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Single dose intra-articular morphine for pain control after knee arthroscopy (Review)

Zou Z, An MM, Xie Q, Chen XY, Zhang H, Liu GJ, Shi XY

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[Intervention Review]

Single dose intra-articular morphine for pain control after knee arthroscopy

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ABSTRACT

Background

Knee arthroscopy is a common procedure and is associated with postoperative pain. Intra-articular (IA) injection of morphine for pain control has been widely studied, but its analgesic effect after knee arthroscopy is uncertain.

Objectives

To evaluate the relative effects on pain relief and adverse events of IA morphine given for pain control after knee arthroscopy compared with placebo, other analgesics (local anaesthetics, non-steroidal anti-inflammatory drugs (NSAIDs), other opioids) and other routes of morphine administration.

Search methods

We searched CENTRAL (*The Cochrane Library* Issue 4, 2015), MEDLINE via Ovid (January 1966 to May 2015), EMBASE via Ovid (January 1988 to May 2015), and the reference lists of included articles. We also searched the metaRegister of controlled trials, clinicaltrials.gov and the World Health Organization (WHO) International Clinical Trials Registry Platform for ongoing trials.

Selection criteria

We identified all the randomised, double-blind controlled trials that compared single dose IA morphine with other interventions for the treatment of postoperative pain after knee arthroscopy. We excluded studies with fewer than 10 participants in each group, using spinal or epidural anaesthesia, or assessing the analgesic effect of IA morphine on chronic pain.

Data collection and analysis

Two authors independently assessed the quality of each trial and extracted information on pain intensity, supplementary analgesics consumption and adverse events. We assessed the evidence using GRADE (Grading of Recommendations Assessment, Development and Evaluation) and created 'Summary of findings' tables.

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Main results

We included 28 small, low quality studies (29 reports) involving 2564 participants. Of 20 studies (21 reports) comparing morphine with placebo, nine studies with adequate data were included in the meta-analysis. Overall, the risk of bias was unclear. Overall, the quality of the evidence assessed using GRADE was low to very low, downgraded primarily due to risk of bias, small study size, and imprecision.

No statistical difference was found between 1 mg IA morphine and placebo in pain intensity (visual analogue scale (VAS)) at early phase (zero to two hours) (mean difference (MD) -0.50, 95% CI -1.15 to 0.14; participants = 297; studies = 7; low quality evidence), medium phase (two to six hours) (MD -0.47, 95% CI -1.09 to 0.14; participants = 297; studies = 7; low quality evidence) and late phase (six to 30 hours) (MD -0.88, 95% CI -1.81 to 0.04; participants = 297; studies = 7; low quality evidence). No significant difference was found between 1 mg and 2 mg morphine for pain intensity at early phase (MD -0.56, 95% CI -1.93 to 0.81; participants = 105; studies = 2; low quality evidence), while 4 mg/5 mg morphine provided better analgesia than 1 mg morphine at late phase (MD 0.67, 95% CI 0.08 to 1.25; participants = 97; studies = 3; low quality evidence). IA morphine was not better than local anaesthetic agents at early phase (MD 1.43, 95% CI 0.49 to 2.37; participants = 248; studies = 5; low quality evidence), NSAIDs at early phase (MD 0.95, 95% CI -0.95 to 2.85; participants = 80; studies = 2; very low quality evidence), sufentanil, fentanyl or pethidine for pain intensity. IA morphine was similar to intramuscular (IM) morphine for pain intensity at early phase (MD 0.21, 95% CI -0.48 to 0.90; participants = 72; studies = 2; very low quality evidence).

Meta-analysis indicated that there was no difference between IA morphine and placebo or bupivacaine in time to first analgesic request. Eleven out of 20 studies comparing morphine with placebo reported adverse events and no statistical difference was obtained regarding the incidence of adverse events (risk ratio (RR) 1.09, 95% CI 0.51 to 2.36; participants = 314; studies = 8; low quality evidence). Seven of 28 studies reported participants' withdrawal. There were not enough data for withdrawals to be able to perform meta-analysis.

Authors' conclusions

We have not found high quality evidence that 1 mg IA morphine is better than placebo at reducing pain intensity at early, medium or late phases. No statistical difference was reported between IA morphine and placebo regarding the incidence of adverse events. The relative effects of 1 mg morphine when compared with IA bupivacaine, NSAIDs, sufentanil, fentanyl and pethidine are uncertain. The quality of the evidence is limited by high risk of bias and small size of the included studies, which might bias the results. More high quality studies are needed to get more conclusive results.

PLAIN LANGUAGE SUMMARY

Morphine injections for pain relief after knee arthroscopy

Background

Knee arthroscopy is a surgical procedure on the knee. The surgery is minimally invasive, which means that only a small cut (incision) is needed. An examination, and sometimes treatment, of damage is performed using an arthroscope, which is inserted into the joint through the small incision. Knee arthroscopy is used to assess or treat many orthopaedic (musculoskeletal) conditions, and patients may have pain after surgery. Morphine injected directly into the knee (intra-articular morphine) to relieve pain has been widely studied, but we do not know how well it works.

Key results and quality of the evidence

In May 2015, this review identified 28 small, low quality studies involving 2564 participants looking at intra-articular morphine for pain relief after knee arthroscopy. From 9/20 studies we did not find evidence that intra-articular morphine given at a dose of 1 mg was better than placebo for pain relief. From the limited evidence available we were unable to determine how intra-articular morphine compared with morphine injected into the muscle (intra-muscular morphine). There was also low quality evidence for the effects of 1 mg intra-articular morphine compared with intra-articular bupivacaine, non-steroidal anti-inflammatory drugs (NSAIDs), sufentanil, fentanyl and pethidine, so we were unsure which worked best. We were unable to determine how similar the rates of side effects such as nausea and vomiting were between intra-articular morphine and placebo. Overall, the quality of the evidence was low.

Future research should focus on finding effective analgesics for knee arthroscopy.

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Summary of findings 1. Morphine compared with placebo for pain control after knee arthroscopy

Morphine compared with placebo for pain control after knee arthroscopy

Patient or population: patients undergoing knee arthroscopy
Settings: inpatients
Intervention: 1 mg morphine administered via the knee joint

Comparison: placebo (saline) administered via the knee joint

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Morphine				
Pain intensity VAS score 0-10 cm VAS score. Scale from: 0 to 10. Follow-up: 0-2 hours	The mean pain score in placebo groups ranged from **2 cm to 5.4 cm**	The mean pain score in the 1 mg morphine groups was **0.5 cm lower** (1.15 lower to 0.14 higher)		297 (7 studies)	⊕⊕⊖⊖ **low** [1,2]	
Pain intensity VAS score 0-10 cm VAS score. Scale from: 0 to 10. Follow-up: 2-6 hours	The mean pain score in placebo groups ranged from **1.7 cm to 4.6 cm**	The mean pain score in the 1 mg morphine groups was **0.47 cm lower** (1.09 lower to 0.14 higher)		297 (7 studies)	⊕⊕⊖⊖ **low** [1,2]	
Pain intensity VAS score 0-10 cm VAS score. Scale from: 0 to 10. Follow-up: 6-30 hours	The mean pain score in placebo groups ranged from **0.8 cm to 4.6 cm**	The mean pain score in the 1 mg morphine groups was **0.88 cm lower** (1.81 lower to 0.04 higher)		297 (7 studies)	⊕⊕⊖⊖ **low** [1,2]	
Analgesia duration Time duration from the end of surgery to the time of first analgesic consumption. Scale from: 0 to 100. Follow-up: 30 hours	See comment	See comment	Not estimable	124 (3 studies)	⊕⊕⊖⊖ **low** [3,4]	The data were not pooled.
Adverse events Percentage of participants with any adverse event Follow-up: 30 hours	**Study population**		**RR 1.09** (0.51 to 2.36)	314 (8 studies)	⊕⊕⊖⊖ **low** [5,6]	
	103 per 1000	**97 per 1000** (51 to 179)				

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Moderate		
80 per 1000	**76 per 1000** (39 to 142)	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk Ratio; **VAS**: Visual analogue scale.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]Downgraded one level due to risk of bias: the included studies had small group size and were of low quality. Some studies did not describe randomisation and allocation concealment processes adequately.
[2] Downgraded one level due to publication bias: we could not extract usable data for 11 out of 20 studies comparing morphine with placebo. Some studies presented data as figures and not enough data can be used.
[3] Downgraded one level due to risk of bias: one of the included studies (Kanbak 1997) was of low quality.
[4] Downgraded one level due to publication bias: only three out of 20 studies presented data of analgesic duration.
[5] Downgraded one level due to risk of bias: two out of eight studies were of low quality.
[6] Downgraded one level due to publication bias: the reported adverse events were not the same. Some only reported the overall incidence of adverse events and some reported a series of adverse events including nausea and vomiting.

Summary of findings 2. Morphine compared with bupivacaine for pain control after knee arthroscopy

Morphine compared with bupivacaine for pain control after knee arthroscopy

Patient or population: patients undergoing knee arthroscopy
Settings: inpatients
Intervention: 1 mg morphine administered via the knee joint

Comparison: bupivacaine administered via the knee joint

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Bupivacaine	Morphine				

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Pain intensity VAS score 0-10 cm VAS score. Scale from: 0 to 10. Follow-up: 0-2 hours	The mean pain score in bupivacaine groups ranged from **0.7 cm to 2.3 cm**	The mean pain score in the morphine groups was **1.43 cm higher** (0.49 to 2.37 higher)		248 (5 studies)	⊕⊕⊖⊖ **low** [1,2]	
Pain intensity VAS score 0-10 cm VAS score. Scale from: 0 to 10. Follow-up: 2-6 hours	The mean pain score in bupivacaine groups ranged from **1.2 cm to 3.8 cm**	The mean pain score in the morphine groups was **0.45 cm higher** (0.47 lower to 1.36 higher)		330 (6 studies)	⊕⊕⊖⊖ **low** [1,3]	
Pain intensity VAS score 0-10 cm VAS score. Scale from: 0 to 10. Follow-up: 6-30 hours	The mean pain score in bupivacaine groups ranged from **1.3 cm to 3.7 cm**	The mean pain score in the morphine groups was **0.71 cm lower** (1.23 to 0.19 lower)		270 (5 studies)	⊕⊕⊖⊖ **low** [1,4]	
Analgesia duration Time duration from the end of surgery to the time of first analgesic consumption. Scale from: 0 to 100. Follow-up: 30 hours	See comment	See comment	Not estimable	162 (3 studies)	⊕⊕⊕⊖ **moderate** [5]	The data were not pooled.
Adverse events Percentage of participants with any adverse event Follow-up: 30 hours	**Study population**		**RR 0.68** (0.09 to 5.17)	210 (4 studies)	⊕⊕⊕⊖ **moderate** [6]	
	76 per 1000	**49 per 1000** (17 to 135)				
	Moderate					
	40 per 1000	**26 per 1000** (9 to 73)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk Ratio; **VAS**: Visual analogue scale.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]Downgraded one level due to risk of bias: the included studies have small group size and are of low quality. Some studies did not describe randomisation and allocation concealment processes adequately.

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[2] Downgraded one level due to publication bias: six out of 12 studies have exact data for meta-analysis and others cannot be included in meta-analysis due to incomplete reporting of outcomes.
[3] Downgraded one level due to publication bias: seven out of 12 studies have exact data for meta-analysis and others cannot be included in meta-analysis due to incomplete reporting of outcomes.
[4] Downgraded one level due to publication bias: five out of 12 studies have exact data for meta-analysis and others cannot be included in meta-analysis due to incomplete reporting of outcomes.
[5] Downgraded one level due to publication bias: three out of ten studies reported analgesic duration.
[6] Downgraded one level due to publication bias: four out of ten studies reported side effects.

Summary of findings 3. Morphine compared with NSAIDs for pain control after knee arthroscopy

Morphine compared with NSAIDs for pain control after knee arthroscopy

Patient or population: patients undergoing knee arthroscopy
Settings: inpatients
Intervention: 1 mg morphine administered via the knee joint

Comparison: NSAIDs administered via the knee joint

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	NSAIDs	Morphine				
Pain intensity VAS score 0-10 cm VAS score. Scale from: 0 to 10. Follow-up: 0-2 hours	The mean pain score in the NSAIDs groups ranged from **1 cm to 6.2 cm**	The mean pain score in the morphine groups was **0.95 cm higher** (0.95 lower to 2.85 higher)		80 (2 studies)	⊕⊖⊖⊖ **very low** [1,2,3]	
Pain intensity VAS score 0-10 cm VAS score. Scale from: 0 to 10. Follow-up: 2-6 hours	The mean pain score in the NSAIDs groups ranged from **2 cm to 2.7 cm**	The mean pain score in the morphine groups was **1.00 cm higher** (0.12 to 1.88 higher)		80 (2 studies)	⊕⊕⊖⊖ **low** [1,2]	
Pain intensity VAS score 0-10 cm VAS score. Scale from: 0 to 10. Follow-up: 6-30 hours	The mean pain score in the NSAIDs groups ranged from **1.3 cm to 2 cm**	The mean pain score in the morphine groups was **0.43 cm higher** (0.54 lower to 1.39 higher)		80 (2 studies)	⊕⊕⊖⊖ **low** [1,2]	
Analgesia duration time duration from the end of surgery to the time of first analgesic consumption. Scale from: 0 to 100.	See comment	See comment	Not estimable	50 (1 study)	⊕⊕⊖⊖ **low** [4,5]	The data were not pooled.

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Follow-up: 30 hours						
Adverse events Percentage of participants with any adverse event Follow-up: 30 hours	**Study population**		**RR 0.75** (0.19 to 3.04)	120 (3 studies)	⊕⊕⊕⊖ **moderate** [6]	
	67 per 1000	**49 per 1000** (11 to 203)				
	Moderate					
	40 per 1000	**29 per 1000** (6 to 129)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk Ratio; **VAS**: Visual analogue scale.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Downgraded one level due to risk of bias: one of the included studies (Guler 2002) was of low quality and has potential risk of bias.
[2] Downgraded one level due to imprecision: the results showed wide confidence intervals.
[3] Downgraded one level due to imprecision: wide confidence intervals.
[4] Downgraded one level due to publication bias: three out of ten studies reported analgesic duration.
[5] Downgraded one level due to publication bias: only one study reported analgesic duration.
[6] Downgraded one level due to risk of bias: one study (Guler 2002) was of low quality.

Summary of findings 4. Different doses of morphine for pain control after knee arthroscopy

1 mg morphine compared with 2 mg/4 mg/5 mg morphine for pain control after knee arthroscopy

Patient or population: patients undergoing knee arthroscopy
Settings: inpatients
Intervention: 1 mg morphine administered via the knee joint

Comparison: 2 mg/5 mg morphine administered via the knee joint

Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of Participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				

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	2 mg / 4 mg/5 mg morphine	1 mg morphine				
Pain intensity VAS score **1 mg morphine vs 2 mg morphine** 0-10 cm VAS score. Scale from: 0 to 10. Follow-up: 0-2 hours	The mean pain score in the 2 mg morphine groups ranged from **1.8 cm to 3.9 cm**	The mean pain score in the 1 mg morphine groups was **0.56 cm lower** (1.93 lower to 0.81 higher)		105 (2 studies)	⊕⊕⊖⊖ **low** [1,2]	
Pain intensity VAS score **1 mg morphine vs 2 mg morphine** 0-10 cm VAS score. Scale from: 0 to 10. Follow-up: 2-6 hours	The mean pain score in the 2 mg morphine groups ranged from **1.6 cm to 3.8 cm**	The mean pain score in the 1 mg morphine groups was **0.32 cm lower** (1.69 lower to 1.05 higher)		105 (2 studies)	⊕⊕⊖⊖ **low** [1,2]	
Pain intensity VAS score **1 mg morphine vs 2 mg morphine** 0-10 cm VAS score. Scale from: 0 to 10. Follow-up: 6-30 hours	The mean pain score in the 2 mg morphine groups is **0.45 cm**	The mean pain score in the 1 mg morphine groups was **0.55 cm higher** (0.30 lower to 1.40 higher)		45 (1 study)	⊕⊕⊖⊖ **low** [1,2]	
Analgesia duration **1 mg morphine vs 2 mg morphine** Time duration from the end of surgery to the time of first analgesic consumption Follow-up: 30 hours	See comment	See comment	Not estimable	60 (1 study)	⊕⊕⊕⊖ **moderate** [3]	The data were not pooled.
Adverse events **1 mg morphine vs 2 mg morphine** Percentage of participants with any adverse event Follow-up: 30 hours	See comment	See comment	Not estimable	None	Not estimable	The were no data available.
Pain intensity VAS score **1 mg morphine vs 4 mg/5 mg morphine** 0-10 cm VAS score. Scale from: 0 to 10. Follow-up: 0-2 hours	The mean pain score in the 5 mg morphine groups ranged from **1.5 cm to 3.5 cm**	The mean pain score in the1 mg morphine groups was **0.46 cm higher** (0.24 lower to 1.16 higher)		67 (2 studies)	⊕⊕⊖⊖ **low** [4,5]	

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Pain intensity VAS score **1 mg morphine vs 4 mg/5 mg morphine** 0-10 cm VAS score. Scale from: 0 to 10. Follow-up: 2-6 hours	The mean pain score in the 5 mg morphine groups ranged from **1.1 cm to 3.7 cm**	The mean pain score in the 1 mg morphine groups was **0.44 cm higher** (0.18 lower to 1.05 higher)		67 (2 studies)	⊕⊕⊖⊖ **low** [4,5]	
Pain intensity VAS score **1 mg morphine vs 4 mg/5 mg morphine** 0-10 cm VAS score. Scale from: 0 to 10. Follow-up: 6-30 hours	The mean pain score in the 5mg morphine groups ranged from **0.28 cm to 3.8 cm**	The mean pain score in the1mg morphine groups was **0.67 cm higher** (0.08 to 1.25 higher)		67 (2 studies)	⊕⊕⊖⊖ **low** [4,5]	
Analgesia duration **1 mg morphine vs 4 mg/5 mg morphine** time duration from the end of surgery to the first time of analgesic consumption Follow-up: 30 hours	See comment	See comment	Not estimable	24 (1 study)	⊕⊕⊕⊖ **moderate** [6]	The data were not pooled.
Adverse events **1 mg morphine vs 4 mg/5 mg morphine** Percentage of participants with any adverse event Follow-up: 30 hours	See comment	See comment	Not estimable	None	Not estimable	The were no data available.

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk Ratio; **VAS**: Visual analogue scale.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Downgraded one level due to publication bias: one out of three studies only presented data as figures and no usable data were available.
[2] Downgraded one level due to imprecision: the results showed wide confidence intervals.
[3] Downgraded one level due to publication bias: only one study reported analgesic duration.
[4] Downgraded one level due to risk of bias: one of the included studies (Kanbak 1997) was of low quality.
[5] Downgraded one level due to imprecision: imprecision arising from the small sample size.
[6] Downgraded one level due to publication bias: only one study reported analgesic duration.

