Local anaesthetics and regional anaesthesia for preventing chronic pain after surgery (Review)

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[Intervention Review]

Local anaesthetics and regional anaesthesia for preventing chronic pain after surgery

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ABSTRACT

Background

Regional anaesthesia may reduce the rate of persistent (chronic) pain after surgery, a frequent and debilitating condition.

Objectives

To compare local anaesthetics and regional anaesthesia versus conventional analgesia for the prevention of persistent pain six or 12 months after surgery.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2012, Issue 4), PubMed (1966 to April 2012), EMBASE (1966 to May 2012) and CINAHL (1966 to May 2012) without any language restriction. We used a combination of free text search and controlled vocabulary search. The results were limited to randomized controlled clinical trials (RCTs). We conducted a handsearch in reference lists of included trials, review articles and conference abstracts.

Selection criteria

We included RCTs comparing local anaesthetics or regional anaesthesia versus conventional analgesia with a pain outcome at six or 12 months after surgery.

Data collection and analysis

Two authors independently assessed trial quality and extracted data, including information on adverse events. We contacted study authors for additional information. Results are presented as pooled odds ratios (OR) with 95% confidence intervals (CI), based on random-effects models (inverse variance method). We grouped studies according to surgical interventions. We employed the Chi^2 test and calculated the I^2 statistic to investigate study heterogeneity.

Main results

We identified 23 RCTs studying local anaesthetics or regional anaesthesia for the prevention of persistent (chronic) pain after surgery. Data from a total of 1090 patients with outcomes at six months and of 441 patients with outcomes at 12 months were presented. No study included children. We pooled data from 250 participants after thoracotomy, with outcomes at six months. Data favoured

regional anaesthesia for the prevention of chronic pain at six months after thoracotomy with an OR of 0.33 (95% CI 0.20 to 0.56). We pooled two studies on paravertebral block for breast cancer surgery; the pooled data of 89 participants with outcomes at five to six months favoured paravertebral block with an OR of 0.37 (95% CI 0.14 to 0.94).The methodological quality of the included studies was intermediate. Adverse effects were not studied systematically and were reported sparsely. Clinical heterogeneity, attrition and sparse outcome data hampered the assessment of effects, especially at 12 months.

Authors' conclusions

Epidural anaesthesia may reduce the risk of developing chronic pain after thoracotomy in about one patient out of every four patients treated. Paravertebral block may reduce the risk of chronic pain after breast cancer surgery in about one out of every five women treated. Our conclusions are significantly weakened by performance bias, shortcomings in allocation concealment, considerable attrition and incomplete outcome data. We caution that our evidence synthesis is based on only a few, small studies. More studies with high methodological quality, addressing various types of surgery and different age groups, including children, are needed.

PLAIN LANGUAGE SUMMARY

Local and regional anaesthesia prevents chronic pain after surgery

Chronic pain that persists long after surgery is frequent. About 10% of mothers complain about chronic pain after caesarean section. After surgery of the lung up to half of the people may continue to experience chronic pain more than six months after surgery. Local anaesthetics (numbing medicine) injected close to the nerves around the time of surgery may reduce the risk of developing chronic pain. This is called local or regional anaesthesia.

We searched the databases (CENTRAL, PubMed, EMBASE and CINAHL) to April 2012. We found 23 randomized controlled trials comparing the use of local or regional anaesthesia after various surgical interventions with conventional pain control regimens. The latter used opioids (like morphine) or non-opioid pain killers (like paracetamol (acetaminophen) or ibuprofen). We presented data from a total of 1090 people with outcomes at five to six months and 441 people with outcomes at 12 months. We pooled the data of 250 people after thoracotomy (lung surgery) and data of 89 people after breast cancer surgery, with outcomes at six months.

