° twice, on day after surgery and day 2, so that 0-60°	by 5 hours lexion each day enced on postoperativ Patients had an initial CPM range of 0-70° increased by 10° twice, on day after surgery and day 2, so that 0-90°	re day 1 Knee placed in an extension splint in the recovery room	6 months 3 lost to follow up Unclear risk of bias as patients were followed up by treating physician. Mean difference in VAS pain 0.1/10 slightly favouring no CPM group (95% CI -0.8, 0.9; P=0.87) Adverse events not known 6 and 12 months 8 patients (12 knees) excluding death High risk of bias due to losses to follow up and limited reporting of methods No separate pain outcome.
those not followed up so groups were 18; 20; 19 Mean 72.5 (95% CI 64.4, 74.98); 72.7 (70.4, 75.0); 69.4 (64.4, 74.98) 64.7%; 50%; 72.2%	before removal of machine at 48	flexion achieved before removal of machine at 48 hours	201	 However, "pain disability" contributed up to 50 points out of a total of 70-point functional score (70 best outcome). No difference between groups in functional score: CPM 0-40 median 56 (range 20, 70); CPM 0-70 52 (1 70); no CPM 52 (25, 70). p=0.80 CPM groups had greater blood loss than controls, p=0.008). 1 manipulation under anaesthesia in no CPM group, 2 revisions du to patellar dislocation in the 0-4 CPM group, 1 PE death in the 0 	
Beaupré etal. 2001[129]	Primary unilateral TKR of which	Standardised exercise a slider board session	v .	ission which included	70 CPM group. 6 months

Canada	92% for	3 sessions (2	-	of two 10-	No intervention	6; 8; 6
1997-1998 1 hospital	osteoarthritis 40; 40; 40 Mean 68 (SD 9); 68 (9); 69 (8) 52.5%; 50%; 30%	hours) with CPM machine per day from POD2. Range increased from starting range 0-30 degrees as tolerated.	minute sli therapy se per day in to one in t standardis exercise. knee flexi extension and lying performed independe tolerated.	essions addition the sed Active on and in sitting positions	further than standardised exercise.	Unclear risk of bias due to losses to follow up Mean WOMAC pain at 6 months 76 (15); 85 (15); 79 (16). No difference over time between groups, p=0.62. Long-term adverse events. Need for MUA: 1; 1; 0. DVT: 0; 1; 0. Cellulitis: 0; 0; 1. Infection 0; 0; 1
Kumar et al. 1996[130] USA Before 1996 1 hospital	Primary unilateral TKR for osteoarthritis 40 (46 knees); 33 (37) Mean 69 (range 52-86); 68 (42-88) 58%; 67%	Standard physiothera CPM from POD 0. Ini hours/ day 0-90° until discharge	itially 10	movemen to 90° 2x/	Passive range of t ("drop and dangle") day initially for 20 ater 30-45 minutes.	6 months 15; 13 lost to follow up High risk of bias due to large losses to follow up No separate pain outcome. KSS CPM 82.7; Drop and dangle 80.7 p=0.78 Haematoma 3;1. Closed
Worland et al. 1998[131] USA 1996 1 hospital	Unilateral or bilateral TKR for osteoarthritis. 91 patients (114 knees randomised). After post- randomisation exclusions: 37 (49 knees); 43 (54 knees) Mean 70.2 (range 44-84) 66.25%	CPM and physiothera At home after dischar machine 3 hours per replaced knee for 10 d	rge, CPM day on	Physical t	nission herapist home visit 1 e times per week for	 manipulation 1;3. DVT 0;0. PE 0 6 months 11 patients (11 knees) Unclear risk of bias due to post- operative exclusions not reporter separately for groups and limited reporting of methods. No separate pain outcome. At 6 months, mean HSS score CPM 95.3 (SD 2.8); physiotherapy 95. (3.0). P=0.49. Adverse events not reported.

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MacDonald et al. 2000[132]	Primary unilateral TKR for	Active ROM, passive using walker or crutcl	6 and 12 months Not reported		
Canada Before 2000 1 hospital	osteoarthritis 40; 40; 40 Age and sex not reported	CPM commenced POD 0. Initially 0- 50 degrees. Provided for 18-24 hour/ day. Increased by 10 degrees/ hour as tolerated. Continued until POD 1	CPM commenced POD 0. Initially 70- 110 degrees. Provided for 18-24 hr/ day. Not increased. Continued until POD 1	No CPM	Unclear risk of bias due to limited and selective reporting. No separate pain outcome. No statistical differences between groups for KSS at 6 and 12 months. Adverse events not reported
Bennett et al. 2005[67] Australia 1997-2000 1 hospital	Primary unilateral TKR for osteoarthritis 47; 48; 52 70.7; 71.4; 71.7 72.3%; 64.6%; 67.3%	Standard in hospital p Standard CPM from 0° to 40° for 2x3 hours on POD 1 increased by 10° per day until POD 6. Extension splint applied overnight	Early flexion CPM commenced in recovery room from 90° to 50° knee flexion. Increased gradually to CPM 90° to 0° for 2x3 hours in day 4-6.	nme No CPM	 12 months 1 patient excluded due to inabilit to achieve 90° flexion Low risk of bias No separate pain outcome. No significant difference in KSS between groups at 1 year. No difference in wound healing between groups
Ersözlü et al. 2009[68] Turkey 2003-2004	Primary unilateral TKR for osteoarthritis 30; 30; 30 Mean 65 (range 54-73); 61 (49- 80); 62 (52-78) 66%; 55%; 57%	Conventional physica CPM set at 30-40° from POD1. Increased as tolerated to POD7. 1 hour CPM 3x/day.	Al therapy CPM set at 60-70° from POD3. Increased by 10°/ day to POD7. 1 hour CPM 3x/day.	No CPM	2 years 1; 1; 2 Low risk of bias No separate pain outcome. KSS scores 98; 95; 92. No significant difference between groups p=0.67. Infection 0; 0; 1. Arrhythmia 0; 1; 0. No difference in complications between groups