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Summary of findings 5. IA morphine compared with IM morphine for pain control after knee arthroscopy

IA morphine compared with IM morphine for pain control after knee arthroscopy

Patient or population: patients undergoing knee arthroscopy
Settings: inpatients
Intervention: 1 mg morphine administered via the knee joint

Comparison: morphine administered intra-muscularly

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	IM morphine	IA morphine				
Pain intensity VAS score 0-10 cm VAS score. Scale from: 0 to 10. Follow-up: 0-2 hours	The mean pain score in the IM morphine groups ranged from **1.4 cm to 2.5 cm**	The mean pain score in the IA morphine groups was **0.21 cm higher** (0.48 lower to 0.9 higher)		72 (2 studies)	⊕⊖⊖⊖ **very low** [1,2,3]	
Pain intensity VAS score 0-10 cm VAS score. Scale from: 0 to 10. Follow-up: 2-6 hours	The mean pain score in the IM morphine groups ranged from 1**cm to 1.7 cm**	The mean pain score in the IA morphine groups was **0.14 cm lower** (0.93 lower to 0.64 higher)		72 (2 studies)	⊕⊕⊖⊖ **low** [1,2]	
Pain intensity VAS score 0-10 cm VAS score. Scale from: 0 to 10. Follow-up: 6-30 hours	The mean pain score in the IM morphine groups is **1.5 cm**	The mean pain score in the IA morphine groups was **0.30 cm lower** (1.39 lower to 0.79 higher)		39 (1 studies)	⊕⊕⊖⊖ **low** [1,4]	
Analgesia duration time duration from the end of surgery to the time of first analgesic consumption. Scale from: 0 to 100. Follow-up: 30 hours	See comment	See comment	Not estimable	None	Not estimable	The were no data available.
Adverse events Percentage of participants with any adverse event Follow-up: 30 hours	See comment	See comment	Not estimable	None	Not estimable	The were no data available.

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk Ratio; **VAS**: Visual analogue scale.

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GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

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[1] Downgraded one level due to risk of bias: four out of five studies are of low quality.
[2] Downgraded one level due to publication bias: only two out of five studies have usable data for meta-analysis.
[3] Downgraded one level due to imprecision: wide confidence intervals.
[4] Downgraded one level due to publication bias: only one out of five studies have usable data for meta-analysis.

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BACKGROUND

Description of the condition

Knee arthroscopy is a very common procedure performed as day surgery and is associated with postoperative pain (Joshi 1992). The incidence of moderate or severe pain within an hour after knee arthroscopy is around 60%. Baseline scores are about 50 mm on the visual analogue scale (VAS) 10 minutes after test drug injection. However, pain scores quickly decreased to about 35 mm by 30 minutes and less than 5 mm by 12 hours (Solheim 2006). Women report more pain after knee arthroscopy than men (Rosseland 2004b). Adequate postoperative analgesia may accelerate the patient's return to normal activity.

Description of the intervention

Many trials have tried to find an ideal regimen which provides sufficient postoperative analgesia with fewer adverse events, including intra-articular (IA) anaesthetics and analgesics for postoperative pain relief. The spinal or intravenous (IV) administration of morphine may cause side effects such as respiratory depression, sedation, dependence, pruritus and urinary retention. However, the adverse events of peripheral IA morphine administration were mild or absent. Morphine may therefore be a promising IA agent that is without obvious central side effects (Sawynok 2003). IA injection of morphine has been widely studied for its simplicity, safety and efficacy.

Opioid binding sites have been identified within synovial tissue, implying that the analgesic effect of morphine may be locally mediated (Khoury 1992). When given at the end of arthroscopic surgery, IA morphine could reduce postoperative pain through peripheral opioid receptors (Stein 1991). It has also been reported to reduce pain through other pathways (Kalso 1997) such as inflammatory reaction (Likar 1998; Stein 1995; Stein 1999). However, different opinions exist as to the postoperative effect of peripheral opioids. The reported dosages of IA morphine in studies vary from 0.5 mg to 5 mg (Joshi 1993). Stein 1991 reported that a dose of 1 mg morphine showed analgesic efficacy, whereas a dose of 0.5 mg did not. Allen 1993 reported that 2 mg morphine showed a better analgesic effect than 1 mg, but no dose response was detected in two other studies (Heine 1994; Laurent 1994). Other controlled trials, however, have failed to show any analgesic effect of morphine compared with placebo (Aasbø 1996; Drosos 2002; Gupta 1999; Ruwe 1995; Soderlund 1997).

In addition to opiates, many other interventions have been widely studied for the reduction of postoperative pain following knee arthroscopy. Local anaesthetics (such as bupivacaine, ropivacaine, carbocaine, lidocaine and prilocaine), non-steroidal anti-inflammatory drugs ((NSAIDs) such as ketorolac and tenoxicam) and other interventions (such as magnesium, clonidine, neostigmine and ketamine) have been intensely studied.

How the intervention might work

Opioid receptors exist on peripheral terminals of primary afferent neurons, demonstrated functionally and morphologically in Bartho 1990 and Stein 1990. As a μ-opioid receptor agonist, morphine is effective in producing peripheral analgesia. Morphine activates peripheral opioid receptors, resulting in their interactions with G-proteins and a decrease in cyclic adenosine monophosphate (cAMP) in sensory nerve terminals, an increase in K^+ efflux and a decrease of Ca^{2+} entry. Thus, the excitability of the peripheral nerve terminal, the propagation of action potentials and release of neuropeptides are attenuated (Sawynok 2003).

Why it is important to do this review

Several systematic reviews have investigated IA morphine for the control of pain after knee surgery, however, consensus on the analgesic effect is still lacking. A previously published qualitative systematic review (Kalso 1997) showed that IA morphine was effective in reducing postoperative pain intensity and the consumption of rescue analgesics. All knee surgeries were included in the review, however, and it failed to focus on the effect of IA morphine on pain relief after knee arthroscopy. Also, no quantitative analysis of pooled data was performed here, nor in the authors' second systematic review on this topic (Kalso 2002). In another systematic review, variability was found not only between studies but also within one study (patient variability) (Gupta 2001). By calculating the weighted mean difference (WMD) of pain scores between treatment groups, Moiniche 1999 found that there was weak evidence for a reduction of postoperative pain after IA instillation of local anaesthetics. More trials comparing morphine and other interventions for knee arthroscopy were available recently and they added new knowledge to inform clinical practice (Rosseland 2003; Rosseland 2004a; Rosseland 2004b). Evidence is still lacking as to whether IA opioids offer clinically relevant pain relief. In light of the existing controversy, this systematic review aimed to investigate the analgesic effect of single dose IA morphine compared with other interventions in the management of pain control after knee arthroscopy.

OBJECTIVES

To evaluate the relative effects on pain relief and adverse events of IA morphine given for pain control after knee arthroscopy compared with placebo, other analgesics (local anaesthetics, non-steroidal anti-inflammatory drugs (NSAIDs), other opioids) and other routes of morphine administration.

METHODS

Criteria for considering studies for this review

Types of studies

We included studies fulfilling the following selection criteria in this systematic review:

1. randomised, double-blind controlled trials;
2. studies comparing single dose IA morphine with other interventions for the treatment of postoperative pain after knee arthroscopy; and
3. studies with more than 10 participants in each group.

We excluded the following studies:

1. studies in which spinal or epidural anaesthesia was used; and
2. studies whose primary aim was to assess the analgesic effect of IA morphine on chronic pain.

Types of participants

We included participants of either gender, aged 15 years or older, and undergoing knee arthroscopy.

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Types of interventions

IA morphine versus any other interventions or administration methods:

1. IA morphine versus placebo;
2. IA morphine versus local anaesthetic agents (such as bupivacaine, ropivacaine, carbocaine, lidocaine and prilocaine);
3. IA morphine versus NSAIDs (such as ketorolac and tenoxicam);
4. different doses of IA morphine;
5. IA morphine versus intravenous (IV) or intra-muscular (IM) morphine;
6. IA morphine versus other opioids.

Types of outcome measures

We included the following outcomes.

Primary outcomes

1. Patient-reported postoperative pain intensity (a 0 - 10 cm VAS score).
2. Use of supplementary analgesic (number of participants using rescue analgesics, time to first rescue analgesics, analgesic drug counts, patient-controlled analgesia opioid consumption, etc.).

Secondary outcomes

1. Adverse events.
2. Withdrawals.

Search methods for identification of studies

Electronic searches

We searched CENTRAL (*The Cochrane Library,* Issue 4, 2015), MEDLINE via Ovid (January 1966 to May 2015), EMBASE via Ovid (January 1988 to May 2015). Please see Appendix 1; Appendix 2; Appendix 3 for the database search strategies. Filters designed to limit the searches to RCTs were added to the MEDLINE and EMBASE strategies.

Searching other resources

Reference lists

We sought additional studies from the references of retrieved randomised trials, meta-analyses and systematic reviews.

Unpublished studies

We searched trials registries for ongoing trials. We searched three web sites: the metaRegister of controlled trials (www.controlled-trials.com/mrct), clinicaltrials.gov (www.clinicaltrials.gov) and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (apps.who.int/trialsearch/) up to May 2015.

Language

The search identified all relevant studies irrespective of language. We assessed non-English language papers and translated as necessary.

Data collection and analysis

Selection of studies

Two authors independently assessed the eligibility of studies included in the review, and another author checked these results. For the studies that were reported several times, we used the first edition and added data from the secondary references to the first study to extract full data. We resolved any disagreement by discussion.

Data extraction and management

Two authors independently extracted data from each identified study and recorded data on a standardised data extraction form. We resolved any disagreement by discussion with a third author when necessary.

Assessment of risk of bias in included studies

Two authors assessed risk of bias for each study independently, based on the methods used to generate allocation sequence, allocation concealment, blinding, follow-up, selective reporting and group size according to the 'Risk of bias' tool (Kjaergard 2001; Moher 1998; Schulz 1995; Higgins 2011a).

We assessed the methods used to deal with incomplete data as: low risk of bias (< 10% of participants did not complete the study or used 'baseline observation carried forward' analysis, or both); unclear risk of bias (used 'last observation carried forward' analysis); and high risk of bias (used 'completer' analysis).

"Size" was added to the 'Risk of bias' table. We assessed studies as low risk of bias ($\geqq$ 200 participants per treatment arm); unclear risk of bias (50 to 199 participants per treatment arm); and high risk of bias (< 50 participants per treatment arm).

We resolved any disagreement by discussion.

Dealing with missing data

We did not contact authors for missing data. We followed intention-to-treat principles. In some studies, the exact mean, standard deviation (SD) and standard error (SE) of pain scores were not reported or were difficult to decipher when results were presented in figures. In this situation, two review authors independently estimated the visual analogue scale (VAS) score presented in the figures in each study using Engauge Digitizer 4.1 (Lan 2010; Ma 2012) and achieved an agreement on the mean ± SE or SD (Gupta 2001). When the number of participants enrolled and the number of participants who reported outcomes were different, we noted this in the 'Characteristics of included studies' table. If the exclusions of participants was justifiable, we would use available data from the studies; if withdrawal of participants were not justifiable, we would carry out intention to treat (ITT) analysis.

Assessment of heterogeneity

We tested the heterogeneity between studies using the Chi^2 test (with $P < 0.1$ indicating significant heterogeneity) and the I^2 statistic, which described the proportion of variability due to heterogeneity (Higgins 2003). When $P > 0.1$, we carried out the meta-analysis using a fixed-effect model; otherwise we used a random-effects model.

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Data synthesis

Quantitative analysis

We performed a statistical analysis of outcomes. We merged both dichotomous and continuous data quantitatively in meta-analysis.

Dichotomous data

For dichotomous data, such as the number of participants who suffered from adverse events, we calculated the risk ratio (RR) using Review Manager software (RevMan) 5.3 (RevMan 2014).

Continuous data

For continuous data, such as postoperative VAS score, analgesic duration of intervention drugs, we calculated mean differences (MDs). We applied a random-effects or fixed-effect model to assess outcomes, depending on the statistical heterogeneity among studies.

Qualitative analysis

Different analgesics were used to relieve postoperative pain and many studies did not report the exact doses consumed. Consequently, statistical analyses were not always possible. In situations where the data extracted from the original studies were insufficiently similar, we did not conduct a meta-analysis but produced a qualitative description of the outcome study by study.

Quality of the evidence

Two review authors independently rated the quality of the outcomes pain intensity, analgesia duration and adverse events. We used the GRADE (Grades of Recommendation, Assessment, Development and Evaluation) system to rank the quality of the evidence using the GRADEprofiler Guideline Development Tool software (GRADEPro GDT 2015), and the guidelines provided in Chapter 12.2 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b).

The GRADE approach uses five considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of the body of evidence for each outcome. The GRADE system uses the following criteria for assigning grade of evidence:

- High = further research is very unlikely to change our confidence in the estimate of effect;
- Moderate = further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate;
- Low = further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate;
- Very low = any estimate of effect is very uncertain.

We decreased grade if:

- Serious (-1) or very serious (-2) limitation to study quality;
- Important inconsistency (-1);
- Some (-1) or major (-2) uncertainty about directness;
- Imprecise or sparse data (-1);
- High probability of reporting bias (-1).

'Summary of findings' table

We included 'Summary of findings' tables to present the main findings in a transparent and simple tabular format. In particular, we included key information concerning the quality of evidence, the magnitude of effect of the interventions examined, and the sum of available data on the outcomes listed above.

Subgroup analysis and investigation of heterogeneity

We carried out subgroup analysis to assess clinical heterogeneity rather than statistical heterogeneity. We carried out separate analyses for the most important clinical parameters as follows.

1. We identified three phases to assess postoperative pain: early phase (zero to two hours), medium phase (two to six hours) and late phase (six to 30 hours). We analysed the data from these different phases separately. Data of two hours and six hours were allocated to early phase and medium phase, respectively.
2. Comparisons: different agents were used as the comparator regimens in various studies. We only quantitatively merged the studies with the same drug categories in meta-analysis.

Sensitivity analysis

We performed sensitivity analysis to evaluate the effect of methodological characteristics (quality assessment) of studies on the results of the meta-analysis.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies.

Results of the search

We identified 724 studies through the initial electronic search. We scanned these studies and found 35 studies which could not be excluded by scrutiny of the title and abstract only. Of these, seven were further excluded for reasons cited in the Characteristics of excluded studies table. Twenty eight studies (29 reports) satisfied the inclusion criteria comparing morphine with placebo or other analgesics (Figure 1). Studies that met the inclusion criteria contained 2482 enrolled participants, with trial size varying from 33 to 320 participants.

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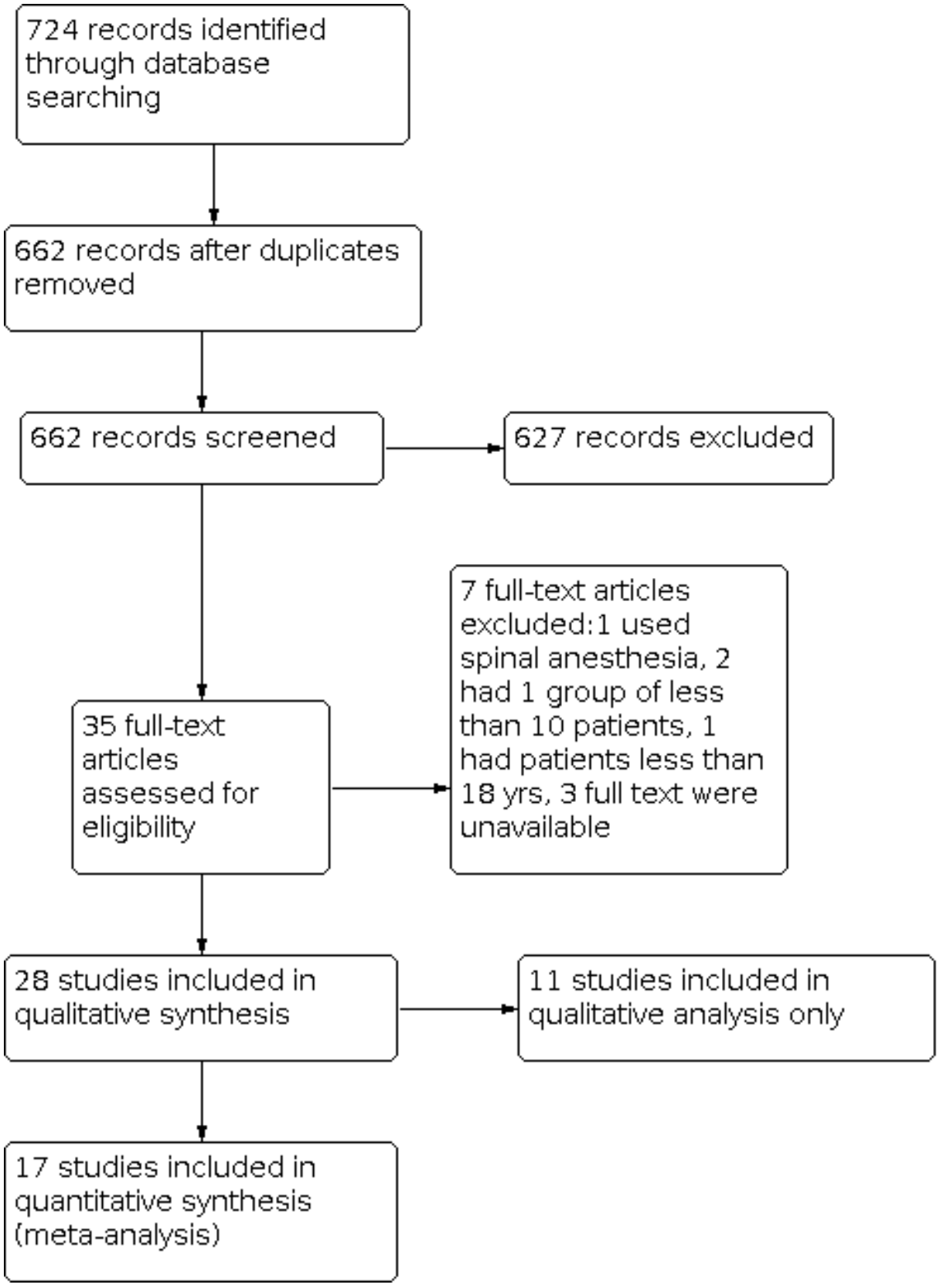
Figure 1. Flowchart showing the stepwise screening of search results



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Included studies

Twenty studies (21 reports) enrolled participants undergoing elective arthroscopic knee surgery of multiple procedures such as diagnostic arthroscopy, meniscectomy, excision of plicae, full arthroscopic lateral retinacular release, synovectomy and chondral debridement (Aasbø 1996; Akinci 2003; Alagol 2005; Allen 1993; Bjornsson 1994; Christensen 1996; Follak 2001; Franceschi 2001; Kazemi 2004; Khoury 1992; Kizilkaya 2005; Likar 1995; Likar 1999; Muller 2001; Raj 2004; Richardson 1997; Rosseland 2003a; Ruwe 1995; Solheim 2006; Varkel 1999; Wrench 1996). Six studies (Calmet 2004; De Andres 1998; Dierking 1994; Elkousy 2013; Kanbak 1997; Lyons 1995) only enrolled participants undergoing arthroscopic meniscectomy and one study (Guler 2002) only enrolled participants undergoing arthroscopic anterior cruciate ligament (ACL) reconstruction with hamstring tendons.