The pooled results show that the use of epidural anaesthesia after thoracotomy and paravertebral block after breast cancer surgery may reduce the risk of chronic pain six months after surgery in about one person out of every four to five people treated. The included studies were not however considered to be of high calibre and included only few people. We need more clinical trials to confirm this effect and to test regional anaesthesia for chronic pain after other surgeries.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Should thoracic epidural anaesthesia versus conventional pain control be used to prevent persistent (chronic) pain after open thoracotomy

Patient or population: open thoracotomy[1]
Settings: University Hospital
Intervention: thoracic epidural anaesthesia[2]
Comparison: conventional pain control[3]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Conventional pain control	Thoracic epidural anaesthesia				
Persistent Pain Six Months after Thoracotomy telephone interview six months after surgery Follow-up: mean 6 months[4]	**Study population**[5]		**OR 0.34** (0.19 to 0.6)	250 (3 studies)	⊕⊕⊕◯ **moderate**[6,7,8,9]	
	649 per 1000	**386 per 1000** (260 to 526)				
	Low[5]					
	250 per 1000	**102 per 1000** (60 to 167)				
	Moderate[5]					
	500 per 1000	**254 per 1000** (160 to 375)				
Adverse Effects of Epidural Anaesthesia - not reported	See comment	See comment	Not estimable	-	See comment	

*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; **OR:** Odds ratio;

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] All studies investigated persistent (chronic) pain after open thoracotomy. The results cannot be extended to video-assisted thoracotomy or other (minimal invasive) surgeries of the chest.
[2] All included studies used thoracic epidural anaesthesia. The results cannot be extended to other interventions like paravertebral blocks.
[3] Conventional pain control with opioids and NSAID was the comparator
[4] There was insufficient data at 12 months after surgery for evidence synthesis.
[5] Event rates of persistent pain after thoracotomy are reported between 25% to 65%.
[6] While outcome observers blinding was described, study participants were not blinded; this is acceptable because participant and provider blinding is difficult in regional anaesthesia.
[7] None of the studies performed an intention to treat analysis. Considerable attrition might have lead to bias.
[8] There was no evidence of heterogeneity. The effects estimates were homogenous.
[9] Thoracic epidural anaesthesia may prevent persistent (chronic) pain after open thoracotomy in one out of four patients treated.

BACKGROUND

Description of the condition

Chronic postoperative pain is frequent and sometimes severe, but is often neglected (Kehlet 2006; Perkins 2000). The risk of developing persistent postsurgical pain varies from 5% after minor surgery to 50% for phantom limb pain or postmastectomy pain syndrome (Jung 2003; Perkins 2000). Persistent pain after surgery may be only mild or it may be severely disabling (Kehlet 2006). Even the relatively low risk (about 10%) of developing persistent postcaesarean pain is a major concern due to the frequency of caesarean sections (Sng 2009). Most clinical studies focus on acute postoperative pain, and few address the preventive effects of regional anaesthesia on persistent (chronic) postsurgical pain (MacRae 2001; MacRae 2008). Recent reviews deplored the poor quality of available studies and documented the high event rate after a variety of surgical interventions, from hernia repair to breast surgery (MacRae 2001; MacRae 2008). Our review focuses on the ability of local anaesthetics or regional anaesthesia to reduce the risk of persistent pain after surgery.

Pain pathways, and hence pain perception, can be modulated, sensitized and permanently altered (Woolf 2000). Persistent pain, postoperative hyperalgesia and allodynia (Kehlet 2006) after surgery are the consequence of neuronal plasticity, that is permanent synaptic neuronal changes in the peripheral and central nervous system in response to tissue trauma and nerve injury; where hyperalgesia refers to pain felt more intensely and allodynia describes a painful sensation after a stimulus that normally is not perceived as pain (Wilder-Smith 2006).

Description of the intervention

In regional anaesthesia, local anaesthetics are applied locally to interrupt the conduction of pain impulses from the site of injury to the central nervous system. This may prevent the sensitization described above. Epidural and spinal anaesthesia act at the nerve roots while nerve blocks, plexus anaesthesia and wound infiltration inhibit peripheral nerves. By blocking sympathetic nerves, local anaesthetics may also have desirable effects on bowel motility or unwanted effects on blood pressure. Systemically (for example intravenously) administered local anaesthetics might also exert beneficial effects including preventing chronic pain, hyperalgesia and allodynia (Duarte 2005; Herroeder 2007; Lavand'homme 2005; Strichartz 2008; Vigneault 2011). We have focused our review on local anaesthetics used with or without opioids or other adjuvants (Kissin 1996) for regional anaesthesia.