10. Electrical stimulation

Author Indication Common rehabilitation strategies

Country Recruitment dates Setting	Number randomised intervention; control Age % female	Intervention	Intervention	Common rehabilitation strategies
Avramidis et al. 2011[69] Greece 2005-2006 1 hospital	Elective primary unilateral TKR for osteoarthritis 38; 38 Mean 70.54 (SD 4.68); 70.66 (3.73) 80%; 82.9%	Standard physiotherapy for 6 we Transcutaneous electric muscle stimulation of the vastus medialis muscle from POD2 2x/ day for 2 hours for 6 weeks.	eeks. No CPM No intervention	1 year 3 (intervention intolerance); 3 Low risk of bias Improved SF-36 bodily pain at 1 year in intervention group compared with control, mean 92 (SD 10.57); 79.48 (12.72). P<0.001. Difference of 12.52 close to MCID of 16.86[82]. No difference in OKS or American KSS Adverse events not reported
Stevens-Lapsley et al. 2012[133] USA 2006-2010 1 hospital	Primary unilateral TKR for osteoarthritis 35; 31 Mean 66.2 (SD 9.1); 64.8 (7.7) 57.1%; 51.6%	Standard inpatient rehabilitation, therapy Neuromuscular electrical stimulation commenced on POD2 for 6 weeks 2x/ day.	home and outpatient physical No intervention	6 months and 1 year 5; 6 Unclear risk of bias due to baseline differences in WOMAC No difference in resting pain (points) at 1 year intervention mean 0.6 (SD 1.4); control 0.4 (1.5). Also similar at 6 months. Mean WOMAC total score better at 1 year in intervention group compared with control, 5.7 (5.9); 10.0 (12.2) and at 6 months. However, probably explained by baseline differences. Authors state no differences for change in WOMAC. DVT 1; 0. Unspecified complication 1; 0. Infection 0; 2. Revision 0; 1

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Levine et al.	Elective unilateral	2 sessions of ROM exercise		6 months
2013[134] USA Before 2013 1 surgeon	TKR for osteoarthritis 35; 35 Mean 68.1; 65.1 76%; 62%	Neuromuscular electrical stimulation commenced 14 days pre-operatively until 1 day before surgery. Recommenced at POD1 for 60 days. After hospital discharge no direct contact with a physical therapist	Formal physical therapy programme with progressive resistive exercises and strengthening in hospital and after discharge supervised by physical therapist.	5; 9 Unclear risk of bias due to larg uneven losses to follow up KSS pain favoured intervention 6 months but not significantly 79.08 (SD 10.97); 75.5 (14.77) 95%CI for difference -3.78, 10 Similar for WOMAC total score 95%CI for difference -3.19, 14 Confusion 2; 0
Moretti et al.	Primary unilateral	Rehabilitation protocol including	CPM	6 and 12 months
2012[70] Italy 2008-2010 1 hospital	TKR for osteoarthritis 15; 15 Mean 70.0 (SD 10.6); 70.5 (8.1) Not reported	Pulsed electromagnetic fields (I-ONE therapy) from POD7, 4 hours/ day for 60 days	No intervention	No losses to follow up Low risk of bias Mean VAS pain (10-point scale lower at 12 months in interven group compared with control, ((SD 1.3); 3.6 (3.9). p< 0.05. M difference of 2.1 (10-point scal greater than MCID of 16.1 (10 point scale)[83] Difference also at 6 months. More swelling of the knee in intervention patients than controls, statistically significan 1 and 2 months
Adravanti et al. 2014[135] Italy 1 hospital	Primary unilateral TKR for osteoarthritis 16; 17 Mean 66 (SD 13); 73 (5) 62.5%; 52.9%	Standard rehabilitation protocol: Pulsed electromagnetic fields (I-ONE therapy) by POD7 for 4 hours/ day for 60 days	active and passive mobilisation No intervention	6 months 4; 3 High risk of bias: small study, proportionately high losses to follow up At 6 months, mean VAS pain i intervention group lower than i controls (p<0.05). At 3 years, 7 intervention patients and 4/12 controls reported severe pain