Some studies had both placebo and active drug as control, and some had more than one active comparator. Twenty studies included a placebo control, whereas 23 used an active drug in the control group. The active drugs relevant to our studies included bupivacaine (Aasbø 1996; Alagol 2005; Allen 1993; Bjornsson 1994; Calmet 2004; De Andres 1998; Follak 2001; Khoury 1992; Richardson 1997; Ruwe 1995), ropivacaine (Franceschi 2001; Muller 2001), tenoxicam (Alagol 2005; Guler 2002), tramadol (Akinci 2003; Likar 1995), sufentanil (Kazemi 2004), fentanyl (Varkel 1999), pethidine (Lyons 1995), morphine injected IV/IM (Christensen 1996; Dierking 1994; Raj 2004; Richardson 1997; Rosseland 2003a) and different doses of morphine (Allen 1993; Kanbak 1997; Kizilkaya 2005; Likar 1999). Morphine was used from 1 mg to 10 mg. Two hundred and seventy three participants took a 1 mg dose (Allen 1993; Bjornsson 1994; Calmet 2004; De Andres 1998; Kanbak 1997; Khoury 1992; Kizilkaya 2005; Likar 1995; Likar 1999; Muller 2001; Richardson 1997; Wrench 1996), 178 took 2 mg (Alagol 2005; Allen 1993; Dierking 1994; Franceschi 2001; Guler 2002; Likar 1999; Rosseland 2003a; Ruwe 1995), 65 took 3 mg (Aasbø 1996; Kazemi 2004; Varkel 1999), 19 took 4 mg (Likar 1999), 325 took 5 mg (Akinci 2003; Bjornsson 1994; Christensen 1996; Follak 2001; Kanbak 1997; Kizilkaya 2005; Lyons 1995; Muller 2001; Richardson 1997; Solheim 2006), and 39 took 10 mg (Raj 2004).

Pain was rated using VAS in 26 trials, and a verbal rating scale (VRS) was used in six (Akinci 2003; Christensen 1996; De Andres 1998; Rosseland 2003a; Solheim 2006; Wrench 1996). One study (Bjornsson 1994) assessed pain intensity using a modified VAS score, which was different from the conventional VAS score. In the modified score, "10" corresponded to "severe pain" instead of the conventional ''worst imaginable'' to increase the sensitivity of the scale. We excluded its results of VAS score from meta-analysis. For those presenting both VAS at rest and VAS with movement, we only abstracted VAS at rest for meta-analysis. However, the studies did not provide all the outcomes of interest. Some studies gave the central tendency of VAS as median, some presented mean values without SD, and some showed results in figures. We abstracted the data from figures using Engauge Digitizer 4.1. We did not include data presented as median and interquartile range in the meta-analysis. Different analgesics and treatment regimens were employed for rescue medication, such as tylenol, paracetamol, tramadol, ketorolac, and metamizol, so a meta-analysis of the rescue medication was not considered feasible.

Excluded studies

We excluded four studies (see Characteristics of excluded studies). One trial used spinal anaesthesia rather than general anaesthesia (Alvarez-Cabo 1998). Two trials included fewer than 10 participants in the intervention group (Lehrberger 1994; Stein 1991). One trial included participants under 15 years old (De Andres 1993). Three studies were classified in Characteristics of studies awaiting classification because full texts were unavailable through database searching, handsearching or inter-library loan (Altan 1994; Uzma 1997; VanNess 1994).

Risk of bias in included studies

All the included studies were prospective randomised double-blind controlled trials (see Characteristics of included studies). We completed a 'Risk of bias' table and results were presented graphically in Figure 2 and summarised in Figure 3.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

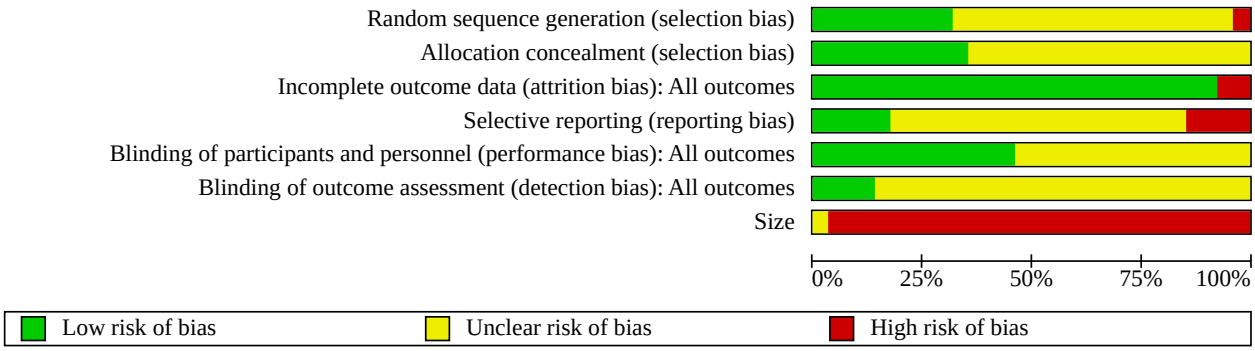

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Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

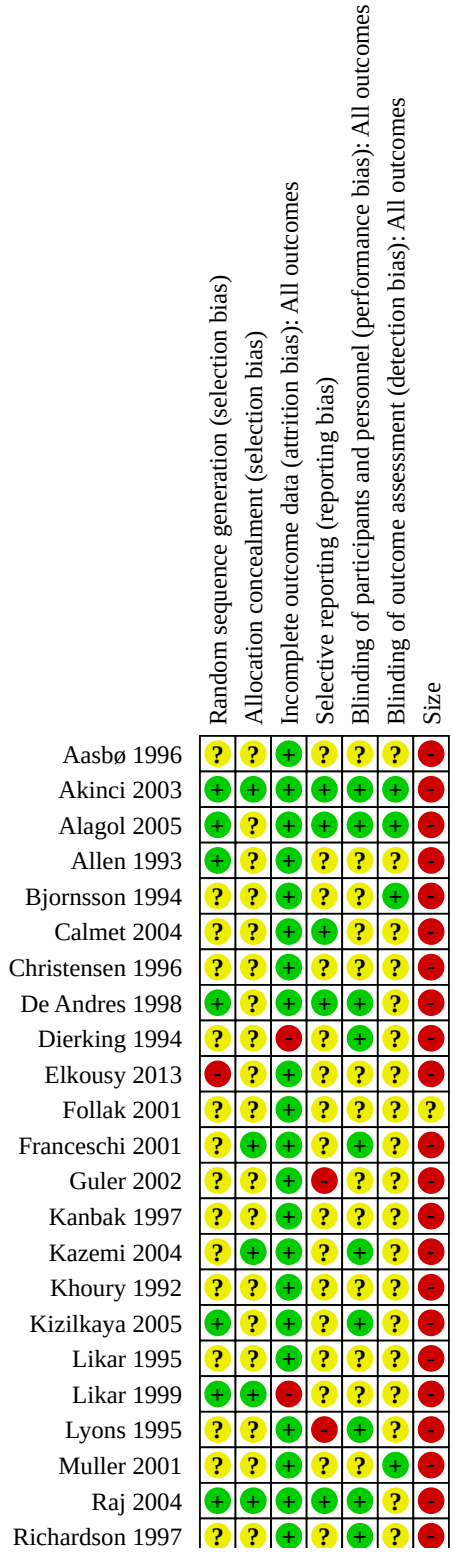

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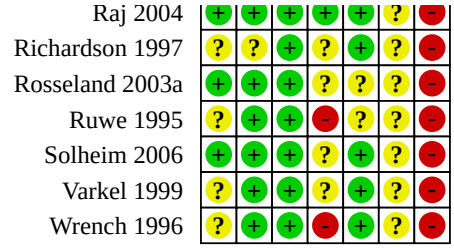
Figure 3. (Continued)



Allocation

All of the studies were described as 'randomised', and nine studies were of low risk (seven were randomised using a random table or a list of random numbers, two had randomisation stratified by a computerised allocation schedule). One study was assessed as high risk for its randomisation methods, which allocated patients according to the odd or even account number given on the day of surgery. Randomisation technique was not described in 18 studies, which were assessed as unclear risk. Allocation concealment was of low risk in 10 studies and of unclear risk in 18 studies. Although some studies failed to report the methods used to ensure randomisation and allocation concealment adequately, we included all of the studies in the analysis. We did sensitivity analysis to measure the effects of methodological quality.

Blinding

Twenty-seven included trials were double-blind and one was single-blind. Thirteen trials stated the methods to maintain blindness of participants and personnel and were of low risk. Four studies stated the blinding of outcome assessment and were assessed as unclear risk.

Incomplete outcome data

Twenty-six of the included studies were assessed as low risk and two studies as high risk. Seven studies (Aasbø 1996; Christensen 1996; Dierking 1994; Likar 1999; Lyons 1995; Raj 2004; Solheim 2006) reported the exact number of participants lost to follow-up. Five studies (Aasbø 1996; Christensen 1996; Likar 1995; Lyons 1995; Raj 2004) had less than 10% of participants who did not complete the study and two studies (Dierking 1994; Likar 1999) had more than 10% withdrawals. Other studies did not mention dropouts. They included all the participants in the analysis as seen from the results section.

Selective reporting

Five studies (Akinci 2003; Alagol 2005; Calmet 2004; De Andres 1998; Raj 2004) were assessed as low risk and four studies (Guler 2002; Lyons 1995; Ruwe 1995; Wrench 1996) were assessed as high risk, while the other nineteen studies were assessed as unclear risk of selective reporting bias.

Other potential sources of bias

We considered study size as a potential source of bias because most of the included studies were small-sized. Studies with fewer than 10 participants in each group were excluded. Twenty seven in 28 studies had fewer than 50 participants in each group, which were rated as high risk. These studies were all of small size and thus made the conclusions less robust. Only one study had a group size larger than 50 participants.

Effects of interventions

See: **Summary of findings 1** Morphine compared with placebo for pain control after knee arthroscopy; **Summary of findings 2** Morphine compared with bupivacaine for pain control after knee arthroscopy; **Summary of findings 3** Morphine compared with NSAIDs for pain control after knee arthroscopy; **Summary of findings 4** Different doses of morphine for pain control after knee arthroscopy; **Summary of findings 5** IA morphine compared with IM morphine for pain control after knee arthroscopy

We used pain intensity VAS score and use of supplementary analgesia (analgesia duration) as primary outcomes to assess analgesic effects of IA morphine, and adverse events and withdrawals as secondary outcomes to assess the safety of IA morphine.

Primary outcomes: patient-reported postoperative pain intensity and use of supplementary analgesic

1. Morphine versus placebo

Twenty studies (20 reports) with 2066 participants compared morphine directly with placebo (Aasbø 1996; Akinci 2003; Alagol 2005; Bjornsson 1994; Calmet 2004; De Andres 1998; Follak 2001; Franceschi 2001; Guler 2002; Kanbak 1997; Kazemi 2004; Likar 1999; Lyons 1995; Muller 2001; Richardson 1997; Rosseland 2003a; Ruwe 1995; Solheim 2006; Varkel 1999; Wrench 1996). Thirteen of these studies found a beneficial effect of morphine (Akinci 2003; Alagol 2005; De Andres 1998; Follak 2001; Franceschi 2001; Guler 2002; Kanbak 1997; Kazemi 2004; Likar 1999; Lyons 1995; Muller 2001; Richardson 1997; Varkel 1999) whereas seven others did not find any beneficial effect (Aasbø 1996; Bjornsson 1994; Calmet 2004; Rosseland 2003a; Ruwe 1995; Solheim 2006; Wrench 1996). Among eight studies that compared 1 mg morphine with placebo (Bjornsson 1994; Calmet 2004; De Andres 1998; Kanbak 1997; Likar 1999; Muller 2001; Richardson 1997; Wrench 1996), four studies found a better analgesia effect of 1 mg morphine (De Andres 1998; Likar 1999; Muller 2001; Richardson 1997). Of the six studies that compared 2 mg morphine with placebo (Alagol 2005; Franceschi 2001; Guler 2002; Likar 1999; Rosseland 2003a; Ruwe 1995), four studies showed better analgesia of 2 mg morphine (Alagol 2005; Franceschi 2001; Guler 2002; Likar 1999).

Of studies comparing morphine with placebo, nine in 20 studies had suitable data for meta-analysis (Calmet 2004; De Andres 1998; Kanbak 1997; Kazemi 2004; Likar 1999; Muller 2001; Richardson 1997; Varkel 1999; Wrench 1996), including seven

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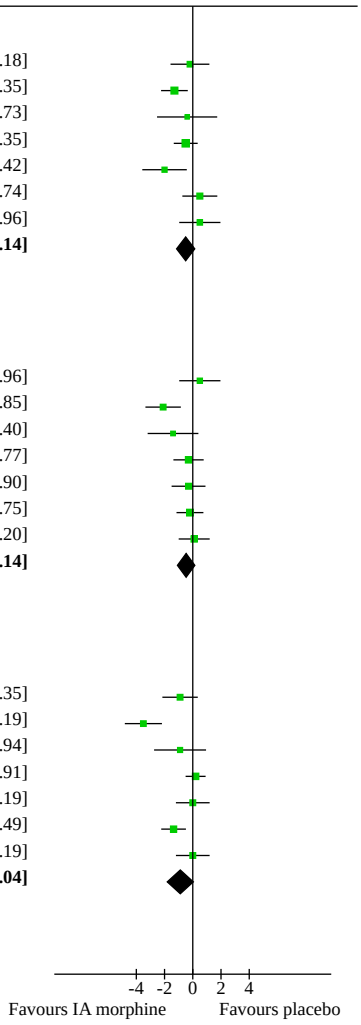
studies comparing 1 mg morphine with placebo and two studies comparing 2 mg morphine with placebo. We included seven studies (297 participants) comparing 1 mg morphine with placebo in meta-analysis. There was no difference between 1 mg IA morphine and placebo in pain intensity (VAS score) at early, medium or late phases (Figure 4). The MD and 95% confidence interval (CI) of resting pain was MD -0.50 (95% CI, -1.15 to 0.14), MD -0.47 (95% CI, -1.09 to 0.14), and MD -0.88 (95% CI, -1.81 to 0.04), respectively.

Figure 4. Forest plot of comparison: 1 pain intensity VAS score, outcome: 1.1 1mg morphine vs placebo.

Study or Subgroup	morphine Mean	morphine SD	morphine Total	placebo Mean	placebo SD	placebo Total	Weight	Mean Difference IV, Random, 95% CI
1.1.1 0-2h								
Calmet 2004	2.3	1.9	20	2.5	2.5	20	13.3%	-0.20 [-1.58 , 1.18]
De Andres 1998	2.2	1.4	27	3.5	2	25	19.6%	-1.30 [-2.25 , -0.35]
Kanbak 1997	5	2	11	5.4	3	11	7.2%	-0.40 [-2.53 , 1.73]
Likar 1999	2.1	1.3	24	2.6	1.6	22	21.4%	-0.50 [-1.35 , 0.35]
Muller 2001	2.8	2.1	15	4.8	2.3	15	11.2%	-2.00 [-3.58 , -0.42]
Richardson 1997	2.5	2.6	36	2	2.6	32	15.0%	0.50 [-0.74 , 1.74]
Wrench 1996	3.3	1.9	19	2.8	2.7	20	12.3%	0.50 [-0.96 , 1.96]
Subtotal (95% CI)			**152**			**145**	**100.0%**	**-0.50 [-1.15 , 0.14]**
Heterogeneity: Tau² = 0.32; Chi² = 10.70, df = 6 (P = 0.10); I² = 44%								
Test for overall effect: Z = 1.54 (P = 0.12)								
1.1.2 2-6h								
Calmet 2004	2.9	2.2	20	2.4	2.5	20	11.6%	0.50 [-0.96 , 1.96]
De Andres 1998	1.4	2.2	27	3.5	2.4	25	13.9%	-2.10 [-3.35 , -0.85]
Kanbak 1997	3.2	2.2	11	4.6	2.1	11	8.7%	-1.40 [-3.20 , 0.40]
Likar 1999	2	1.8	24	2.3	1.9	22	16.5%	-0.30 [-1.37 , 0.77]
Muller 2001	3.5	1.1	15	3.8	2.1	15	14.7%	-0.30 [-1.50 , 0.90]
Richardson 1997	1.5	2	36	1.7	2	32	18.5%	-0.20 [-1.15 , 0.75]
Wrench 1996	1.8	1.7	19	1.7	1.8	20	16.1%	0.10 [-1.00 , 1.20]
Subtotal (95% CI)			**152**			**145**	**100.0%**	**-0.47 [-1.09 , 0.14]**
Heterogeneity: Tau² = 0.30; Chi² = 10.71, df = 6 (P = 0.10); I² = 44%								
Test for overall effect: Z = 1.50 (P = 0.13)								
1.1.3 6-30h								
Calmet 2004	1.5	1.7	20	2.4	2.3	20	14.0%	-0.90 [-2.15 , 0.35]
De Andres 1998	1.1	2.2	27	4.6	2.6	25	13.6%	-3.50 [-4.81 , -2.19]
Kanbak 1997	2.5	2.3	11	3.4	2.1	11	10.8%	-0.90 [-2.74 , 0.94]
Likar 1999	1	1.5	24	0.8	0.9	22	16.9%	0.20 [-0.51 , 0.91]
Muller 2001	4.1	1.9	15	4.1	1.4	15	14.3%	0.00 [-1.19 , 1.19]
Richardson 1997	0.84	1.1	36	2.2	2.3	32	16.1%	-1.36 [-2.23 , -0.49]
Wrench 1996	2	1.9	19	2	1.9	20	14.3%	0.00 [-1.19 , 1.19]
Subtotal (95% CI)			**152**			**145**	**100.0%**	**-0.88 [-1.81 , 0.04]**
Heterogeneity: Tau² = 1.17; Chi² = 28.61, df = 6 (P < 0.0001); I² = 79%								
Test for overall effect: Z = 1.88 (P = 0.06)								
Test for subgroup differences: Chi² = 0.59, df = 2 (P = 0.75), I² = 0%								



Eleven out of 20 studies reported time to first request of supplementary analgesics (Aasbø 1996; Akinci 2003; Alagol 2005; Calmet 2004; De Andres 1998; Follak 2001; Franceschi 2001; Kanbak 1997; Likar 1999; Kizilkaya 2005; Lyons 1995) and 17 out of 20 studies reported consumption of rescue medication (Aasbø 1996; Akinci 2003; Alagol 2005; Calmet 2004; Follak 2001; Guler 2002; Kanbak 1997; Kazemi 2004; Likar 1999; Lyons 1995; Muller 2001; Richardson 1997; Rosseland 2003a; Ruwe 1995; Solheim 2006; Varkel 1999; Wrench 1996). However, most studies did not present the exact dosages consumed and the number of different analgesic regimens was large. The data could not be subjected to any statistical analysis, so we summarised the results of each study. Three of 10 studies showed a significantly longer time to first analgesic request in the IA morphine group than the placebo group (Alagol 2005; Franceschi 2001; Kanbak 1997) while the remaining seven studies did not find a significant difference. Meta-analysis of three studies (Alagol 2005; De Andres 1998; Kanbak 1997) indicated no difference between the IA morphine and placebo groups of time to first analgesic request. An I^2 statistic of 100% represented highly inconsistent findings across studies, and might indicate an error in the data. Seven studies showed a decrease in the postoperative consumption of analgesics in the IA morphine group (Alagol 2005; Kanbak 1997; Kazemi 2004; Likar 1999; Muller 2001; Richardson 1997; Varkel 1999), and four studies found that the number of participants who consumed supplementary analgesics in the IA morphine group was lower than the control group (Aasbø 1996; Calmet 2004; Follak 2001; Lyons 1995). Seven of 13 studies with significant differences favouring morphine also showed a decreased consumption of analgesics in the IA morphine group (Alagol 2005; Follak 2001; Kanbak 1997; Kazemi 2004; Likar

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1999; Muller 2001; Varkel 1999), while in three studies analgesic consumption was equivalent between the IA morphine group and the placebo group (Akinci 2003; Lyons 1995; Richardson 1997).