The local and regional anaesthesia techniques described above are an alternative to conventional pain control (Appendix 1). Opioids like morphine and non-steroidal anti-inflammatory drugs (NSAIDs) such as acetaminophen and ibuprofen are the most frequently used conventional pain killers. They are administered systemically and, therefore, often cause systemic side effects that limit their use, like the nausea and constipation caused by opioids (Appendix 1).

How the intervention might work

We hypothesize that preventing pain transmission using local or regional anaesthesia during or soon after surgery, or both, reduces the risk of persistent postoperative pain (Woolf 1993). Local anaesthetics applied close to the nerves will block pain perception and prevent the central sensitization in the spinal cord that leads to hyperalgesia and chronic pain (Kehlet 2006) (see: Description of the condition). However, systemic toxicity of local anaesthetics is well described (Brown 1995), either as a side effect after absorption or when given intravenously (Herroeder 2007; Strichartz 2008).

Our review focuses on preventive analgesia. We define preventive analgesia as antinociception with local anaesthetics or regional anaesthesia to reduce the risk of chronic pain after surgery regardless of the timing of the intervention in relation to surgery (Kissin 2000). We did not study if local anaesthetics or regional anaesthesia are more effective if applied before, during or after surgery (Lavand'homme 2011).

Why it is important to do this review

Persistent (chronic) pain after surgery is frequent and difficult to treat (Kehlet 2006). Hence prevention would be paramount. It remains unclear if regional anaesthesia can reduce the event rate of this unwanted outcome. Clinical trials report conflicting results. For example, epidural anaesthesia may reduce the risk of persistent pain after thoracotomy (Ju 2008; Lu 2008; Senturk 2002) but these effects have not been consistently reproduced (Ochroch 2006). No meta-analysis is presently available on the effect of local or regional anaesthesia on chronic pain six to 12 months after surgery. A systematic review by Ong focused mostly on immediate postoperative pain control and the timing of regional anaesthesia (Ong 2005); and some have questioned his results and methods (Møiniche 2002). Existing narrative reviews of regional anaesthesia for chronic pain after surgery have not attempted evidence synthesis (MacRae 2001; MacRae 2008).

OBJECTIVES

We compared the effectiveness of local anaesthetics and regional anaesthesia versus conventional analgesia for the prevention of pain six or 12 months after surgery.

METHODS

Criteria for considering studies for this review

Types of studies

We included studies with a randomized controlled study design. We also included single-blinded trials because regional anaesthesia causes numbness of the affected body part and, therefore, neither patient nor anaesthesia provider can be reliably blinded to the intervention. However, blinding of the outcome observer was a prerequisite for inclusion.

Types of participants

We included studies in adults and children undergoing elective surgical procedures, encompassing general, thoracic, abdominal, orthopaedic, vascular, gynaecological and other surgery. This includes the main groups of surgery with a high event rate of persistent pain after surgery, that is breast surgery, hernia repair, limb amputation and thoracotomy.

Types of interventions

We included studies comparing local anaesthetics or regional anaesthesia versus conventional pain control (Appendix 1).

Interventions

We included studies comparing local anaesthetics and regional anaesthesia versus conventional pain control.
The inclusion criteria for the intervention group were as follows.
Studies administering local anaesthetics or regional anaesthesia, including:

- studies that employed local anaesthetics or regional anaesthesia for any length of time during the perioperative period;
- studies which employed local anaesthetics by any route (Appendix 1);
- studies which may also have employed adjuvants or opioids, either locally or systemically, in any one group.

The exclusion criteria for the interventions group were:

- studies that only compared different regional anaesthesia techniques or varying dose regimens of local anaesthetics during the same perioperative time span;
- studies using local anaesthetics for other than anaesthetic or analgesic purposes (for example as anti-arrhythmics).

The inclusion criteria for the comparator group were:

- studies which used conventional postoperative pain control (Appendix 1).

Types of outcome measures

We studied primary and secondary outcomes as follows.