	No difference between groups in swelling at 6 months.
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11. Rehabilitation

Author	Indication	Common rehabilitation stra	ategies	Follow up
Country Recruitment dates Setting Number randomised intervention; control Age % female		Intervention Control		Losses to follow up intervention; control Risk of bias issues Key results
Walking guidance a	nd training	No		
Li et al. 2017[71] China 2015-2016 1 hospital	Primary unilateral TKR for osteoarthritis 43; 43 Mean 76.33 (SD 5.28); 78.47 (5.50) 55.8%; 51.2%	muscle strength, use of aids, methods and precautions. Knee passive flexion and ext muscle strength training com straight leg raising exercises increased joint activities and	ce on joint activities, quadriceps diet guidance, correct walking tension to 90° and quadriceps menced on POD 1. POD 3-7, . 2 weeks after replacement, muscle strength training, centre nb weight training, and walking No additional rehabilitation	6 months 0; 0 Low risk of bias Mean VAS pain at 6 months: 0.51 (SD 0.74); 2.83 (0.88) favouring walking intervention group, p<0.01. Difference of 2.42 (10 point scale) greater than the MCID of 16.1 (100- point scale)[83]. HSS scores at 6 months favoured intervention, p<0.01. No infection, allergic reaction or immune reaction in either group. Intervention not associated with swelling, pain, prosthesis loosening, thrombosis, or delayed wound healing
Aquatic therapy		O	un altimon alaite after anna a tait	
Liebs et al. 2012[72] Germany 2003-2004 4 hospitals	Elective primary unilateral TKR for osteoarthritis 87;98	suction drains. Programme o motion activities; exercises for	nce, coordination and gait; and	6, 12 and 24 months 13.8%; 19.4% excluding deaths and unexplained reasons Low risk of bias

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	Mean 68.5 (SD 8.6); 70.9 (7.5) 70.1%;73.5%	Aquatic therapy for 30 postoperative week 5 proprioception, coord float cuffs, training kic	5. Pool ex lination a	xercises ain and strength	ned at training of ening with aid of	WOMAC pain at 12 months: early aquatic mean 13.2 (SD 15.0); late aquatic 17.4 (22.4) p=0.22. No difference at 6 and 24 months.
	A.	Aquatic therapy begir on the 6th postoperat day with the wound covered with a watern adhesive dressing.	tive	exercise a	erapy as pool fter the completion nealing on the 14th tive day	5 early aquatic therapy patients and late aquatic therapy patient readmitted to hospital within 3 months. 2 early aquatic patients and 1 late aquatic patient readmission directly or indirectly related to the intervention.
Rahmann et al.Unilateral2009[136]primary TKR orAustraliaTHR for		Standard ward-based physiotherapy treatment with an occlusive, war	ent per c	day. Surgica	al wounds covered	6 months 4;2;0 for combined THR and TKR
Australia 2003-2005 1 hospital with 2 surgeons	osteoarthritis (50% TKR) 18;19;17 (11 had been excluded post- randomisation due to complications in hospital Mean 69.4 (SD 6.5); 69.0 (8.9); 70.4 (9.2) 44.4%; 63.2%; 70.6%	From day 4, 1 to 1 individual physiotherapy. Aquatic physiotherapy programme to maximize function and strength. 40 mins/ day. Fast pace metronome 80-88 bpm	From da individua physioth Water ex program general not targe specific retrainin aquatic environn	y 4, 1 to 1 al erapy. xercise me with exercises eted at functional g in the nent. Slow etronome	From day 4, 1 to 1 individual ward- based physiotherapy. 40 mins/ day	 Unclear risk of bias as TKR patients more likely to receive ward-based control intervention. THR and TKR analysed together No difference in overall WOMAC outcome at 6 months in THR and TKR patients combined between aquatic at fast pace and ward-based (p=0.929) and aquatic at 2 paces (p=0.872). No adverse events reported after intervention commenced.
Supported early d		Innotiont physiotheres	<u></u>			12 months
Mahomed et al.Primary unilateral008[137]TKR or THR forcanadaosteoarthritis000-200250% TKR)centres119;11568				to independent ation centre for 14	No losses to follow up Low risk of bias (analysis by actual treatment received showed similar results) WOMAC pain at 12 months marginally favoured home-based	