We judged the quality of evidence for pain intensity VAS score, for morphine versus placebo, to be low. We downgraded the quality of evidence by two levels due to risk of bias and publication bias.

We judged the quality of evidence for analgesia duration, for morphine versus placebo, to be low. We downgraded the quality of evidence by two levels due to risk of bias and publication bias.

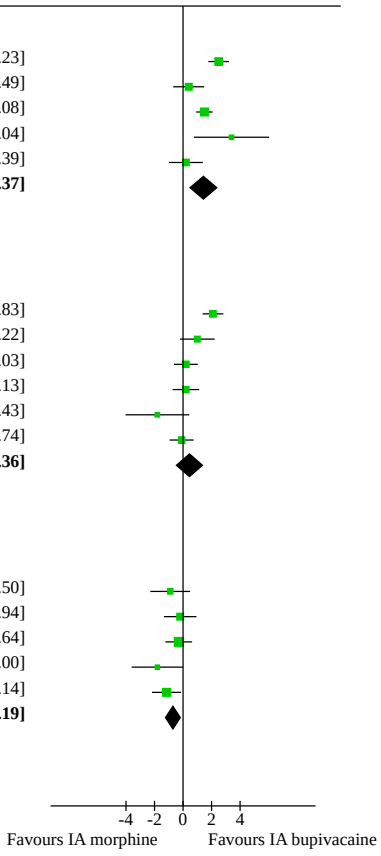
See Summary of findings 1.

2. Morphine versus local anaesthetics

Twelve studies (12 reports) compared IA morphine with IA local anaesthetics (Aasbø 1996; Alagol 2005; Allen 1993; Bjornsson 1994; Calmet 2004; De Andres 1998; Follak 2001; Franceschi 2001; Khoury 1992; Muller 2001; Richardson 1997; Ruwe 1995). Among the 10 studies that compared IA morphine with IA bupivacaine, five studies found a better analgesia effect of bupivacaine (Allen 1993; De Andres 1998; Follak 2001; Khoury 1992; Ruwe 1995) and the other five studies did not find significant differences. Of the six studies comparing 1 mg morphine with bupivacaine, three studies found IA bupivacaine provided better analgesia than IA morphine (Allen 1993; De Andres 1998; Khoury 1992), and the other three studies did not find a difference (Bjornsson 1994; Calmet 2004; Richardson 1997). Allen 1993 indicated that participants who received 1 mg IA morphine in combination with 0.25% bupivacaine provided superior postoperative analgesia for up to 24 hours after knee arthroscopy versus morphine or bupivacaine alone. Meta-analysis of six studies comparing IA morphine with IA bupivacaine found no better analgesic effects of morphine (Figure 5). The MD and 95% CI of pain at rest was MD 1.43 (95% CI 0.49 to 2.37; participants = 248; studies = 5); at early phase, MD 0.45 (95% CI -0.47 to 1.36; participants = 330; studies = 6), and MD -0.71 (95% CI -1.23 to -0.19; participants = 270; studies = 5), respectively (Summary of findings 2). The results were highly heterogeneous because of the small size of the included studies. Three studies (Alagol 2005; Allen 1993; De Andres 1998) reported time to first analgesic request, and two studies (Allen 1993; De Andres 1998) found morphine had long analgesic duration. Two studies compared ropivacaine with morphine (Franceschi 2001; Muller 2001), where no significant difference of analgesic effect was found in one study (Franceschi 2001), and the other study (Muller 2001) favoured ropivacaine.

Figure 5. Forest plot of comparison: 1 pain intensity VAS score, outcome: 1.2 1mg morphine vs bupivacaine.

Study or Subgroup	morphine Mean	morphine SD	morphine Total	bupivacaine Mean	bupivacaine SD	bupivacaine Total	Weight	Mean Difference IV, Random, 95% CI
1.2.1 0-2h								
Allen 1993	3.9	1.8	30	1.4	0.93	30	24.6%	2.50 [1.77 , 3.23]
Calmet 2004	2.2	1.9	20	1.8	1.6	20	20.8%	0.40 [-0.69 , 1.49]
De Andres 1998	2.2	1.4	27	0.7	0.59	25	26.0%	1.50 [0.92 , 2.08]
Khoury 1992	5.6	3.3	11	2.2	3	11	8.8%	3.40 [0.76 , 6.04]
Richardson 1997	2.5	2.6	36	2.3	2.6	38	19.8%	0.20 [-0.99 , 1.39]
Subtotal (95% CI)			**124**			**124**	**100.0%**	**1.43 [0.49 , 2.37]**
Heterogeneity: Tau² = 0.80; Chi² = 17.79, df = 4 (P = 0.001); I² = 78%								
Test for overall effect: Z = 2.98 (P = 0.003)								
1.2.2 2-6h								
Allen 1993	3.8	1.8	30	1.7	0.93	30	19.4%	2.10 [1.37 , 2.83]
Calmet 2004	2.9	2.2	20	1.9	1.7	20	15.9%	1.00 [-0.22 , 2.22]
De Andres 1998	1.4	2.2	27	1.2	0.23	25	18.7%	0.20 [-0.63 , 1.03]
Elkousy 2013	3	2.3	47	2.8	2	35	18.0%	0.20 [-0.73 , 1.13]
Khoury 1992	1.4	2.3	11	3.2	3	11	9.5%	-1.80 [-4.03 , 0.43]
Richardson 1997	1.5	1.9	36	1.6	1.8	38	18.6%	-0.10 [-0.94 , 0.74]
Subtotal (95% CI)			**171**			**159**	**100.0%**	**0.45 [-0.47 , 1.36]**
Heterogeneity: Tau² = 0.99; Chi² = 25.30, df = 5 (P = 0.0001); I² = 80%								
Test for overall effect: Z = 0.96 (P = 0.34)								
1.2.3 6-30h								
Calmet 2004	1.5	1.7	20	2.4	2.7	20	13.9%	-0.90 [-2.30 , 0.50]
De Andres 1998	1.1	2.2	27	1.3	2	25	20.8%	-0.20 [-1.34 , 0.94]
Elkousy 2013	1.5	1.9	47	1.8	2.3	35	30.9%	-0.30 [-1.24 , 0.64]
Khoury 1992	1.9	2	11	3.7	2.3	11	8.3%	-1.80 [-3.60 , 0.00]
Richardson 1997	0.84	1.1	36	2	3	38	26.1%	-1.16 [-2.18 , -0.14]
Subtotal (95% CI)			**141**			**129**	**100.0%**	**-0.71 [-1.23 , -0.19]**
Heterogeneity: Tau² = 0.00; Chi² = 3.73, df = 4 (P = 0.44); I² = 0%								
Test for overall effect: Z = 2.68 (P = 0.007)								



We judged the quality of evidence for pain intensity VAS score, for morphine versus bupivacaine, to be low. We downgraded the quality of evidence by two levels due to risk of bias and publication bias.

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We judged the quality of evidence for analgesia duration, for morphine versus bupivacaine, to be moderate. We downgraded the quality of evidence by one level due to publication bias.

See Summary of findings 2.

3. Morphine versus NSAIDs

Three studies (Alagol 2005; Calmet 2004; Guler 2002) compared morphine with NSAIDs. Two studies (Alagol 2005; Guler 2002) compared 20 mg tenoxicam with 2 mg morphine and no difference was found in VAS score in meta-analysis. One study (Alagol 2005) suggested tenoxicam had better analgesic effects and a lower analgesic consumption compared with morphine. The other study (Alagol 2005) did not find a difference on VAS score between tenoxicam and morphine, while the tenoxicam group consumed fewer analgesics than the morphine group. The available data were few, and did not provide robust evidence. Another study (Calmet 2004) compared morphine with ketorolac and concluded that ketorolac was more effective than morphine in pain relief.

We judged the quality of evidence for pain intensity VAS score, for morphine versus NSAIDs, to be very low. We downgraded the quality of evidence by three levels due to risk of bias and imprecision.

We judged the quality of evidence for analgesia duration, for morphine versus NSAIDs, to be low. We downgraded the quality of evidence by two levels due to risk of bias and publication bias.

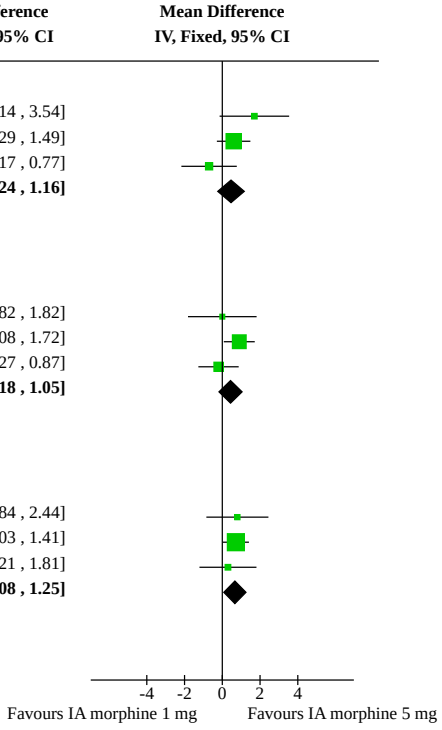
See Summary of findings 3.

4. Different doses of morphine

Four studies (four reports) compared different doses of IA morphine (Allen 1993; Kanbak 1997; Kizilkaya 2005; Likar 1999), of which three studies (Allen 1993; Kanbak 1997; Likar 1999) had usable data for meta-analysis. Results of one study (Kizilkaya 2005) were presented as figures, which could not be used in meta-analysis. No difference was found between 1 mg morphine and 2 mg morphine in meta-analysis of two studies (Allen 1993; Likar 1999). Two studies (Kanbak 1997; Likar 1999) compared 1 mg morphine with 4 mg/5 mg morphine and meta-analysis showed intensity of pain was lower in the 4 mg/5 mg morphine group than in the 1 mg morphine group at early, medium and late phases (Figure 6). Two studies (Kanbak 1997; Kizilkaya 2005) concluded that the analgesic effects of morphine were dose-dependent and that 5 mg morphine might have systemic effects on pain relief in participants. Two studies reported analgesic duration, and no difference was found among different doses of morphine. The limited number of studies might bias the conclusion. The number of participants included was small and the differences between groups were not clinically significant. The limited number of studies on dose effects suggests there is a need for more clinical trials.

Figure 6. Forest plot of comparison: 1 pain intensity VAS score, outcome: 1.6 1mg morphine vs 5mg morphine.

Study or Subgroup	1mg morphine Mean	SD	Total	5mg morphine Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
1.6.1 0-2h								
Kanbak 1997	5	2	11	3.3	2.6	13	14.5%	1.70 [-0.14 , 3.54]
Likar 1999	2.1	1.3	24	1.5	1.6	19	62.6%	0.60 [-0.29 , 1.49]
Muller 2001	2.8	2.1	15	3.5	2	15	22.9%	-0.70 [-2.17 , 0.77]
Subtotal (95% CI)			**50**			**47**	**100.0%**	**0.46 [-0.24 , 1.16]**
Heterogeneity: Chi² = 4.24, df = 2 (P = 0.12); I² = 53%								
Test for overall effect: Z = 1.29 (P = 0.20)								
1.6.2 2-6h								
Kanbak 1997	3.2	2.7	11	3.2	1.6	13	11.3%	0.00 [-1.82 , 1.82]
Likar 1999	2	1.8	24	1.1	0.87	19	55.8%	0.90 [0.08 , 1.72]
Muller 2001	3.5	1.1	15	3.7	1.8	15	32.9%	-0.20 [-1.27 , 0.87]
Subtotal (95% CI)			**50**			**47**	**100.0%**	**0.44 [-0.18 , 1.05]**
Heterogeneity: Chi² = 2.82, df = 2 (P = 0.24); I² = 29%								
Test for overall effect: Z = 1.40 (P = 0.16)								
1.6.3 6-30h								
Kanbak 1997	2.5	2.3	11	1.7	1.7	13	12.7%	0.80 [-0.84 , 2.44]
Likar 1999	1	1.5	24	0.28	0.76	19	72.2%	0.72 [0.03 , 1.41]
Muller 2001	4.1	1.9	15	3.8	2.3	15	15.1%	0.30 [-1.21 , 1.81]
Subtotal (95% CI)			**50**			**47**	**100.0%**	**0.67 [0.08 , 1.25]**
Heterogeneity: Chi² = 0.27, df = 2 (P = 0.87); I² = 0%								
Test for overall effect: Z = 2.23 (P = 0.03)								
Test for subgroup differences: Chi² = 0.33, df = 2 (P = 0.85), I² = 0%								



We judged the quality of evidence for pain intensity VAS score, for 1 mg morphine vs 2 mg morphine, to be low. We downgraded the quality of evidence by two levels due to publication bias and imprecision.

We judged the quality of evidence for analgesia duration, for 1 mg morphine vs 2 mg morphine, to be moderate. We downgraded the quality of evidence by one level due to publication bias.

See Summary of findings 4.

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5. Different routes of administration

Five studies (five reports) compared different administration routes of morphine, including IA injection, IV injection and IM injection (Bjornsson 1994; Christensen 1996; Dierking 1994; Raj 2004; Richardson 1997). Of the four studies that compared IA morphine with IM morphine, three studies concluded that no significant difference in pain scores or in requirements for supplemental morphine was observed between participants receiving IA versus IM morphine (Bjornsson 1994; Christensen 1996; Dierking 1994). Only one study concluded that IA morphine provided better analgesia than the same dose of IM morphine and indicated a peripheral mechanism of IA morphine (Raj 2004). Two studies (72 participants) were included in meta-analysis and no difference was found in pain intensity between IA and IM morphine (Analysis 1.4). The study comparing IA morphine with IV morphine indicated that IA morphine group had a lower VAS score and fewer additional analgesics (Richardson 1997).

We judged the quality of evidence for pain intensity VAS score at early phase (0 - 2 hours), for IM morphine versus IA morphine, to be very low. We downgraded the quality of evidence by three levels due to risk of bias, publication bias and imprecision.

No data were available for analgesia duration.

See Summary of findings 5.

6. Morphine versus other opioids

IA morphine was compared with tramadol, sufentanil, fentanyl and pethidine (Akinci 2003; Kazemi 2004; Likar 1995; Lyons 1995; Varkel 1999). Sufentanil, fentanyl and pethidine showed improved analgesia compared to morphine (Kazemi 2004; Lyons 1995; Varkel 1999). IA injection of morphine and sufentanil both reduced the post-arthroscopic-knee procedural pain and the need for supplementary analgesics, but sufentanil 5 µg was more effective than morphine 3 mg (Kazemi 2004). Better postoperative analgesia was achieved with 50 µg IA fentanyl than with 3 mg IA morphine (Varkel 1999). The local anaesthetic effect of pethidine may have been responsible for the improved early analgesia, but its duration of action appeared to be less than that of morphine (Lyons 1995). Of the two studies that compared morphine with tramadol, one study found no difference between 5 mg morphine and 50 mg tramadol (Akinci 2003); while the other showed better analgesia of 1 mg morphine compared with 10 mg tramadol (Likar 1995). Because of the limited number of studies, no meta-analysis was carried out.

Secondary outcomes: adverse events and withdrawals

In this review, twelve studies (13 reports) reported incidence of adverse events, and no difference was reported between groups. Eleven out of 20 studies comparing morphine with placebo reported side effects and nine studies (364 participants) were included in the meta-analysis. No statistical difference was obtained regarding the incidence of side effects between IA morphine and placebo in meta-analysis (Analysis 3.1). Two studies showed significant differences between IA morphine and IV morphine/ropivacaine. One study (Franceschi 2001) reported that three participants (10%) of the IA morphine group complained of nausea while no side effects were noted in ropivacaine group. One study (Richardson 1997) reported that the incidence of nausea was larger in the IV morphine group than in the IA morphine group.

We judged the quality of evidence for adverse events, for morphine versus placebo, to be low. We downgraded the quality of evidence by two levels due to risk of bias and publication bias.

We judged the quality of evidence for adverse events, for morphine versus bupivacaine, to be moderate. We downgraded the quality of evidence by one level due to publication bias.

We judged the quality of evidence for adverse events, for morphine versus NSAIDs, to be moderate. We downgraded the quality of evidence by one level due to risk of bias.

Seven of 28 studies reported participants' withdrawal. Five studies (Aasbø 1996; Christensen 1996; Likar 1995; Lyons 1995; Raj 2004) had less than 10% of participants who did not complete the study and two studies (Dierking 1994; Likar 1999) had more than 10% withdrawals. Only one study (Raj 2004) reported the allocated group of the participants lost to follow-up. One participant withdrew from the IM morphine group while no participants withdrew from the IA morphine group. There were not enough data for meta-analysis.

Sensitivity analysis

We excluded nine low-quality studies (743 participants) from meta-analysis (Aasbø 1996; Christensen 1996; Dierking 1994; Elkousy 2013; Follak 2001; Guler 2002; Kanbak 1997; Khoury 1992; Likar 1995) to measure the effects of methodological quality. The pain intensity VAS score comparisons of 1 mg IA morphine with placebo and 1 mg morphine with bupivacaine did not change.