Primary outcomes

Our primary outcomes was persistent pain (chronic pain) at six or 12 months after surgery.
We studied dichotomous pain outcomes as reported in the studies, that is pain versus no pain; pain or use of pain medication, or both, versus no pain. We also assessed differences in scores based on validated pain scales, such as the visual analogue scale (VAS); the verbal rating score; or the McGill pain questionnaire.

Secondary outcomes

1. Allodynia and hyperalgesia
2. Use of pain medication

Search methods for identification of studies

We performed an electronic search of common databases and handsearched references lists of relevant studies and conference abstracts.

Electronic searches

We searched for studies on local anaesthetics or regional analgesia for the prevention of chronic pain after surgery in the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2012, Issue 4), PubMed (1966 to April 2012), Ovid EMBASE (1982 to May 2012) and CINAHL via EBSCOhost (1980 to May 2012).
We limited the results using the Cochrane highly sensitive search strategy as described in the 2006 edition of the Cochrane handbook (Higgins 2006). We did not impose a language restriction. We combined a free text search with a controlled vocabulary search, covering from the inception of the database to the present. We searched for studies using local or regional anaesthesia for painful postsurgical conditions with an outcome follow-up of weeks or months. Our MEDLINE, CINAHL, EMBASE and CENTRAL search terms are reproduced in the appendices (see: Appendix 2; Appendix 3; Appendix 4; Appendix 5).