	About 67% women	subsequent management along a multidisciplinary clinical pathway (4-16 visits). Then outpatient physiotherapy or self- directed programme.		rehabilitation mean 87 (SD 16); 83 SD (20), p=0.08 but this was not statistically significant. Mean difference of 4 less than MCID of 8- 9[77]. Results did not differ between TKR and THR patients. Similar rates of dislocation, DVT and readmissions between groups. 2% inpatient group developed infections compared with 0 in home group
Hill et al. 2000[138] UK 1997-1998 1 centre	Unilateral, primary TKR, irrespective of diagnosis or concomitant disease 70 randomised, with 32;28 eligible for trial at day 5	Care pathway for medical, nurs from admission until day 5 Outreach team domiciliary visit prior to admission with assessment of home environment. At days 5–7, patients assessed to ensure discharge safe. Outreach team visit on day of discharge with further visits as required. 1+ physiotherapist visit linked with nurses to monitor knee performance. Discharge when skin clips removed, wound healed and specialist orthopaedic assistance not required, usually day 10–12	sing and physiotherapy care Inpatient care until removal of skin clips and wound healing.	 year No losses to follow up reported after commencement of intervention Unclear risk of bias due to limited reporting of methods. No pain outcome or patient reported outcome. Control group had better mean KSS scores, but this did not reach statistical significance at 1 year or earlier. 1;1 serious infection, other wound infections 1;6, painful joints 9;4, other minor complications similar between groups
Flexion or extension	•			
Wang et al. 2014[74] China 2009-2010 1 centre	Primary unilateral TKR for osteoarthritis 40; 40 Mean 68.34 (SD 7.09), 67.87 (6.47) 17.5%; 22.5%	No patellar replacement or late Articular capsule, soft tissue and skin enclosed in 90° flexion which was maintained for 1-2 min after wound closure.	eral retinacular release Wound closure performed in full extension	6 months No losses to follow up Low risk of bias Mean VAS pain in flexion group 1.15 (SD 0.73); extension group 1.12 (0.68), p=0.64

		fractu	vound complications, patella ure or infection requiring surgery her group
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12. Wound management

Author	Indication	Common wound manageme	nt strategies	Follow up
Country Recruitment dates Setting	Number randomised intervention; control Age % female	Intervention	Control	Losses to follow up intervention; control Risk of bias issues Key results
Kong et al. 2014[75] South Korea 2011 1 surgeon	Primary cemented unilateral TKR for osteoarthritis 50; 50 Mean 69.0 (SD 7.7); 68.0 (4.8) 89.6%; 87.5%	Skin staples removed on day applied for 5 days After removal of wound closure strip, patients managed operation scars with application of silicone gel for 1 month after stitches removed	10 and wound closure strip After removal of wound closure strip, patients managed operation scars with application of petroleum gel for 1 month after stitches removed	6 and 12 months 2; 2 lost to follow up Low risk of bias At 12 months, VAS pain in silicone gel group mean 2.50 (SD 1.16); control 2.92 (1.90). P=0.201. No difference at 6 months, p=0.886. No wound dehiscence or infection associated with application of silicone gel or petroleum
13. Anabolic ster	oids Indication	Common rehabilitation strat	egies	Follow up
Country	Number	Intervention	Control	Losses to follow up intervention:

13. Anabolic steroids

Author	Indication	Common rehabilitation strat	Common rehabilitation strategies	
Country Recruitment dates Setting	Number randomised intervention; control Age % female	Intervention	Control	Losses to follow up intervention; control Risk of bias issues Key results
		Cold compression and CPM		6, 9 and 12 months

Hohmann et al. 2010[76] Australia Before 2010 1 surgeon	Primary unilateral TKR for osteoarthritis 5; 5 Mean 66.2 (range 58, 72); 65.2 (59, 72) 20%; 40%	On day 5, intramuscular injection of 50 mg Nandrolone decanoate solution. Patients visited every 2 weeks and injections continued for 6 months.	On day 5, intramuscular injection of saline. Patients visited every 2 weeks and injections continued for 6 months.	0; 0 lost to follow up Low risk of bias (but small feasibility study) No separate pain outcome. KSS at 12 months in intervention group mean 91.4 (SD 3.5); control 81.2 (SD 7.1). p=0.03. Difference also at 6 months (p=0.04), marginal at 9 months (p=0.06). Difference in means at 12 months of 10.2 close to MCID of 12.3[79].
		T Do		Intervention group had smaller decrease in bone mineral density at 6 months than controls but not significant

14. **Guided imagery**

4. Guided image Author	ery Indication	Common rehabilitation strat	egies	Follow up
Country Recruitment dates Setting	Number randomised intervention; control Age % female	Intervention	Control	Losses to follow up intervention; control Risk of bias issues Key results
Jacobson et al. 2016[139] USA 2011-2012 1 surgeon	Primary unilateral TKR for osteoarthritis 42; 40 (41; 39 received treatment) Mean 65.0 SD 8.6) 62.2%	Participants listened to a 19- 21-minute CD each day for 2 weeks before and 3 weeks after surgery. Content covered concerns and hopes about TKR with aim to facilitate mind–body connections to promote optimal TKR outcomes.	Participants listened to a 17- 21-minute CD each day for 2 weeks before and 3 weeks after surgery. Content comprised poetry, short stories and essays	6 months 12; 10 of patients receiving treatments High risk of bias due to large losses to follow up Mean WOMAC pain 2.7 (SD 3.1); 3.4 (SD 3.3). P<0.001 Adverse events not reported

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CD compact disc; CPM Continuous passive motion; DN4 Douleur Neuropathique 4; FNB Femoral nerve block; HSS Hospital for Special Surgery; i.v. intravenous; KOOS Knee injury and Osteoarthritis Outcome Score; KSS Knee Society Score; LIA local infiltration analgesia; NRS Numerical rating scale; OKS Oxford Knee Score; ONB obturator nerve block; PCA Patient controlled analgesia; PNB psoas nerve block; SF-36 Short Form 36 Health Survey; S-LANSS Leeds assessment of Neuropathic Symptoms and Signs Pain Scale; SNB Sciatic nerve block; TKR Total knee replacement; VAS Visual analogue scale; VTE Venous thromboembolism; WOMAC Western Ontario and McMaster Universities Osteoarthritis Index.