DISCUSSION

Summary of main results

This review evaluated the relative effects on pain intensity and adverse events of IA morphine after knee arthroscopy. We compared IA morphine with placebo, active analgesics (local anaesthetics, NSAIDs, other opioids) and other routes of morphine administration. We found that IA morphine did not show beneficial effects in pain intensity compared with placebo. IA morphine was not better than IA bupivacaine, NSAIDs, sufentanil, fentanyl and pethidine in pain control. The comparison of effects between morphine and bupivacaine at different time points presented for the comparison of morphine and bupivacaine varied (zero to two hours favoured bupivacaine but this effect had reversed at 24 to 30 hours). The evidence was low quality and the relative effects of the interventions listed were uncertain. The conclusion is not robust because some of the included studies were of low quality and were poorly reported.

Of the 20 studies that compared IA morphine with placebo, we included nine studies with suitable data in the meta-analysis, which did not show a difference between 1 mg IA morphine and placebo in pain intensity at early, medium or late phases. There was low quality evidence for IA morphine compared with IA bupivacaine, NSAIDs, sufentanil, fentanyl and pethidine, and the relative effects are uncertain. Meta-analysis indicated no difference between IA morphine and placebo/bupivacaine in time to first analgesic request. None of the included studies showed any statistical difference regarding the incidence of adverse events between IA morphine and placebo.

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Overall completeness and applicability of evidence

We searched for published and ongoing trials on IA morphine to identify all the relevant studies. We could only extract useful data from 17 of the 28 included studies. Our evidence showed that IA morphine given after knee arthroscopy did not have beneficial effects in pain relief compared with placebo, and IA morphine was not better than IA bupivacaine, NSAIDs, sufentanil, fentanyl or pethidine. We could not find any robust evidence to support the analgesic effects of IA morphine.

Included studies enrolled participants undergoing elective arthroscopic knee surgery of multiple procedures, such as diagnostic arthroscopy, meniscectomy, excision of plicae, full arthroscopic lateral retinacular release, synovectomy, and chondral debridement, covering most of the knee arthroscopic surgeries. The number of studies favouring morphine exceeded the number of studies without significant difference.

More than half of the included studies did not report adverse events. Of the studies reporting adverse events, we found no statistical difference regarding the incidence of side effects between IA morphine and placebo. No severe side effects of IA morphine were reported.

Quality of the evidence

This systematic review was limited by the quality of existing data. All the included studies were described as randomised and double-blind, however, some studies failed to report the methods used to ensure randomisation and blinding adequately. In addition, we could not pool some data due to divergent outcome measurements and different types of rescue agents used in the studies. The group sizes of the included studies were small, which indicated low quality of the included studies. Some of the included RCTs with usable information were of low methodological quality. Lack of allocation concealment and blinding might be a source of bias which threatened the validity of the reported results. There was clinical heterogeneity among some trials, which resulted in high levels of statistical heterogeneity in some analyses. Most outcomes were assessed as low quality according to GRADE. Three full texts were unavailable and some outcomes were not fully reported, which might have had an impact on the quality of this review.

Potential biases in the review process

Thirty five studies appeared to satisfy the inclusion criteria through searching, but seven studies were not included in this review (see Figure 1). For example, despite our great efforts, three full texts were unavailable through database searching, handsearching or inter-library loan (Altan 1994; Uzma 1997; VanNess 1994) (Characteristics of studies awaiting classification). The previously related published systematic reviews also did not include these three studies. Several studies were excluded from meta-analysis because not enough data were presented in the text. Moreover, not all the included studies reported all the outcomes of interest. Two high-quality studies only presented results as median and interquartile. The retrieved studies were heterogenous in data and the results of the meta-analyses might then be less robust.

Agreements and disagreements with other studies or reviews

Four systematic reviews focusing on the same topic have been published previously. Three of them (Gupta 2001; Kalso 1997; Kalso 2002) came up with a positive conclusion that IA morphine might alleviate postoperative pain after knee arthroscopy, while one study found no analgesic effects of morphine compared with placebo (Rosseland 2004b). In the first review by Kalso in 1997, 33 RCTs published before 1996 were included, with no quantitative analysis of pooled data made. Seven RCTs from the included articles showed a significant analgesic effect of IA morphine compared with placebo. The study authors felt that sensitivity of analgesic measurement was important, based on the judgment that low pain intensity in the immediate postoperative period could render the studies insensitive (i.e. no significant difference). In the review, the effectiveness of internal sensitivity was defined as a significant difference between the active and placebo in pain intensity or total consumption of rescue analgesics, as reported by original studies. For example, bupivacaine as an active control in four studies showed a significantly lower VAS compared with placebo, and these four studies were considered sensitive (i.e. significant differences between groups), and the comparison between IA morphine and placebo can be made.

Later, bupivacaine was found to have no better analgesic effect than placebo, thus it was not suitable for testing study sensitivity. Therefore, in 2002, Kalso et al suggested a study was sensitive if VAS was above 3/10 in the control group. Fifteen of 25 trials were considered sensitive. The article concluded that IA morphine was superior to placebo, especially when a dose of 5 mg was used. However, the author also thought that a systemic effect still had to be considered with 5 mg of IA morphine.

In another systematic review (Gupta 2001), the authors did a quantitative analysis of data from 19 (of 45) studies and found an improvement in analgesia in the morphine group compared with placebo. However, in this review, the original articles included participants who underwent arthroscopic knee procedures under local, regional or general anaesthesia. Minor surgeries often cause less tissue damage and less postoperative pain, and spinal anaesthesia can provide longer lasting analgesia compared with general anaesthesia. Therefore, in our present systematic review, only patients under general anaesthesia were included.

Different from the above three reviews, the negative result from Rosseland 2004b suggested that, in properly controlled trials, there was no added analgesic effect of IA morphine compared with placebo alone. The authors thought that most trials with positive results were of low quality or had a small sample size, which must be interpreted cautiously because of the high likelihood of having a randomisation failure. The authors also considered that the definition of sensitive studies in previous systematic reviews (Kalso 1997; Kalso 2002) possibly introduced a bias, because it was difficult to document a baseline pain, making high pain intensity in the placebo group and the positive results simply an outcome of imbalanced allocation of participants.

Two studies compared IA morphine with placebo given to participants who experienced baseline pain of moderate to severe intensity after knee arthroscopy (Rosseland 2003a; Solheim 2006). They found no difference between groups. They had an IA catheter inserted at the end of arthroscopy and only included participants

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who reported moderate or severe postoperative pain during the first hour after surgery. One of the studies (Solheim 2006) reported 40 of 60 participants (67%) developed moderate to severe pain within one hour. They found that a significantly higher proportion of women (24/26) than men (26/39) reported at least moderate pain (P = 0.018) during the first hour after surgery. The study authors found no difference between IA 5 mg morphine and placebo in pain intensity or pain relief at any time during the 48-hour observation period and concluded that IA 5 mg morphine did not produce clinically significant pain relief in participants with moderate or severe pain after knee arthroscopy. These controversies originated from the preemptive design of the included articles. Besides, according to Rosseland et al, the incidence of moderate to severe pain after arthroscopy was only 60%. We had to take the participants with mild postoperative pain into account in clinical practice, therefore, we did no test of internal sensitivity, especially when the test may have actually turned out to be biased itself, and just combined data as Gupta et al did.

Of the four dose-response comparisons, only one was defined as sensitive by Kalso 2002. The result showed that 5 mg of IA morphine provided statistically significantly better analgesia compared with 1 mg of IA morphine. This was confirmed by our meta-analysis, although the data were quite limited even after all these years of researching.

We believed that a systemic effect of 5 mg IA morphine still had to be considered, particularly in the early period, because no difference could be detected in the efficacy of 5 mg of morphine whether it was injected through IA or IM (Kalso 1997). Additionally, Kalso et al found that 1 mg IA morphine in a 20 ml injection was equivalent to a concentration of about 50 μg/ml. This high concentration would be expected to saturate all the opioid receptors in the knee joint (Kalso 1997). From this point of view, any dose response may be a consequence of systemic effect and residual morphine concentration. The proper dose of IA morphine, and whether this specific dose of morphine is superior to placebo, are still uncertain with the evidence currently available. More trials are needed to make dose-response comparisons.

AUTHORS' CONCLUSIONS

Implications for practice

This review did not find high quality evidence that 1 mg IA morphine is better than placebo at reducing pain intensity at early, medium or late phases. No statistical difference was reported between IA morphine and placebo regarding the incidence of adverse events. The relative effects of 1 mg morphine when compared with IA bupivacaine, NSAIDs, sufentanil, fentanyl and pethidine are uncertain. The quality of the evidence is limited by high risk of bias and small size of the included studies, which might bias the results. More high quality studies are needed to get more conclusive results.

Implications for research

Though many trials in this area have been conducted, the quality of reporting in these trials is disappointing. Most of the included studies were of small size, so likely to introduce bias and make the conclusions less robust. Some of the studies did not set a primary end point or calculate sample size. Most studies were published at least ten years before we ran our search. Data from the studies were insufficient to show whether IA morphine is beneficial or not.

New standards for clinical trials are now in place, which aim to make clinical trials more strict and precise. Several previous systematic reviews reached different conclusions to this review, but high quality trials with at least 200 participants in each arm are needed to get a more conclusive result of the efficacy and safety of single dose intra-articular morphine for post-operative pain after knee arthroscopy. Future trials should focus on quality of reporting, for example by specifying the randomisation process and attempting to conceal allocation of participants to study groups. Better reporting of adverse events and withdrawal is required to fully evaluate the safety of morphine. The incidence of adverse events and their severity should be clearly reported in the trials.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Aasbø 1996

Study characteristics		
Methods	Prospective, randomised double-blind trial	
Participants	107 patients scheduled for elective, diagnostic knee arthroscopy	
Interventions	Group 1: 20 ml of bupivacaine 2.5 mg/ml with 3 mg of morphine; Group 2: 20 ml of bupivacaine 2.5 mg/ml; Group 3: 20 ml isotonic saline with 3 mg morphine; Group 4: 20 ml of isotonic saline	
Outcomes	VAS, time to first analgesic administered, analgesic consumption	
Notes	No additional analgesic effect of IA morphine or bupivacaine	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: The participants were randomly assigned to double-blind administration of 20 ml of the test drug
Allocation concealment (selection bias)	Unclear risk	Quote: The test drugs were drawn into a syringe by an independent nurse
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no patient was excluded, but 3 in 107 (less than 10%) participants did not complete the questionnaire.

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Aasbø 1996 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Comment: insufficient data were available
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: was given to the surgeon who administrated the injection at the end of the procedure without knowing the contents
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: not specified
Size	High risk	Comment: < 50 participants per treatment arm.

Akinci 2003

Study characteristics	
Methods	Prospective double-blind randomised trial
Participants	75 patients having elective arthroscopic surgery of the knee, included diagnostic arthroscopy, menisectomy, and minimal debridement or loose body removal, or both
Interventions	3 groups - IA tramadol 50 mg (tramadol group), IA morphine 5 mg (morphine group), or IA normal saline (control group), injected through the arthroscope with the study drug supplied in a coded syringe
Outcomes	VRS, supplemental analgesic requirements, incidence of side effects
Notes	There was no significance with respect to the pain scores postoperatively except the first VRS pain score when the participants arrived at the PACU. Nausea and vomiting were reported in 32% of participants in the control group and 24% of participants in both the morphine and the tramadol groups (P>0.05). Somnolence was noted in 24% of the control group, 16% of the morphine group, and 8% of the tramadol group (P=0.10)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: a computerized allocation schedule
Allocation concealment (selection bias)	Low risk	Quote: coded syringes containing the study drugs
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no participants withdrew from the study
Selective reporting (reporting bias)	Low risk	Comment: all the outcomes in methods section were reported. And VRS score of continuous time course were reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: the coded syringes were prepared by an anaesthesiologist not involved in the administration of the drug, patient care, or data collection

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Akinci 2003 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: A blinded observer recorded pain, supplemental analgesic requirements, and incidence of side effects
Size	High risk	Comment: < 50 participants per treatment arm

Alagol 2005

Study characteristics	
Methods	Randomised, placebo-controlled, double-blinded study
Participants	150 patients undergoing arthroscopic knee surgery, multiple arthroscopic procedures
Interventions	Group N received 500 µg neostigmine, Group M received 2 mg morphine, Group T received 20 mg tenoxicam, Group C received clonidine, Group B received 100 mg bupivacaine and Group S received saline 20 ml.
Outcomes	VAS, duration of analgesia
Notes	Neostigmine, clonidine, tenoxicam, morphine and bupivacaine decreased postoperative pain intensity and reduced analgesic consumption when compared with placebo. The most effective drugs that are administered intra articularly are neostigmine and clonidine among the five drugs we studied. Tenoxicam provided longer analgesia when compared with morphine and bupivacaine, postoperatively

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: a table of random numbers
Allocation concealment (selection bias)	Unclear risk	Comment: not specified
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no participants withdrew from the study
Selective reporting (reporting bias)	Low risk	Comment: all the outcomes in methods section were reported and VAS score of continuous time course were reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: The solutions were prepared in 20-ml volume by an anaesthesiologist and administered by a surgeon who was blinded to the contents of the syringe
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: After extubation, participants were observed in the postanaesthesia care unit for 1 h and in the clinic of orthopaedic surgery by an anaesthesiologist who was blinded to the groups
Size	High risk	Comment: < 50 participants per treatment arm

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Allen 1993

Study characteristics	
Methods	Randomised, double-blind trial
Participants	120 patients ASA 1-2, need arthroscopy surgery
Interventions	Group 1: bupivacaine Group 2: 1 mg morphine Group 3: 2 mg morphine Group 4: morphine & bupivacaine
Outcomes	VAS, duration
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: use a random table to ensure randomisation
Allocation concealment (selection bias)	Unclear risk	Comment: not specified
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no participants withdrew from the study
Selective reporting (reporting bias)	Unclear risk	Comment: insufficient data were available
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: not specified
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: not specified
Size	High risk	Comment: < 50 participants per treatment arm

Bjornsson 1994

Study characteristics	
Methods	Two-stage, randomised, double-blind, controlled trial
Participants	149 patients ASA 1-2, part 1: 78 part 2: 71
Interventions	Morphine 1 mg, saline, bupivacaine, morphine & bupivacaine

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Bjornsson 1994 *(Continued)*

	5 mg morphine IA, saline, 5 mg morphine IM
Outcomes	VAS (severe, sensitivity)
Notes	VAS scores similar

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: not specified
Allocation concealment (selection bias)	Unclear risk	Comment: not specified
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no participants withdrew from the study.
Selective reporting (reporting bias)	Unclear risk	Comment: insufficient data were available
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: not specified
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: After the operation, a nurse who was blind to the method asked the patient to assess the severity of pain
Size	High risk	Comment: < 50 participants per treatment arm

Calmet 2004

Study characteristics	
Methods	Prospective, double-blind, randomised study
Participants	80 consecutive patients were studied who had been diagnosed with torn meniscus and recommended to have arthroscopic surgery
Interventions	Group 1 participants (n = 20) received postoperative injection of 60 mg IA ketorolac, Group 2 participants (n = 20) 10 cc IA bupivacaine 0.25% Group 3 participants (n = 20) 1 mg IA morphine diluted in 10 cc saline, and Group 4 participants (n = 20, controls) only 10 cc saline
Outcomes	VAS, analgesic duration
Notes	The best analgesic effect was IA ketorolac
Risk of bias	

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Calmet 2004 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: not specified
Allocation concealment (selection bias)	Unclear risk	Comment: not specified
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no participants withdrew from the study.
Selective reporting (reporting bias)	Low risk	Comment: all the outcomes in methods section were reported and VAS score of continuous time course were reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: not specified
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: not specified
Size	High risk	Comment: < 50 participants per treatment arm

Christensen 1996

Study characteristics	
Methods	A controlled, randomised and double-blind study
Participants	61 ASA 1-2, having elective arthroscopic surgery of the knee (61 participants recruited, 58 participants completed trial)
Interventions	Group 1: (n = 29) 5 mg morphine IA, Group 2: (n = 29) 5 mg morphine IM
Outcomes	VRS and VAS, analgesic consumption
Notes	The clinical analgesic effect of 5 mg morphine given intra-articularly is equal to 5 mg morphine given intra-muscularly. The occurrence of villous synovitis seems to be of no clinical importance concerning the local effect of morphine.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: not specified
Allocation concealment (selection bias)	Unclear risk	Comment: not specified

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Christensen 1996 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: 3/61 participants excluded, < 10% of participants did not complete the study
Selective reporting (reporting bias)	Unclear risk	Comment: insufficient data were available
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: not specified.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: all participants were assessed by an observer blinded to the randomisation of the patient
Size	High risk	Comment: < 50 participants per treatment arm

De Andres 1998

Study characteristics	
Methods	Randomised double-blind, placebo-controlled trial
Participants	78 patients having elective arthroscopic meniscectomy
Interventions	Group 1 (n = 25): 0.25% bupivacaine (50 mg) (IA), Group 2 (n = 27): 1 mg morphine, Group 3 (n = 26): morphine bupivacaine mixture, Group 4 (n = 25): normal saline
Outcomes	VAS, VRS, side effect, time to first request of analgesics
Notes	Side effects occurred in 13.7% of the participants, with urinary retention being the most common (n = 8, 10%). In this regard there were no significant differences. These results show no significant differences between the groups

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: a random number table
Allocation concealment (selection bias)	Unclear risk	Comment: not specified
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no participants withdrew from the study
Selective reporting (reporting bias)	Low risk	Comment: all the outcomes in methods section were reported and VRS score of continuous time course were reported

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De Andres 1998 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: The surgeon injected 20 ml solution into the knee joint. The patient, the anaesthesiologist in charge and the surgeon were blind to the solution injected. Participants were informed pre-operatively by a blinded observer about all pain scores
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: not specified
Size	High risk	Comment: < 50 participants per treatment arm

Dierking 1994

Study characteristics		
Methods	Double-blind, randomised study	
Participants	40 healthy patients undergoing elective arthroscopic meniscectomy	
Interventions	18 participants received IA morphine and 15 participants IM morphine 2 mg	
Outcomes	VAS	
Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: not specified
Allocation concealment (selection bias)	Unclear risk	Comment: not specified
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: 7 in 40 of participants did not complete the study, used 'completer analysis'
Selective reporting (reporting bias)	Unclear risk	Comment: insufficient data were available
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: Study medication was drawn from coded ampoules to ensure the double-blind nature of the study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: not specified
Size	High risk	Comment: < 50 participants per treatment arm

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Elkousy 2013

Study characteristics	
Methods	Randomised
Participants	82 patients underwent partial meniscectomy, chondral debridement, or both
Interventions	10 mg morphine versus 10 cc bupivacaine
Outcomes	VAS score, side effects
Notes	Quasi-randomised trial

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Comment: group assignment was determined by an odd or even account number given on the day of surgery
Allocation concealment (selection bias)	Unclear risk	Comment: insufficient data were available
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: eighteen participants (11 in the morphine group and 7 in the bupivacaine group) had data available through hospital discharge but no data in the subsequent 24 hours. The remaining 64 participants (36 in the morphine group and 28 in the bupivacaine group) had post-anaesthesia care unit data, as well as follow-up VAS and medication use data through 24 hours postoperatively.
Selective reporting (reporting bias)	Unclear risk	Comment: insufficient data were available. The time point of VAS recording was not clear
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: single-blind. The participants were blinded to group assignment, but the investigators were not
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: not specified
Size	High risk	Comment: < 50 participants per treatment arm

Follak 2001

Study characteristics	
Methods	Prospective, randomised, double-blind study
Participants	320 patients, subdivided into 4 groups of 80, who underwent arthroscopic knee surgery
Interventions	Each of the 4 groups received a different solution: 15 ml of bupivacaine 0.5%, 5 mg of morphine in 15 ml of isotonic saline solution,

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Follak 2001 *(Continued)*

	15 ml of bupivacaine 0.5% with epinephrine 0.0005% 15 ml of isotonic saline solution (control group)
Outcomes	VAS, consumption of analgesics and time point of first analgesic application
Notes	Bupivacaine 0.5% with epinephrine 0.0005% was found to be the most effective

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: not specified
Allocation concealment (selection bias)	Unclear risk	Comment: not specified
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no participants withdrew from the study
Selective reporting (reporting bias)	Unclear risk	Comment: insufficient data were available
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: not specified
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: not specified
Size	Unclear risk	Comment: 50 to 199 participants per treatment arm

Franceschi 2001

Study characteristics	
Methods	Randomised, double-blind
Participants	90 patients scheduled to undergo elective knee arthroscopy
Interventions	Group 1 received ropivacaine 75 mg, Group 2 received 2 mg morphine, Group 3 received 20 ml of saline solution.
Outcomes	VAS, duration, side effects
Notes	
Risk of bias	

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Franceschi 2001 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: not specified
Allocation concealment (selection bias)	Low risk	Quote: the 3 different analgesics were administered in a double-blinded randomised fashion from a coded syringe into the joint space
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no participants withdrew from the study
Selective reporting (reporting bias)	Unclear risk	Comment: insufficient data were available
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: the 3 different analgesics were administered in a double-blinded randomised fashion from a coded syringe
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: not specified
Size	High risk	Comment: < 50 participants per treatment arm

Guler 2002

Study characteristics	
Methods	Randomised, double-blind
Participants	42 patients only arthroscopic ACL reconstruction using hamstring tendons
Interventions	Group 1: 20 mg tenoxicam, Group 2: 2 mg morphine, Group 3: control NS
Outcomes	VAS, analgesic requirements, side effects
Notes	VAS data without SD

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: not specified
Allocation concealment (selection bias)	Unclear risk	Comment: not specified
Incomplete outcome data (attrition bias)	Low risk	Comment: no participants withdrew from the study

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Guler 2002 *(Continued)*

All outcomes		
Selective reporting (reporting bias)	High risk	Comment: insufficient data were available. Data of VAS score were presented as figures only
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: not specified
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: not specified
Size	High risk	Comment: < 50 participants per treatment arm

Kanbak 1997

Study characteristics		
Methods	Prospective, randomised, controlled, double-blinded	
Participants	35 patients, included partial or total meniscectomy and repair of ruptured ligaments	
Interventions	Group 1: n = 11, NS intra-articularly Group 2: n = 11, 1 mg morphine intra-articularly Group 3: n = 13, 5 mg morphine intra-articularly	
Outcomes	VAS, analgesic consumption, side effects	
Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: not specified
Allocation concealment (selection bias)	Unclear risk	Comment: not specified
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no participants withdrew from the study
Selective reporting (reporting bias)	Unclear risk	Comment: insufficient data were available
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: not specified.

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Kanbak 1997 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: VAS score recorded by a blinded observer
Size	High risk	Comment: < 50 participants per treatment arm

Kazemi 2004

Study characteristics		
Methods	Prospective, double-blind study	
Participants	45 patients who were ASA physical status I and II and scheduled for arthroscopic knee surgery	
Interventions	Sufentanil 5 µg (group S), morphine 3 mg (group M) or normal saline 20 cc as placebo (group p), intra-articularly at the end of arthroscopic knee surgery	
Outcomes	VAS, consumption of rescue medication	
Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: not specified
Allocation concealment (selection bias)	Low risk	Quote: The contents of these syringes were unknown to anesthesiologist and surgeon who performed the study. The codes were not revealed until completion of the study.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no participants withdrew from the study
Selective reporting (reporting bias)	Unclear risk	Comment: insufficient data were available
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: the content of syringe in unknown to surgeon and anaesthesiologists
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: not specified
Size	High risk	Comment: < 50 participants per treatment arm

Khoury 1992

Study characteristics

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Khoury 1992 *(Continued)*

Methods	Randomised, double-blind
Participants	33 patients of various kinds of knee surgeries
Interventions	Group 1:1 mg morphine Group 2: 0.25% bupivacaine Group 3: morphine + bupivacaine
Outcomes	VAS, analgesic consumption
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: not specified
Allocation concealment (selection bias)	Unclear risk	Comment: not specified
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no participants withdrew from the study
Selective reporting (reporting bias)	Unclear risk	Comment: insufficient data were available
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: not specified
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: not specified
Size	High risk	Comment: < 50 participants per treatment arm

Kizilkaya 2005

Study characteristics

Methods	Double-blind, randomised
Participants	72 patients scheduled for arthroscopic knee surgery either for diagnostic purposes or for partial meniscectomy
Interventions	Group C (n = 18), 20 ml of IA isotonic saline and 5 mg morphine in 5 ml of isotonic saline IV; Group M5 (n = 17) received 5 mg morphine in 20 ml of isotonic saline intra-articularly and 5 ml isotonic saline IV;

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Kizilkaya 2005 *(Continued)*

	Group M1 (n = 18) received 1 mg morphine in 20 ml of isotonic saline intra-articularly and 5 ml of isotonic saline IV; Group M1M (n = 19) received 1 mg morphine plus 40 mg methylprednisolone in 20 ml of isotonic saline intra-articularly and 5 ml of isotonic saline IV. Injected the solution through the arthro-scope
Outcomes	VAS, analgesic consumption
Notes	The analgesic effect of morphine given intra-articularly is dose dependent and that combination of methylprednisolone with morphine has an additive effect on analgesia

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	By a computer-generated randomisation sequence
Allocation concealment (selection bias)	Unclear risk	Comment: not specified
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no participants withdrew from the study
Selective reporting (reporting bias)	Unclear risk	Comment: iInsufficient data were available
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: without knowing the contents measured and recorded by a anaesthesiologist who is blind to the group allocation
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: not specified
Size	High risk	Comment: < 50 participants per treatment arm

Likar 1995

Study characteristics

Methods	Randomised, double-blind
Participants	93 patients (93 recruited, 86 completed trial), multiple kinds of knee surgeries
Interventions	Group 1: n = 41, 1 mg morphine Group 2: n = 45, 10 mg tramadol
Outcomes	VAS, analgesic consumption
Notes	

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Likar 1995 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: not specified
Allocation concealment (selection bias)	Unclear risk	Comment: not specified
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: 7 participants were excluded from centre 2, < 10% of participants did not complete the study
Selective reporting (reporting bias)	Unclear risk	Comment: insufficient data were available
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: not specified
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: not specified
Size	High risk	Comment: < 50 participants per treatment arm

Likar 1999

Study characteristics	
Methods	Randomised, double-blind
Participants	108 patients (108 recruited, 86 completed trial), various kinds of knee surgeries
Interventions	Group 1: NS Group 2: morphine 1 mg Group 3: morphine 2 mg Group 4: morphine 4 mg
Outcomes	VAS, analgesic consumption
Notes	Increasing doses of IA morphine were associated with better analgesic effect and less analgesic consumption

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: using a random table

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Likar 1999 *(Continued)*

Allocation concealment (selection bias)	Low risk	Quote: each bottle of test solution was coded by the hospital pharmacy
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: 22 in 108 of participants did not complete the study, used 'completer analysis'.
Selective reporting (reporting bias)	Unclear risk	Comment: insufficient data were available
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: not specified.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: VAS scores were recorded by a blinded observer
Size	High risk	Comment: < 50 participants per treatment arm

Lyons 1995

Study characteristics		
Methods	Randomised, double-blind	
Participants	66 patients (66 recruited, 60 completed trial, without ITT analysis), only enrolled participants undergoing arthroscopic meniscectomy	
Interventions	Group 1: pethidine 50 mg Group 2: morphine 5 mg Group 3: NS	
Outcomes	VAS, analgesic consumption	
Notes	Morphine & pethidine effective	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: not specified
Allocation concealment (selection bias)	Unclear risk	Quote: each injection was drawn up by an anaesthesiologist not involved in the study
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: replies were received from 90% (60/66) of participants studied. < 10% of participants did not complete the study

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Lyons 1995 *(Continued)*

Selective reporting (reporting bias)	High risk	Comment: no exact data were provided. Only one figure showed the results. No exact P value was provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: anaesthesiologists and operating surgeon involved were not aware of the contents of the Injectate
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: not specified
Size	High risk	Comment: < 50 participants per treatment arm

Muller 2001

Study characteristics	
Methods	Prospective randomised, double-blind controlled trial
Participants	135 patients > 18 yrs, knee arthroscopy
Interventions	9 groups, each has 15 participants 1A NS 2A morphine 5 mg 3A morphine 1 mg 4A mor + ropivacaine 5A ropivacaine 20 mg 1B NS 2B morphine 5 mg 3B morphine 1 mg 4B mor + ropivacaine 5B ropivacaine 20 mg
Outcomes	VAS, tramadol consumption
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: not specified
Allocation concealment (selection bias)	Unclear risk	Comment: not specified

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Muller 2001 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no participants withdrew from the study
Selective reporting (reporting bias)	Unclear risk	Comment: insufficient data were available
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: not specified
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: outcome assessor was blind
Size	High risk	Comment: < 50 participants per treatment arm

Raj 2004

Study characteristics		
Methods	Randomised, double-blind	
Participants	40 patients, various kinds of knee surgery	
Interventions	Group 1: n = 20, 10 mg morphine IA Group 2: n = 19, 10 mg morphine IM	
Outcomes	VAS, plasma concentration	
Notes	IA morphine is better than IM morphine	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: allocated randomly using Lab5.1
Allocation concealment (selection bias)	Low risk	Quote: using a sealed envelope method
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: one out of 40 participants withdrew from the study
Selective reporting (reporting bias)	Low risk	Comment: all the outcomes in methods section were reported and VAS score of continuous time course were reported. Exact P value was reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: all participants received a small dressing where the IM injection would have been or actually placed. The anaesthetist involved was not aware of which treat the participants received

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Raj 2004 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: not specified
Size	High risk	Comment: < 50 participants per treatment arm

Richardson 1997

Study characteristics		
Methods	Two prospective, randomised, double-blind clinical trials	
Participants	Trial 1: n = 106 Trial 2: n = 48, various kinds of knee surgery	
Interventions	Trial 1: 1A 1 mg morphine in 20 ml normal saline IA, 1B 20 ml normal saline IA, 1C 20 ml 0.5% bupivacaine IA Trial 2: 20 ml normal saline IA plus 5 mg morphine in 10 ml normal saline IV, 2B 1 mg morphine in 20 ml normal saline IA plus 10 ml normal saline IV 2C 5 mg morphine in 20 ml normal saline IA plus 10 ml normal saline IV	
Outcomes	VAS, analgesia consumption	
Notes	5 mg IA was the most effective analgesic following knee arthroscopy	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: not specified
Allocation concealment (selection bias)	Unclear risk	Comment: not specified
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no participants withdrew from the study
Selective reporting (reporting bias)	Unclear risk	Comment: insufficient data were available
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: solution was injected into the knee by the surgeon, who was blinded to its contents
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: not specified
Size	High risk	Comment: < 50 participants per treatment arm

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Rosseland 2003a

Study characteristics	
Methods	A randomised, double-blind controlled clinical study
Participants	40 patients (59 recruited, 40 included in analysis), various kinds of knee surgery
Interventions	Saline 10 ml with morphine 2 mg (n = 19), without morphine (n = 21)
Outcomes	VAS, VRS, analgesic time and consumption
Notes	Only 70% of 57 participants had pain of moderate to severe intensity within 1 h after an arthroscopic procedure of the knee joint under general anaesthesia. IA injection of saline 10 ml and saline 10 ml with morphine 2 mg were both associated with pain relief

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: list of random numbers
Allocation concealment (selection bias)	Low risk	Quote: by a person not involved in the study. Block size and randomisation codes were not revealed to the investigators until all measurements and calculations had been entered into the database.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no participants withdrew from the study
Selective reporting (reporting bias)	Unclear risk	Comment: insufficient data were available
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: maintain blinding of both participants and examiner throughout the study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: not specified
Size	High risk	Comment: < 50 participants per treatment arm

Ruwe 1995

Study characteristics	
Methods	A double-blind, randomised trial
Participants	124 patients elective outpatient arthroscopic knee surgery
Interventions	Group 1 (n = 23) received 15 ml of 0.5% bupivacaine and 5 ml of normal saline Group 2 (n = 26) received 15 ml of normal saline and 2 mg of morphine in 5 ml of normal saline

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Ruwe 1995 *(Continued)*

	Group 3 (n = 25) received 15 ml of 0.5% bupivacaine with 1 mg morphine in 5 ml of normal saline Group 4 (n = 22) received 15 ml of 0.5% bupivacaine with 2 mg morphine in 5 ml of normal saline Group 5 (n = 28) received 20 ml of normal saline
Outcomes	VAS, supplemental analgesic, weightbearing status
Notes	Our results failed to show any beneficial effect of morphine used for postoperative analgesia, either alone or in combination with bupivacaine

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: not specified
Allocation concealment (selection bias)	Low risk	Quote: Syringes were coded by the pharmacy with their contents unknown to the investigators
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no participants withdrew from the study
Selective reporting (reporting bias)	High risk	Comment: no exact data were provided. Only one figure showed the results. No exact P value was provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: not specified
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: not specified
Size	High risk	Comment: < 50 participants per treatment arm

Solheim 2006

Study characteristics

Methods	Randomised, double blind
Participants	40 patients (60 recruited, 40 included in analysis), scheduled for day-case knee arthroscopy, such as meniscectomies, removal of loose body, or shaving and lavage of degenerated cartilage
Interventions	IA injection was given through a 20-gauge catheter IA saline 1 ml (placebo) or IA morphine 5 mg and to immediate or delayed removal of IA catheter
Outcomes	VAS, VRS, time to and consumption of rescue analgesic drugs, side effects
Notes	

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Solheim 2006 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: by using a list of random numbers
Allocation concealment (selection bias)	Low risk	Quote: by the senior author who did not deal with the participants. Block size and randomisation codes were not revealed to the investigators until all measurements and calculations had been entered into the database
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: None lost to follow-up during hospital day and 9 participants lost to follow-up during 1 and 2 day. Used all the included participants' data in the analysis
Selective reporting (reporting bias)	Unclear risk	Comment: insufficient data were available
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: To maintain blinding of both participants and examiner throughout the study, syringes for each patient were prepared in the morning of surgery by a nurse not involved in the treatment or assessment of the participants
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: not specified
Size	High risk	Comment: < 50 participants per treatment arm

Varkel 1999

Study characteristics	
Methods	Double blind, randomised
Participants	69 patients, arthroscopic surgery
Interventions	Group I (n = 23) fentanyl in 20 ml saline; Group II (n = 24) 3 mg morphine in 20 ml saline; Group III (n = 22) 20 ml saline
Outcomes	VAS, consumption of rescue medication
Notes	Better postoperative analgesia was achieved with 50 Hg IA fentanyl than with 3 mg IA morphine

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Comment: not specified

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Varkel 1999 *(Continued)*

Allocation concealment (selection bias)	Low risk	Quote: using a sealed envelope technique
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no participants withdraw from the study
Selective reporting (reporting bias)	Unclear risk	Comment: insufficient data were available
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: by an observer blinded to patient group assignment
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: not specified, double blind, probably done
Size	High risk	Comment: < 50 participants per treatment arm

Wrench 1996

Study characteristics	
Methods	A randomised double-blind placebo-controlled trial
Participants	60 patients (ASA 1 or 2) scheduled to undergo day-case arthroscopic knee surgery
Interventions	(i) 0.9% saline 20 ml, n=20 (ii) morphine 1 mg in 20 ml of 0.9% saline 20 ml, n=19 (iii) buprenorphine 30 jig in 20 ml of 0.9% saline 20 ml, n=19
Outcomes	VRS, consumption of rescue medication
Notes	There were no differences in pain scores among groups, first 24 h postoperatively

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Comment: not specified
Allocation concealment (selection bias)	Low risk	Quote: these solutions were prepared by an anaesthetist who was not one of the investigators
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no participants withdrew from the study
Selective reporting (reporting bias)	High risk	Comment: no exact data were provided. Only one figure showed the results. No exact P value was provided

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Wrench 1996 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: These solutions were prepared by an anaesthetist who was not one of the investigators; the patient and the investigator were blinded to the identity of the test solution
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: not specified
Size	High risk	Comment: < 50 participants per treatment arm

IA: Intra-articular
IM: Intramuscular
IV: Intravenous
NS: Normal saline
VAS: Visual analogue scale
VRS: Verbal rating scales
PACU: Postanesthesia care unit

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Alvarez-Cabo 1998	Participants received spinal anaesthesia
De Andres 1993	Some participants were younger than 15 years old
Lehrberger 1994	Group size. Number of participants in group who completed the study less than ten
Stein 1991	Group size. Number of participants in group who completed the study less than ten

Characteristics of studies awaiting classification *[ordered by study ID]*

Altan 1994

Methods	Randomised clinical trial
Participants	ASA I, II 60 participants
Interventions	3 groups: 1. 0.5 % bupivacaine, 2. 0.025% morphine, 3. normal saline IA
Outcomes	VAS score
Notes	Only abstract

Uzma 1997

Methods	A randomised, double-blind trial
Participants	Sixty participants who underwent arthroscopic knee surgery

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Uzma 1997 *(Continued)*

Interventions	4 groups, Group M: morphine, Group B: bupivacaine Group M+B: morphine+bupivacaine, Group SF: normal saline
Outcomes	VAS
Notes	Only abstract.