ITT, ITT CC, POD, MI, PE

Supplementary material. Risk of bias assessment

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blind outcome assessment	Incomplete outcome data	Selective reporting	Other bias	Summary
Pain manageme	ent							
Albrecht et al. 2014[34]	Computer generated	Anaesthetist blind to allocation	Physiotherapists, surgeons, research assistants collecting data, and members of the Acute Pain Service were kept blinded to group allocation.	Physiotherapists, surgeons, research assistants collecting data, and members of the Acute Pain Service were kept blinded to group allocation.	ITT analysis low losses to follow up	No but not checked protocol	Study was terminated early with 61% of planned recruitment completed due to change in standard anaesthesia at hospital	Low
Anastase et al. 2014[113]	Method of the Ulm Institute of Statistics	Method of the Ulm Institute of Statistics	No	No	15:14 lost to follow up	No but not checked protocol	ASA comorbidities differed between groups	High
Aveline et al. 2014[52]	Computer generated	opaque sealed envelopes	Blinded syringes prepared by nurse not involved in study	Yes	Low losses to follow up	Consistent with short term follow up paper	No	Low
Bergeron et al. 2009[105]	Blocks of different sizes according to list preprepared by study epidemiologist	Not described	Anaesthetist not blind. Patients blind	Nurse observers collecting data blind to allocation	32/59 lost to follow up	No but not checked protocol	No	High
Buvanendran et al. 2010[53]	computer generated	Yes, physicians and nurses blind	Yes	Yes	ITT	Protocol not checked	No	Low

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Choy et al. 2011[35]	Computer generated	sealed envelope	No, the catheter was removed at either day 3 or 7	Patient reported outcome. Other outcomes by blinded independent physician	Low losses to follow up	Protocol not checked but reasonable range of outcomes	No	Low
Davidson et al. 2016[111]	Computer generated	Sealed opaque envelopes	Subjects and investigators were not masked to treatment group	Subjects and investigators were not masked to treatment group. PROM	31; 29 lost to follow up	None apparent but protocol not checked	Combined data from 2 RCTs	High
Fan et al. 2016[36]	No details	sealed opaque envelopes	Patients and assessors blind to randomisation	Patients and assessors blind to randomisation	2% protocol violation	No but not checked protocol	No	Low
Foadi et al. 2017[117]	Computer generated	Not described	Not described	Patient reported outcome	>70% questionnaire return	None apparent but protocol not checked	Described as pilot study	Unclea
Gao et al. 2017[37]	Random number table	Not described	Blind to patients	Blind to observers	2; 1; 0	None apparent but protocol not checked	Groups similar at baseline	Low
llfeld et al. 2009[108]	Computer generated	Investigators, patients, and all clinical staff were unaware of treatment group assignments	Investigators, patients, and all clinical staff were unaware of treatment group assignments	Investigators, patients, and all clinical staff were unaware of treatment group assignments	4:1 lost to follow up	No but not checked protocol	Basal infusion halved on POD1 in 10 intervention patients compared with 3 controls	High
llfeld et al. 2011[109]	Computer generated tables	Solutions prepared by investigational pharmacist	Yes. Intervention and control solutions indistinguishable	Patient reported outcomes. Staff masked to treatment group	11;12 did not have 4 measures out	Protocol not checked	WOMAC and WOMAC domain scores	High

				assignment performed all measures and assessments	of 6 up to 12 months	but seems reasonable	somewhat lower pre- intervention in extended infusion group. Authors report change scores	
Macrinici et al. 2017[38]	Computer generated	Staff performing injections blind	Anaesthesiologist, surgeons, patients and physical therapists blind to allocation	Yes	3; 4 lost to follow up. 6; 3 complications	None apparent but protocol not checked	Groups similar at baseline	Low
McDonald et al. 2016[45]	Computerised blocked	Study coordinator independent of care and surgery	Patients blind. Surgeon aware of study	Outcome assessment blind to allocation	1; 4 unexplained	None apparent, protocol not checked	Groups similar at baseline	Low
Meunier et al. 2007[51]	Computer generated	Sealed envelope	Randomisation code broken after 1 year	Yes	ITT reported except for 12 month pain outcome	No but not checked protocol	M/F ratio differed	Low
Morin et al. 2005[110]	Allocated randomly	Sealed envelope	All patients received some form of nerve block. Anaesthesiologist not blind to intervention	Observers not blinded	Per protocol analysis	No but not checked protocol	Difference between groups in anesthetist's opinion of difficulty of catheter placement. BMI differed between groups	High
Motififard et al. 2017[46]	Computer generated	Study coordinator independent of care and surgery	Patients blind. Surgeon aware of study	Outcome assessment blind to allocation	3; 7 (1; 4 unexplained)	None apparent, protocol not checked	Groups similar at baseline	Low

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Nader et al. 2012[39]	Computer generated	Opaque envelope	No	Patient reported outcome	1:1 lost to follow up	Protocol not checked but reasonable range of outcomes	FNB group somewhat higher BMI	Low
Niemeläinen et al. 2014[47]	No details	Opaque sealed envelopes	Only research nurse preparing infiltrate aware of randomisation. All other personnel unaware until after 1 year follow up	Only research nurse preparing infiltrate aware of randomisation. All other personnel unaware until after 1 year follow up	All patients who received intervention completed follow up	No but not checked protocol	No	Low
Peng et al. 2014[40]	Computer generated	Not possible	Not possible	Patient reported outcome	31:38 lost at 12 months but ITT and per- protocol analysis	No but not checked protocol	No	Low
Perrin and Purcell 2009[107]	No details	Sealed syringe code stored in pharmacy department	yes	Yes	4 failed to complete protocol	No but not checked protocol	Pilot investigation. High risk of bias due to recruitment difficulties leading to small trial	Higl
Reinhardt et al. 2014[41]	Computer generated	Maintained by pharmacy department for blinding	Patients blind to intervention	Blinded research assistant and partially physical therapist	0 reported lost to follow up of those who received interventions	No but not checked protocol	No	Low
Seah et al. 2011[48]	Randomisation tables	Sealed envelopes. Anaesthetist and surgeon blind before opening of	Blinding of patients not stated	Blind outcome assessors and PROMs	No losses to follow up reported	No but not checked protocol	No	Low

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		sealed envelope						
Shum et al. 2009[106]	No details	No details	Anaesthetist performing the blocks was not involved in the postoperative follow-up and data collection	Patient reported	14% and 20%	No but not checked protocol	Mean patient weight lower in no FNB group. More favourable mean OKS in no FNB group. Two groups combined for 2 year outcome but not for earlier	High
Spreng et al. 2012[115], Spreng et al. 2010[116]	Hospital pharmacy	Epidural catheter or sham set-up taped along the back of the patient and connected to an infusion pump covered in an opaque bag. Also sham knee catheter	Patients blind	Blind outcome assessment	13%	Limited reporting in conference abstract	Conference abstract only so limited information additional to early follow up paper	Unclear
Wang et al. 2015[112]	No details	No details	Not stated	Not stated	2:4 lost to follow up	No but not checked protocol	No	Unclear
Wegener et al. 2013[42]	No details	Opaque envelope	Patients, surgeons and researchers not blind to intervention	Patients not blinded	2:7:5 lost to follow up	No. Protocol checked	no	Low
Widmer et al. 2012[43]	Coded envelope	Coded envelope	Except for anaesthetist and surgeon	Both the investigators and patients were blinded	None reported as incomplete	No but protocol not checked	No	Low

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Williams et al. 2013[49]	Computer generated	Not stated	Patients and assessors blind	Patients and assessors blind	3:1 of those who received treatment	No but not checked protocol	No	Low
Wu and Wong 2014[44]	Computer	Sealed envelopes	No	No	Available cases	No but not checked protocol	No	Low
Wylde et al. 2015[50]	Trials unit	Trials unit	Surgeon and anaesthetist not blind to allocation, Patients blind	Patients and research nurses blind to allocation	ITT with imputed data	No as per protocol	No	Low
Yue et al. 2013[114]	No details	No details	Surgeons and patients were double-blinded to the injection administered	surgeons and patients were double-blinded to the injection administered	Losses to follow up not reported	Limited reporting	No	Unclea
	iger point dry ne		Γ	1			1	
Mayoral et al. 2013[118]	Computerised	Not described	Patient and other researchers apart from physical therapist blind	Patient outcomes	4: 5 loss to follow up	None apparent but protocol not checked	No	High
Tourniquet	·		•					
Abdel-Salam and Eyres 1995[119]	Card system	Not described	No	No	No losses to follow up	None apparent but protocol not checked	No	Unclea
Ejaz et al. 2014[54]	Block randomised	Sealed envelopes	Patients unaware	PROM	No losses to follow up of those who received treatments	None apparent but protocol not checked	No	Low
Huang et al. 2017[55]	Computer generated	Sealed opaque envelopes	Surgeons not blind. Patients blind to allocation	Data collector blind to allocation	No losses to follow up reported	None apparent but protocol	Groups similar at baseline	Low