VanNess 1994

Methods	A prospective study
Participants	Participants undergoing elective knee arthroscopy performed under general anaesthesia
Interventions	Group 1 (n = 41) received 30 cc of 0.25% bupivacaine with 1:200,000 epinephrine; Group 2 (n = 40) received 2 mg morphine (1 mg/cc) in 28 cc normal saline (total volume 30 cc)
Outcomes	Postoperative pain scores and the amount of supplemental analgesic agents used in a 24-hour period
Notes	Only abstract

DATA AND ANALYSES

Comparison 1. Pain intensity VAS score

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 1mg morphine vs placebo	7		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1.1 0-2h	7	297	Mean Difference (IV, Random, 95% CI)	-0.50 [-1.15, 0.14]
1.1.2 2-6h	7	297	Mean Difference (IV, Random, 95% CI)	-0.47 [-1.09, 0.14]
1.1.3 6-30h	7	297	Mean Difference (IV, Random, 95% CI)	-0.88 [-1.81, 0.04]
1.2 1mg morphine vs bupivacaine	6		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.2.1 0-2h	5	248	Mean Difference (IV, Random, 95% CI)	1.43 [0.49, 2.37]
1.2.2 2-6h	6	330	Mean Difference (IV, Random, 95% CI)	0.45 [-0.47, 1.36]
1.2.3 6-30h	5	270	Mean Difference (IV, Random, 95% CI)	-0.71 [-1.23, -0.19]
1.3 morphine vs NSAIDs	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.3.1 0-2h	2	80	Mean Difference (IV, Random, 95% CI)	0.95 [-0.95, 2.85]

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Outcome or sub-group title	No. of studies	No. of partici-pants	Statistical method	Effect size
1.3.2 2-6h	2	80	Mean Difference (IV, Random, 95% CI)	1.00 [0.12, 1.88]
1.3.3 6-30h	2	80	Mean Difference (IV, Random, 95% CI)	0.43 [-0.54, 1.39]
1.4 IA morphine vs IM morphine	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.4.1 0-2h	2	72	Mean Difference (IV, Fixed, 95% CI)	0.21 [-0.48, 0.90]
1.4.2 2-6h	2	72	Mean Difference (IV, Fixed, 95% CI)	-0.14 [-0.93, 0.64]
1.4.3 6-30h	1	39	Mean Difference (IV, Fixed, 95% CI)	-0.30 [-1.39, 0.79]
1.5 1mg morphine vs 2mg morphine	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.5.1 0-2h	2	105	Mean Difference (IV, Random, 95% CI)	-0.56 [-1.93, 0.81]
1.5.2 2-6h	2	105	Mean Difference (IV, Random, 95% CI)	-0.32 [-1.69, 1.05]
1.5.3 6-30h	1	45	Mean Difference (IV, Random, 95% CI)	0.55 [-0.30, 1.40]
1.6 1mg morphine vs 4mg/5mg morphine	3		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.6.1 0-2h	3	97	Mean Difference (IV, Fixed, 95% CI)	0.46 [-0.24, 1.16]
1.6.2 2-6h	3	97	Mean Difference (IV, Fixed, 95% CI)	0.44 [-0.18, 1.05]
1.6.3 6-30h	3	97	Mean Difference (IV, Fixed, 95% CI)	0.67 [0.08, 1.25]

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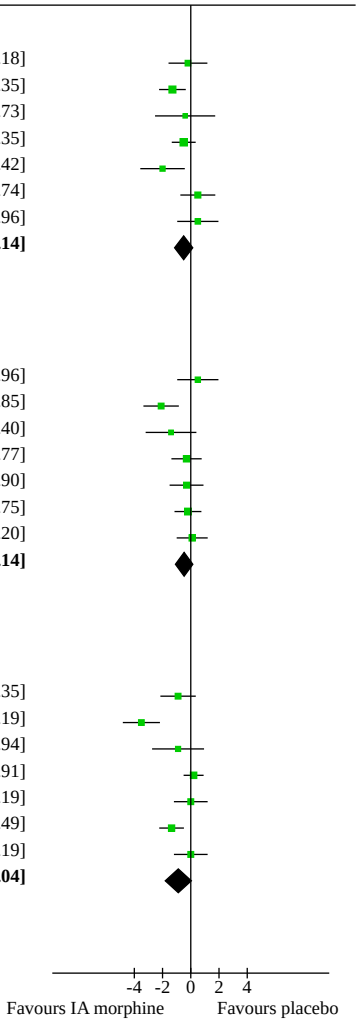
Analysis 1.1. Comparison 1: Pain intensity VAS score, Outcome 1: 1mg morphine vs placebo

Study or Subgroup	morphine Mean	morphine SD	morphine Total	placebo Mean	placebo SD	placebo Total	Weight	Mean Difference IV, Random, 95% CI
1.1.1 0-2h								
Calmet 2004	2.3	1.9	20	2.5	2.5	20	13.3%	-0.20 [-1.58 , 1.18]
De Andres 1998	2.2	1.4	27	3.5	2	25	19.6%	-1.30 [-2.25 , -0.35]
Kanbak 1997	5	2	11	5.4	3	11	7.2%	-0.40 [-2.53 , 1.73]
Likar 1999	2.1	1.3	24	2.6	1.6	22	21.4%	-0.50 [-1.35 , 0.35]
Muller 2001	2.8	2.1	15	4.8	2.3	15	11.2%	-2.00 [-3.58 , -0.42]
Richardson 1997	2.5	2.6	36	2	2.6	32	15.0%	0.50 [-0.74 , 1.74]
Wrench 1996	3.3	1.9	19	2.8	2.7	20	12.3%	0.50 [-0.96 , 1.96]
Subtotal (95% CI)			**152**			**145**	**100.0%**	**-0.50 [-1.15 , 0.14]**
Heterogeneity: Tau² = 0.32; Chi² = 10.70, df = 6 (P = 0.10); I² = 44%								
Test for overall effect: Z = 1.54 (P = 0.12)								
1.1.2 2-6h								
Calmet 2004	2.9	2.2	20	2.4	2.5	20	11.6%	0.50 [-0.96 , 1.96]
De Andres 1998	1.4	2.2	27	3.5	2.4	25	13.9%	-2.10 [-3.35 , -0.85]
Kanbak 1997	3.2	2.2	11	4.6	2.1	11	8.7%	-1.40 [-3.20 , 0.40]
Likar 1999	2	1.8	24	2.3	1.9	22	16.5%	-0.30 [-1.37 , 0.77]
Muller 2001	3.5	1.1	15	3.8	2.1	15	14.7%	-0.30 [-1.50 , 0.90]
Richardson 1997	1.5	2	36	1.7	2	32	18.5%	-0.20 [-1.15 , 0.75]
Wrench 1996	1.8	1.7	19	1.7	1.8	20	16.1%	0.10 [-1.00 , 1.20]
Subtotal (95% CI)			**152**			**145**	**100.0%**	**-0.47 [-1.09 , 0.14]**
Heterogeneity: Tau² = 0.30; Chi² = 10.71, df = 6 (P = 0.10); I² = 44%								
Test for overall effect: Z = 1.50 (P = 0.13)								
1.1.3 6-30h								
Calmet 2004	1.5	1.7	20	2.4	2.3	20	14.0%	-0.90 [-2.15 , 0.35]
De Andres 1998	1.1	2.2	27	4.6	2.6	25	13.6%	-3.50 [-4.81 , -2.19]
Kanbak 1997	2.5	2.3	11	3.4	2.1	11	10.8%	-0.90 [-2.74 , 0.94]
Likar 1999	1	1.5	24	0.8	0.9	22	16.9%	0.20 [-0.51 , 0.91]
Muller 2001	4.1	1.9	15	4.1	1.4	15	14.3%	0.00 [-1.19 , 1.19]
Richardson 1997	0.84	1.1	36	2.2	2.3	32	16.1%	-1.36 [-2.23 , -0.49]
Wrench 1996	2	1.9	19	2	1.9	20	14.3%	0.00 [-1.19 , 1.19]
Subtotal (95% CI)			**152**			**145**	**100.0%**	**-0.88 [-1.81 , 0.04]**
Heterogeneity: Tau² = 1.17; Chi² = 28.61, df = 6 (P < 0.0001); I² = 79%								
Test for overall effect: Z = 1.88 (P = 0.06)								
Test for subgroup differences: Chi² = 0.59, df = 2 (P = 0.75), I² = 0%								



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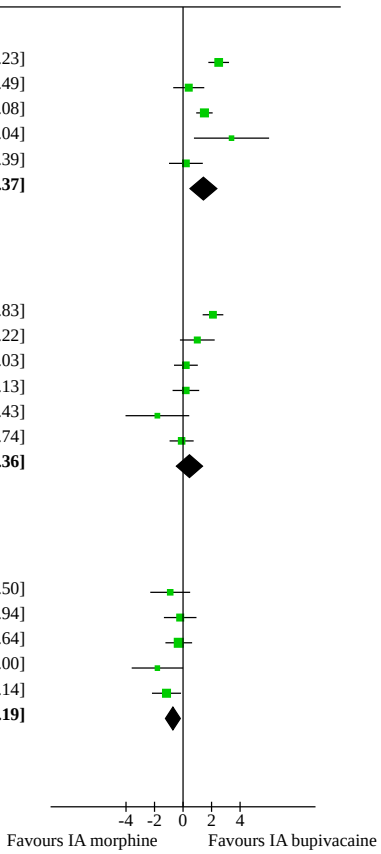
Analysis 1.2. Comparison 1: Pain intensity VAS score, Outcome 2: 1mg morphine vs bupivacaine

Study or Subgroup	morphine Mean	morphine SD	morphine Total	bupivacaine Mean	bupivacaine SD	bupivacaine Total	Weight	Mean Difference IV, Random, 95% CI
1.2.1 0-2h								
Allen 1993	3.9	1.8	30	1.4	0.93	30	24.6%	2.50 [1.77 , 3.23]
Calmet 2004	2.2	1.9	20	1.8	1.6	20	20.8%	0.40 [-0.69 , 1.49]
De Andres 1998	2.2	1.4	27	0.7	0.59	25	26.0%	1.50 [0.92 , 2.08]
Khoury 1992	5.6	3.3	11	2.2	3	11	8.8%	3.40 [0.76 , 6.04]
Richardson 1997	2.5	2.6	36	2.3	2.6	38	19.8%	0.20 [-0.99 , 1.39]
Subtotal (95% CI)			**124**			**124**	**100.0%**	**1.43 [0.49 , 2.37]**
Heterogeneity: Tau² = 0.80; Chi² = 17.79, df = 4 (P = 0.001); I² = 78%								
Test for overall effect: Z = 2.98 (P = 0.003)								
1.2.2 2-6h								
Allen 1993	3.8	1.8	30	1.7	0.93	30	19.4%	2.10 [1.37 , 2.83]
Calmet 2004	2.9	2.2	20	1.9	1.7	20	15.9%	1.00 [-0.22 , 2.22]
De Andres 1998	1.4	2.2	27	1.2	0.23	25	18.7%	0.20 [-0.63 , 1.03]
Elkousy 2013	3	2.3	47	2.8	2	35	18.0%	0.20 [-0.73 , 1.13]
Khoury 1992	1.4	2.3	11	3.2	3	11	9.5%	-1.80 [-4.03 , 0.43]
Richardson 1997	1.5	1.9	36	1.6	1.8	38	18.6%	-0.10 [-0.94 , 0.74]
Subtotal (95% CI)			**171**			**159**	**100.0%**	**0.45 [-0.47 , 1.36]**
Heterogeneity: Tau² = 0.99; Chi² = 25.30, df = 5 (P = 0.0001); I² = 80%								
Test for overall effect: Z = 0.96 (P = 0.34)								
1.2.3 6-30h								
Calmet 2004	1.5	1.7	20	2.4	2.7	20	13.9%	-0.90 [-2.30 , 0.50]
De Andres 1998	1.1	2.2	27	1.3	2	25	20.8%	-0.20 [-1.34 , 0.94]
Elkousy 2013	1.5	1.9	47	1.8	2.3	35	30.9%	-0.30 [-1.24 , 0.64]
Khoury 1992	1.9	2	11	3.7	2.3	11	8.3%	-1.80 [-3.60 , 0.00]
Richardson 1997	0.84	1.1	36	2	3	38	26.1%	-1.16 [-2.18 , -0.14]
Subtotal (95% CI)			**141**			**129**	**100.0%**	**-0.71 [-1.23 , -0.19]**
Heterogeneity: Tau² = 0.00; Chi² = 3.73, df = 4 (P = 0.44); I² = 0%								
Test for overall effect: Z = 2.68 (P = 0.007)								



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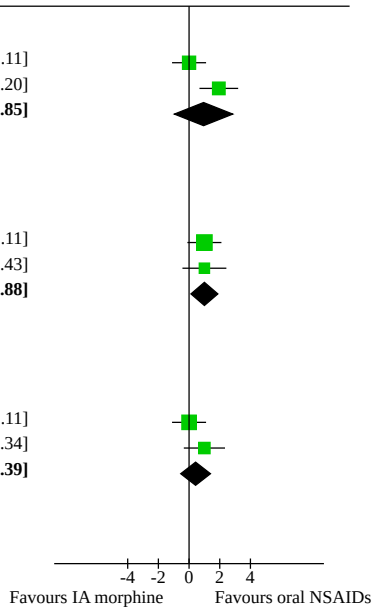
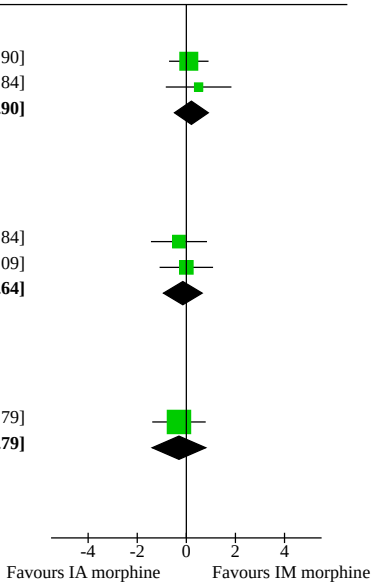
Analysis 1.3. Comparison 1: Pain intensity VAS score, Outcome 3: morphine vs NSAIDs

Study or Subgroup	morphine Mean	morphine SD	morphine Total	NSAIDS Mean	NSAIDS SD	NSAIDS Total	Weight	Mean Difference IV, Random, 95% CI
1.3.1 0-2h								
Alagol 2005	1	2	25	1	2	25	51.2%	0.00 [-1.11 , 1.11]
Guler 2002	8.14	1.95	15	6.2	1.55	15	48.8%	1.94 [0.68 , 3.20]
Subtotal (95% CI)			**40**			**40**	**100.0%**	**0.95 [-0.95 , 2.85]**
Heterogeneity: Tau² = 1.51; Chi² = 5.13, df = 1 (P = 0.02); I² = 81%								
Test for overall effect: Z = 0.98 (P = 0.33)								
1.3.2 2-6h								
Alagol 2005	3	2	25	2	2	25	62.5%	1.00 [-0.11 , 2.11]
Guler 2002	3.7	2	15	2.7	2	15	37.5%	1.00 [-0.43 , 2.43]
Subtotal (95% CI)			**40**			**40**	**100.0%**	**1.00 [0.12 , 1.88]**
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 1.00); I² = 0%								
Test for overall effect: Z = 2.24 (P = 0.03)								
1.3.3 6-30h								
Alagol 2005	2	2	25	2	2	25	57.4%	0.00 [-1.11 , 1.11]
Guler 2002	2.3	1.85	15	1.3	1.9	15	42.6%	1.00 [-0.34 , 2.34]
Subtotal (95% CI)			**40**			**40**	**100.0%**	**0.43 [-0.54 , 1.39]**
Heterogeneity: Tau² = 0.11; Chi² = 1.27, df = 1 (P = 0.26); I² = 21%								
Test for overall effect: Z = 0.86 (P = 0.39)								
Test for subgroup differences: Chi² = 0.78, df = 2 (P = 0.68), I² = 0%								



Analysis 1.4. Comparison 1: Pain intensity VAS score, Outcome 4: IA morphine vs IM morphine

Study or Subgroup	IA morphine Mean	IA morphine SD	IA morphine Total	IM morphine Mean	IM morphine SD	IM morphine Total	Weight	Mean Difference IV, Fixed, 95% CI
1.4.1 0-2h								
Dierking 1994	1.5	1	18	1.4	1.3	15	73.4%	0.10 [-0.70 , 0.90]
Raj 2004	3	1.8	20	2.5	2.4	19	26.6%	0.50 [-0.84 , 1.84]
Subtotal (95% CI)			**38**			**34**	**100.0%**	**0.21 [-0.48 , 0.90]**
Heterogeneity: Chi² = 0.25, df = 1 (P = 0.62); I² = 0%								
Test for overall effect: Z = 0.59 (P = 0.56)								
1.4.2 2-6h								
Dierking 1994	0.7	0.9	18	1	2.1	15	47.6%	-0.30 [-1.44 , 0.84]
Raj 2004	1.7	1.4	20	1.7	2	19	52.4%	0.00 [-1.09 , 1.09]
Subtotal (95% CI)			**38**			**34**	**100.0%**	**-0.14 [-0.93 , 0.64]**
Heterogeneity: Chi² = 0.14, df = 1 (P = 0.71); I² = 0%								
Test for overall effect: Z = 0.36 (P = 0.72)								
1.4.3 6-30h								
Raj 2004	1.2	1.4	20	1.5	2	19	100.0%	-0.30 [-1.39 , 0.79]
Subtotal (95% CI)			**20**			**19**	**100.0%**	**-0.30 [-1.39 , 0.79]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.54 (P = 0.59)								
Test for subgroup differences: Chi² = 0.76, df = 2 (P = 0.68), I² = 0%								



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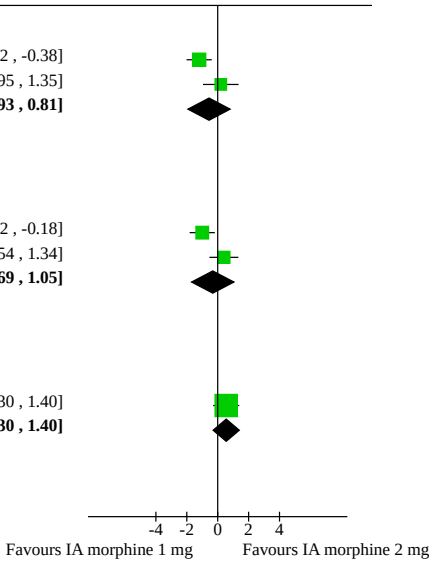
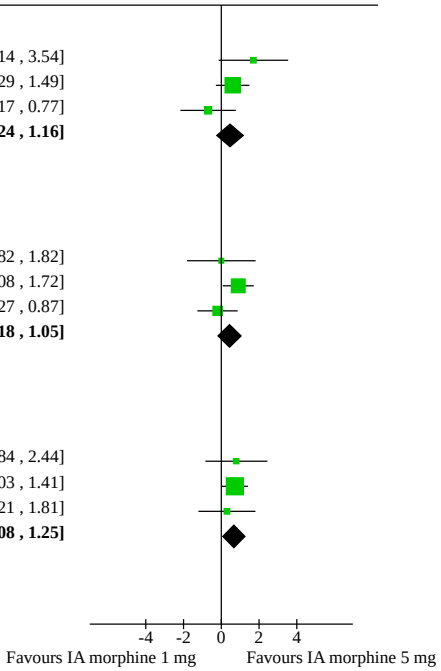
Analysis 1.5. Comparison 1: Pain intensity VAS score, Outcome 5: 1mg morphine vs 2mg morphine

Study or Subgroup	1mg morphine Mean	SD	Total	2mg morphine Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.5.1 0-2h								
Allen 1993	2.7	1.4	30	3.9	1.8	30	54.4%	-1.20 [-2.02 , -0.38]
Likar 1999	2	1.3	24	1.8	2.4	21	45.6%	0.20 [-0.95 , 1.35]
Subtotal (95% CI)			**54**			**51**	**100.0%**	**-0.56 [-1.93 , 0.81]**
Heterogeneity: Tau² = 0.72; Chi² = 3.78, df = 1 (P = 0.05); I² = 74%								
Test for overall effect: Z = 0.80 (P = 0.42)								
1.5.2 2-6h								
Allen 1993	2.8	1.4	30	3.8	1.8	30	51.4%	-1.00 [-1.82 , -0.18]
Likar 1999	2	1.8	24	1.6	1.4	21	48.6%	0.40 [-0.54 , 1.34]
Subtotal (95% CI)			**54**			**51**	**100.0%**	**-0.32 [-1.69 , 1.05]**
Heterogeneity: Tau² = 0.78; Chi² = 4.88, df = 1 (P = 0.03); I² = 80%								
Test for overall effect: Z = 0.46 (P = 0.65)								
1.5.3 6-30h								
Likar 1999	1	1.5	24	0.45	1.4	21	100.0%	0.55 [-0.30 , 1.40]
Subtotal (95% CI)			**24**			**21**	**100.0%**	**0.55 [-0.30 , 1.40]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.27 (P = 0.20)								
Test for subgroup differences: Chi² = 2.34, df = 2 (P = 0.31), I² = 14.4%								



Analysis 1.6. Comparison 1: Pain intensity VAS score, Outcome 6: 1mg morphine vs 4mg/5mg morphine

Study or Subgroup	1mg morphine Mean	SD	Total	5mg morphine Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
1.6.1 0-2h								
Kanbak 1997	5	2	11	3.3	2.6	13	14.5%	1.70 [-0.14 , 3.54]
Likar 1999	2.1	1.3	24	1.5	1.6	19	62.6%	0.60 [-0.29 , 1.49]
Muller 2001	2.8	2.1	15	3.5	2	15	22.9%	-0.70 [-2.17 , 0.77]
Subtotal (95% CI)			**50**			**47**	**100.0%**	**0.46 [-0.24 , 1.16]**
Heterogeneity: Chi² = 4.24, df = 2 (P = 0.12); I² = 53%								
Test for overall effect: Z = 1.29 (P = 0.20)								
1.6.2 2-6h								
Kanbak 1997	3.2	2.7	11	3.2	1.6	13	11.3%	0.00 [-1.82 , 1.82]
Likar 1999	2	1.8	24	1.1	0.87	19	55.8%	0.90 [0.08 , 1.72]
Muller 2001	3.5	1.1	15	3.7	1.8	15	32.9%	-0.20 [-1.27 , 0.87]
Subtotal (95% CI)			**50**			**47**	**100.0%**	**0.44 [-0.18 , 1.05]**
Heterogeneity: Chi² = 2.82, df = 2 (P = 0.24); I² = 29%								
Test for overall effect: Z = 1.40 (P = 0.16)								
1.6.3 6-30h								
Kanbak 1997	2.5	2.3	11	1.7	1.7	13	12.7%	0.80 [-0.84 , 2.44]
Likar 1999	1	1.5	24	0.28	0.76	19	72.2%	0.72 [0.03 , 1.41]
Muller 2001	4.1	1.9	15	3.8	2.3	15	15.1%	0.30 [-1.21 , 1.81]
Subtotal (95% CI)			**50**			**47**	**100.0%**	**0.67 [0.08 , 1.25]**
Heterogeneity: Chi² = 0.27, df = 2 (P = 0.87); I² = 0%								
Test for overall effect: Z = 2.23 (P = 0.03)								
Test for subgroup differences: Chi² = 0.33, df = 2 (P = 0.85), I² = 0%								



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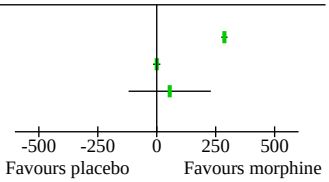
Comparison 2. Analgesia duration

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 morphine vs placebo	3		Mean Difference (IV, Random, 95% CI)	Totals not selected
2.2 morphine vs bupivacaine	3		Mean Difference (IV, Random, 95% CI)	Totals not selected
2.3 morphine vs NSAIDS	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.4 1mg morphine vs 2mg morphine	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.5 1mg morphine vs 5mg morphine	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

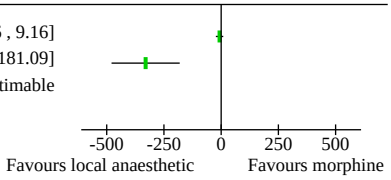
Analysis 2.1. Comparison 2: Analgesia duration, Outcome 1: morphine vs placebo

	morphine			placebo			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Random, 95% CI	IV, Random, 95% CI
Alagol 2005	301	32	25	14	11	25	287.00 [273.74 , 300.26]	
De Andres 1998	126	36	27	126	18	25	0.00 [-15.30 , 15.30]	
Kanbak 1997	280	225	11	225	191	11	55.00 [-119.41 , 229.41]	



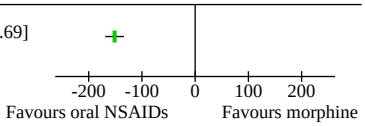
Analysis 2.2. Comparison 2: Analgesia duration, Outcome 2: morphine vs bupivacaine

	morphine			bupivacaine			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Random, 95% CI	IV, Random, 95% CI
Alagol 2005	301	32	25	308	26	25	-7.00 [-23.16 , 9.16]	
Allen 1993	90	174	30	420	378	30	-330.00 [-478.91 , -181.09]	
De Andres 1998	126	36	27	510	0	25	Not estimable	



Analysis 2.3. Comparison 2: Analgesia duration, Outcome 3: morphine vs NSAIDS

	morphine			NSAIDS			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Alagol 2005	300.6	31.5	25	452	32.4	25	-151.40 [-169.11 , -133.69]	



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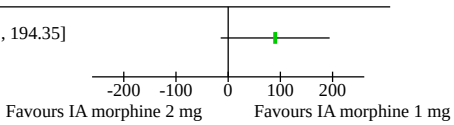
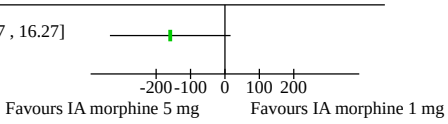
Analysis 2.4. Comparison 2: Analgesia duration, Outcome 4: 1mg morphine vs 2mg morphine

Study or Subgroup	1mg morphine Mean	SD	Total	2mg morphine Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Allen 1993	180	234	30	90	174	30	90.00 [-14.35 , 194.35]



Analysis 2.5. Comparison 2: Analgesia duration, Outcome 5: 1mg morphine vs 5mg morphine

Study or Subgroup	1mg morphine Mean	SD	Total	5mg morphine Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Kanbak 1997	280.4	224.9	11	439.4	210.2	13	-159.00 [-334.27 , 16.27]



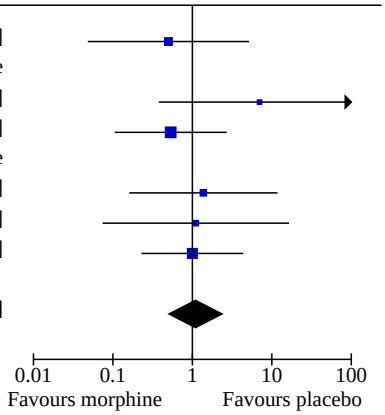
Comparison 3. Adverse events

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 morphine vs placebo	8	314	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.51, 2.36]
3.2 morphine vs bupivacaine	4	210	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.09, 5.17]
3.3 morphine vs NSAIDs	3	120	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.19, 3.04]

Analysis 3.1. Comparison 3: Adverse events, Outcome 1: morphine vs placebo

Study or Subgroup	morphine Events	Total	placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Alagol 2005	1	25	2	25	17.9%	0.50 [0.05 , 5.17]
Calmet 2004	0	20	0	20		Not estimable
Franceschi 2001	3	30	0	30	4.5%	7.00 [0.38 , 129.93]
Guler 2002	2	15	3	12	29.9%	0.53 [0.11 , 2.70]
Kanbak 1997	0	11	0	11		Not estimable
Likar 1999	3	24	1	11	12.3%	1.38 [0.16 , 11.78]
Rosseland 2003a	1	19	1	21	8.5%	1.11 [0.07 , 16.47]
Solheim 2006	3	20	3	20	26.9%	1.00 [0.23 , 4.37]
Total (95% CI)		**164**		**150**	**100.0%**	**1.09 [0.51 , 2.36]**
Total events:	13		10			

Heterogeneity: Chi² = 2.80, df = 5 (P = 0.73); I² = 0%
Test for overall effect: Z = 0.23 (P = 0.82)
Test for subgroup differences: Not applicable



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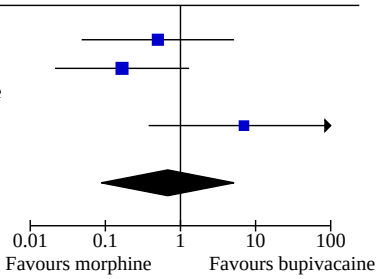
Analysis 3.2. Comparison 3: Adverse events, Outcome 2: morphine vs bupivacaine

Study or Subgroup	morphine Events	Total	bupivacaine Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Alagol 2005	1	25	2	25	34.4%	0.50 [0.05 , 5.17]
Allen 1993	1	30	6	30	38.3%	0.17 [0.02 , 1.30]
Calmet 2004	0	20	0	20		Not estimable
Franceschi 2001	3	30	0	30	27.4%	7.00 [0.38 , 129.93]
Total (95% CI)		**105**		**105**	**100.0%**	**0.68 [0.09 , 5.17]**
Total events:	5		8			

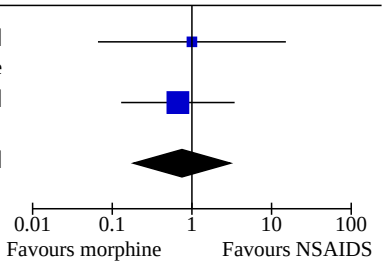
Heterogeneity: Tau² = 1.72; Chi² = 4.27, df = 2 (P = 0.12); I² = 53%
Test for overall effect: Z = 0.38 (P = 0.71)
Test for subgroup differences: Not applicable



Analysis 3.3. Comparison 3: Adverse events, Outcome 3: morphine vs NSAIDs

Study or Subgroup	morphine Events	Total	NSAIDs Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Alagol 2005	1	25	1	25	25.0%	1.00 [0.07 , 15.12]
Calmet 2004	0	20	0	20		Not estimable
Guler 2002	2	15	3	15	75.0%	0.67 [0.13 , 3.44]
Total (95% CI)		**60**		**60**	**100.0%**	**0.75 [0.19 , 3.04]**
Total events:	3		4			

Heterogeneity: Chi² = 0.06, df = 1 (P = 0.80); I² = 0%
Test for overall effect: Z = 0.40 (P = 0.69)
Test for subgroup differences: Not applicable



APPENDICES

Appendix 1. Search strategy for CENTRAL

#1 MESH DESCRIPTOR Analgesics, Opioid EXPLODE ALL TREES

#2 MESH DESCRIPTOR Opioid Peptides EXPLODE ALL TREES

#3 MESH DESCRIPTOR Morphine EXPLODE ALL TREES

#4 ((opiate* or opioid* or endorphin* or morphin*)):TI,AB,KY

#5 MESH DESCRIPTOR Knee Joint EXPLODE ALL TREES

#6 MESH DESCRIPTOR Menisci, Tibial EXPLODE ALL TREES

#7 MESH DESCRIPTOR Arthroscopy EXPLODE ALL TREES

#8 MESH DESCRIPTOR Injections, Intra-Articular EXPLODE ALL TREES

#9 (((inject* or needl*) near10 (joint* or articul* or intra-articular or intraarticular or "intra articular"))):TI,AB,KY

#10 ((arthroscop* or menisect* or (knee* near6 surg*))):TI,AB,KY

#11 #1 OR #2 OR #3 OR #4

#12 #5 OR #6 OR #7 OR #10

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#13 #8 OR #9

#14 #11 AND #12 AND #13

Appendix 2. Search strategy for MEDLINE (via Ovid)

[mp=title, original title, abstract, name of substance word, subject heading word, unique identifier]

1 exp Analgesics, Opioid/

2 exp Opioid Peptides/

3 exp Morphine/

4 (opiate* or opioid* or endorphin* or morphin*).mp.

5 exp Knee Joint/

6 exp Menisci, Tibial/

7 exp Arthroscopy/

8 (arthroscop* or menisect* or (knee* adj6 surg*)).mp.

9 exp Injections, Intra-Articular/

10 ((inject* or needl*) adj10 (joint* or articul* or intra-articular or intraarticular or "intra articular")).mp.

11 1 or 2 or 3 or 4

12 5 or 6 or 7 or 8

13 9 or 10

14 11 and 12 and 13

15 randomized controlled trial.pt.

16 controlled clinical trial.pt.

17 randomized.ab.

18 placebo.ab.

19 drug therapy.fs.

20 randomly.ab.

21 trial.ab.

22 or/15-21

23 exp animals/ not humans.sh.

24 22 not 23

25 14 and 24

Appendix 3. Search strategy for EMBASE

1 exp Narcotic analgesic agent/

2 exp Opiate peptide/

3 exp Morphine/

4 (opiate* or opioid* or endorphin* or morphin*).mp.

5 exp Knee/

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6 exp Knee meniscus/

7 exp Arthroscopy/

8 (arthroscop* or menisect* or (knee* adj6 surg*)).mp.

9 exp Intraarticular drug administration/

10 ((inject* or needl*) adj10 (joint* or articul* or intra-articular or intraarticular or "intra articular")).mp.

11 1 or 2 or 3 or 4

12 5 or 6 or 7 or 8

13 9 or 10

14 11 and 12 and 13

15 random$.tw.

16 factorial$.tw.

17 crossover$.tw.

18 cross over$.tw.

19 cross-over$.tw.

20 placebo$.tw.

21 (doubl$ adj blind$).tw.

22 (singl$ adj blind$).tw.

23 assign$.tw.

24 allocat$.tw.

25 volunteer$.tw.

26 Crossover Procedure/

27 double-blind procedure.tw.

28 Randomized Controlled Trial/

29 Single Blind Procedure/

30 or/15-29

31 (animal/ or nonhuman/) not human/

32 30 not 31

33 14 and 32

WHAT'S NEW

Date	Event	Description
25 January 2021	Review declared as stable	See Published notes.

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HISTORY

Protocol first published: Issue 1, 2011
Review first published: Issue 5, 2016

Date	Event	Description
3 December 2018	Review declared as stable	See Published notes.

CONTRIBUTIONS OF AUTHORS

Draft the protocol	Zui Zou, Xue Yin Shi
Develop a search strategy	Mao Mao An, Zui Zou
Search for trials	Zui Zou, Xiao-Yan Chen
Obtain copies of trials	Xiao-Yan Chen
Select which trials to include	Xue-Yin Shi, Qun Xie, Xue Yin Shi (arbiter)
Extract data from trials	Zui Zou, Qun Xie
Enter data into RevMan	Qun Xie
Carry out the analysis	Qun Xie
Interpret the analysis	Qun Xie
Draft the final review	Xue-Yin Shi, Zui Zou
Update the review	Xue-Yin Shi, Zui Zou
Content expert	Xue-Yin Shi
Methodologist	Mao Mao An
Statistician	Guan-Jian Liu

DECLARATIONS OF INTEREST

Zui Zou: none known.

Mao Mao An: none known.

Qun Xie: none known.

MMA: none known.

Xiao Y Chen: none known.

Hao Zhang: none known.

Guan J Liu: none known.

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Xue Y Shi: none known.

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Internal sources

- National Nature Science Foundation of China, China

  81000525
- Shanghai Chen-guang program, China

  10CG40
- Shanghai Health Bureau, China

  XYQ2011022

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The subgroup analyses of additional analgesics and different types of operation proposed in our protocol were not performed due to the lack of data available to perform subgroup analysis.

We separated the outcomes into primary and secondary. Patient-reported pain intensity and use of supplementary analgesic are listed as primary outcomes. These outcomes can reflect the efficacy of the drug.

Subgroup analysis about different methods of application of morphine (wound/synovial infiltration/intra-articular instillation, etc.) is called IA morphine versus IM morphine. In all the included studies, neither wound nor synovial infiltration was used, and IM morphine was used. So we compared IA morphine with IM morphine in the subgroup analysis.

We considered 'size' and 'selective outcome reporting' as potential sources of bias so we added these two domains in the characteristics of studies table.

Ten out of 20 studies reported time to first request of supplementary analgesics and 17 out of 20 studies reported consumption of rescue medication. However, many studies did not present the exact dosage consumed and the number of different analgesic regimens was large. The data could not be subjected to any statistical analysis as no usable data could be extracted from studies, so we summarised the results of each study.

We added IA morphine versus other opioids to Types of interventions.

NOTES

Assessed for updating in 2018

A restricted search in December 2018 identified one potentially relevant study which is unlikely to change the conclusions (J Clin Diagn Res. 2017 Apr;11(4):UC13-15). Therefore, this review has now been stabilised for two years following discussion with the authors and editors. If appropriate, we will update the review sooner if new evidence likely to change the conclusions is published, or if standards change substantially which necessitate major revisions.

Assessed for updating in 2021

At January 2021 we are not aware of any potentially relevant studies likely to change the conclusions. Therefore, the PaPaS editorial team has stabilised this review which will be reassessed for updating in two years. If appropriate, we will update the review before this date if new evidence likely to change the conclusions is published, or if standards change substantially which necessitate major revisions.

INDEX TERMS

Medical Subject Headings (MeSH)

Analgesia [methods]; Analgesics, Opioid [*administration & dosage]; Anesthetics, Local [administration & dosage]; Anti-Inflammatory Agents, Non-Steroidal [administration & dosage]; Arthroscopy [*adverse effects]; Drug Administration Routes; Injections, Intra-

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Articular; Knee Joint [*surgery]; Morphine [*administration & dosage]; Pain Measurement; Pain, Postoperative [*drug therapy]; Randomized Controlled Trials as Topic; Time Factors

MeSH check words

Humans

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