					not checked		
Excel	Not described	Patients blind	PROM	No losses	None apparent but protocol not checked.	No	Low
Computer generated	Sealed opaque envelopes	Patient blind	Outcome assessors blind. PROM	5:2	None apparent but protocol not checked	Study stopped because of high risk of transfusion in short tourniquet duration group	Low
Computer generated	Not described	Possibly patients	Outcome assessors blind	No losses to follow up	KSS outcome noted in methods but not presented in results	No	High
Excel	Randomisation by blinded researcher.	Patients and nurses on ward blind	Not clear	No losses reported	None apparent but protocol not checked	Groups similar at baseline	Low
Randomly allocated	Not clear	Not clear	Not clear	Not clear	HSS outcome noted in methods but not presented in results	No	High
	Computer generated Computer generated Excel Randomly	Computer generatedSealed opaque envelopesComputer generatedNot describedComputer generatedNot describedExcelRandomisation by blinded researcher.RandomlyNot clear	Computer generatedSealed opaque envelopesPatient blindComputer generatedNot describedPossibly patientsComputer generatedNot describedPossibly patientsExcelRandomisation by blinded researcher.Patients and nurses on ward blindRandomlyNot clearNot clear	Computer generatedSealed opaque envelopesPatient blindOutcome assessors blind. PROMComputer generatedNot describedPossibly patientsOutcome assessors blind. PROMComputer generatedNot describedPossibly patientsOutcome assessors blindExcelRandomisation by blinded researcher.Patients and nurses on ward blindNot clearRandomlyNot clearNot clearNot clear	Computer generatedSealed opaque envelopesPatient blindOutcome assessors blind. PROM5:2Computer generatedNot describedPossibly patientsOutcome assessors blind. PROMNo losses to follow upComputer generatedNot describedPossibly patientsOutcome assessors blindNo losses to follow upExcelRandomisation by blinded researcher.Patients and nurses on ward blindNot clearNo losses reportedRandomlyNot clearNot clearNot clearNot clearNot clear	ExcelNot describedPatients blindPROMNo lossesNone apparent but protocol not checked.Computer generatedSealed opaque envelopesPatient blindOutcome assessors blind. PROM5:2None apparent but protocol not checked.Computer generatedNot describedPossibly patientsOutcome assessors blind. PROM5:2None apparent but protocol not checkedComputer generatedNot describedPossibly patientsOutcome assessors blindNo losses to follow upKSS outcome noted in methods but not presentedExcelRandomisation by blinded researcher.Patients and blindNot clearNot clearNot clearNot clearRandomly allocatedNot clearNot clearNot clearNot clearNot clearHSS outcome noted in methods but protocol 	excelNot describedPatients blindPROMNo lossesNone apparent but protocol not checked.NoComputer generatedSealed opaque envelopesPatient blindOutcome assessors blind. PROM5:2None apparent but protocol not checked.Study stopped because of high risk of transfusion in short touriquet duration groupComputer generatedNot describedPossibly patientsOutcome assessors blind. PROMNo losses to follow upNo losses to outcome assessors blind. Protocol not checkedNoNoComputer generatedNot describedPossibly patientsOutcome assessors blindNo losses to follow upNoNoExcelRandomisation by blinded researcher.Patients and nurses on ward blindNot clearNot clearNo losses reportedNone apparent but not protocol not checkedGroups similar at baselineRandomly allocatedNot clearNot clearNot clearNot clearHSS outcome neetods but not presentedNo

Brock et al. 2017[122]	Web-based	Not specified	Not possible	No but PROMs	4; 2 of those receiving intervention	None apparent but protocol not checked	Groups similar at baseline	Low
<i>Blood conserva</i> Hourlier et al. 2015[60]	ation Computer generated	Opaque envelopes	Anaethsetist, surgeon and patient blind to treatment allocation	Assessors blind	No missing data	None apparent but protocol not checked	No	Low
	Computer generated	Sealed opaque envelopes	Surgeons not blind. Patients blind to allocation	Data collector blind to allocation	No losses to follow up reported	None apparent but protocol not checked	Groups similar at baseline	Low
Kim et al. 2014[61]	Computer generated	Not stated	patients blind to allocation	Clinical investigator blind to allocation	No missing data	None apparent but protocol not checked	No	Low
Kusuma et al. 2013[62]	Computer generated	Sealed envelopes	Surgeon and patient blind	Outcome assessor blind	No missing data	None apparent but protocol not checked	No	Lov
Napier et al. 2014[63]	Computer generated	Sealed envelopes	Unlikely	Not stated but PROM	low losses to follow up	None apparent but protocol not checked	No	Low
Sa- Ngasoongsong et al. 2011[64]	Computer generated	Sealed envelopes	Surgeon and patient blind	Outcome assessor blind	No missing data	None apparent but	No	Low

						protocol not checked		
Sa- Ngasoongsong et al. 2013[65]	Computer generated	Sealed envelopes	Surgeon and patient blind	Outcome assessor blind	No missing data	None apparent but protocol not checked	Some difference between groups in pre- operative Hb	Low
Thomas et al. 2001[123]	Not described	not stated	Not reported	Not reported but PROM	Not reported but ITT	None apparent but protocol not checked	No	Unclear
Platelet rich pla		L -					_	<u> </u>
Aggarwal et al. 2014[124]	Not described	Opaque envelopes	Patients blind	Patients and examiners blind	No losses to follow up reported	None apparent but protocol not checked	Odd numbers in groups from randomisation	High
Cryotherapy								•
Wang 2017[125]	No details	No details	No details	No details	No losses to follow up	None apparent but protocol not checked	Groups similar at baseline	Unclear
Denusomab								
Ledin et al. 2017[66]	Randomisation list produced by the study monitor	Syringes prepared independently	Investigators and patients blind	Unblinding was done after all the data had been locked	0; 2	None apparent but protocol not checked	No	Low
Continuous pas				1		1	1	
Beaupré etal.	Computer generated	Sealed envelopes	No	Researcher unaware and	6:8:6. Results carried	No	4 controls; 1 SB	Unclear

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					forward for missing data		reassigned to CPM	
Bennett et al. 2005[67]	Block	Not stated	Operating surgeon blind. Patient not	Independent assessor blind	1 not included in analyses as not able to achieve 90 degree flexion	No	No	Low
Ersözlü et al. 2009[68]	Divided into groups by random selection	Not described	No	Surgeon score	A diabetic patient from the control group was excluded because of a superficial wound infection, a patient with a cardiac problem in group II due to dysrhythmia, and two patients due to insufficient follow-up.	Not apparent	No differences baseline	Unclea
Kumar et al. 1996[130]	Random number generator	Not stated	No	Not described	Large loss to follow up	Not all data clearly reported	No	High
Leach et al. 2006[126]	Allocation by date of birth	No	No	Blinded evaluation	Large loss to follow up	No	No	High
MacDonald et al. 2000[132]	Computer generated	Allocation concealed	No	Not described	Not reported	Yes, not all outcomes reported in full	No	Unclea
Pope et al. 1997[128]	Not described	Not described	Not described	Not described	No separate reporting. 8 patients (12 knees)	None apparent but protocol	No	High

					excluding 1 death	not checked		
Sahin et al. 2006[127]	Not described	Not stated	No	Followed up by treating physician	Low loss to follow up	No	No	Unclea
Worland et al. 1998[131]	Not described	Not described	No	Researcher blind	Not reported separately	None apparent but protocol not checked	No	Unclear
Electrical stime		T	1	ſ		-	1	1
Adravanti et al. 2014[135]	Computer generated	Not described	Research assistant not involved in patient assessment	Principal investigator and all physicians in charge of clinical controls were blinded to patient allocation	78% retained at 6 months	Not apparent but protocol not checked	No	High
Avramidis et al. 2011[69]	Computer generated	Not described	No	Independent assessors blind	3 (intolerance of intervention); 3	Not apparent	Baseline similar	Low
Levine et al. 2013[134]	Drawing papers from hat	Not described	No	Not described. WOMAC PROM	5:9 for KSS pain and WOMAC	Not apparent but protocol not checked	No	Unclea
Moretti et al. 2012[70]	Computer generated	Not described	Physicians, as well as medical assessors, were blinded to the allocation of patients in the study groups	Physicians, as well as medical assessors, were blinded to the allocation of patients in the study groups	No losses reported	Not apparent but protocol not checked	No	Low
Stevens- Lapsley et al. 2012[133]	Stratified	Concealed	No	no but standardised scripts used	5; 6	Not apparent but protocol	WOMAC, BMI unequal at baseline	Unclear

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						not		
D I I I I I I I I I I						checked		
Rehabilitation								
Hill et al. 2000[138]	Not described	Not stated	Not possible	Not described	No losses to follow up after initial 23222	No but protocol not checked	No	Unclea
Li et al. 2017[71]	Random number table	Not stated	Not possible	Not described but PROM	No losses to follow up	No but protocol not checked	Groups similar at baseline	Low
Liebs et al. 2012[72]	Computer generated	Allocation concealed	Not possible	No but PROM	Low losses to follow up (<20% if deaths and other explained reasons not counted)	No but protocol not checked	No	Low
Mahomed et al. 2008[137]	Block randomisation	Not stated	Not possible	PROM	No loss	No but protocol not checked	ITT gave similar results to analysis according to actual discharge destination (20 inpatient group received home based)	Low
Rahmann et al. 2009[136]	Not described	Sealed numbered envelopes	Not possible	Assessor blind to intervention. Patient reported outcome	Low losses to follow up	No but protocol not checked	TKR patients more likely to receive ward- based control intervention. THR and TKR analysed together	Unclea
Wang et al. 2014[74]	Computer generated	Surgeons did not participate	Surgery was performed by the	Postoperative evaluation was	No loss to follow up	None apparent	No baseline differences	Low

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		in pre- operative grouping	physicians who did not participate in the preoperative grouping and postoperative evaluation	conducted by the physicians who were unaware of the grouping.		but protocol not checked		
<i>Wound manag</i> Kong et al. 2014[75]	ement Not described	Not described	Placebo used	Patient outcome	Low loss to follow up	None apparent but protocol not checked	Similar at baseline	Low
Anabolic stero Hohmann et al. 2010[76]	<i>ids</i> Internet based	Not reported	Placebo trial	Double-blind design minimized systemic error and eliminated observer and experimenter's bias	0 loss to follow up	None apparent	None apparent but small study	Low
Guided imager	v			bido				
Jacobson et al. 2016[139]	Permuted blocks	Opaque CD holders	Personnel yes, participants no	Yes	12; 10 of patients receiving treatment	None apparent but protocol not checked	No	High

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