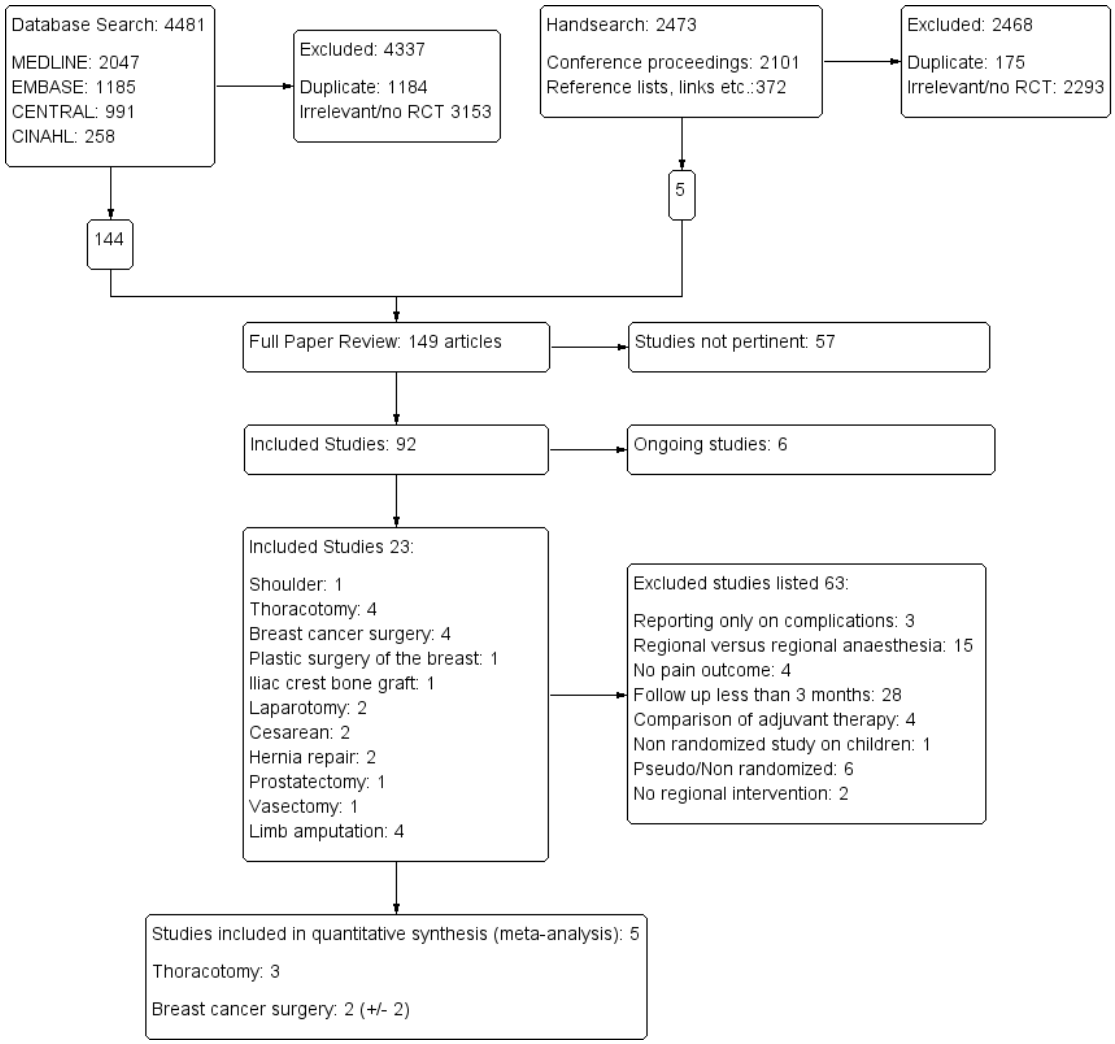
Searching other resources

We conducted a handsearch of the reference lists of included trials, review articles and other identified relevant studies for additional citations and in the conference abstracts of the International Anesthesia Research Society (IARS) and the European Society of Regional Anaesthesia (ESRA) for 2005 through to 2007. We followed links for related articles in Pubmed 2010.

Data collection and analysis

We present a diagram illustrating the process of the searches and selection and we followed the recommendations of the QUORUM and PRISMA statements (Moher 1999; Moher 2010) (Figure 1).

Figure 1. Study flow diagram



Selection of studies

The review authors (MHA and DAA) screened the citations and abstracts of all publications obtained by the search strategies. To avoid location bias, we went to great length to obtain all articles detected by our search through interlibrary loans. For trials that appeared to be eligible randomized controlled trials (RCTs), we obtained and inspected the full articles to assess their relevance based on the preplanned criteria for inclusion. We noted the reasons for study exclusion and inserted them into the table (see: Characteristics of excluded studies).

Data extraction and management

We developed a standard data collection form based on a template provided by the Cochrane Anaesthesia Review Group (CARG) (Appendix 6). We recorded details of trial design, participant characteristics, interventions and outcome measures. We performed a pilot run and revised our data sheet accordingly (Appendix 6). Data were extracted independently by two authors (MHA and DAA). These two authors (MHA and DAA) checked and entered the data into the Cochrane Review Manager (RevMan 5.1) computer software.

We extracted the following primary outcome data.

1) Pain at six and at 12 months.

Where dichotomous data on pain were not reported in the study we attempted to obtain these from the authors. If unavailable, continuous measures were used.

2) Pain score at six and 12 months.

The following secondary outcomes were extracted, where provided: allodynia and hyperalgesia, use of pain medication.

We also extracted the following data: exclusion criteria, comorbidity, regional anaesthesia technique and local anaesthetic used, quality assurance of the intervention, quality of pain control, assessment of hyperalgesia and allodynia, use of adjuvants, and surgery performed. We extracted data on adverse effects and attrition.

Assessment of risk of bias in included studies

Two review authors (MHA and DAA) independently evaluated each report meeting the inclusion criteria. We contacted authors for missing information regarding their methods. We graded study quality in a table of risk of bias on the basis of a checklist of design components. This comprised randomization, concealed allocation, observer blinding, and intention-to-treat analysis. We achieved consensus by informal discussion. We summarized the adequacy in each category as 'no', 'uncertain', or 'yes' (Higgins 2011).

In regional anaesthesia interventions, blinding of patients and anaesthesia providers can be difficult and hence this criterion received less weight in the evaluation of performance bias, but not with regard to detection bias. We listed excluded studies with detailed reason (see: Characteristics of excluded studies).

If the randomization and allocation process was open to significant bias, for example pseudo-randomization, we did not include the study data in the data analysis.

Measures of treatment effect

As the summary statistic for our dichotomous primary outcome, we chose the odds ratio (OR). We reported the ORs with 95% confidence intervals (CI). We calculated the number needed to treat for the subgroups of thoracotomy and breast cancer surgery (Cook 1995). Risk ratios and ORs are equally accepted measures of treatment effect (Higgins 2011). The planned integration of dichotomous outcomes with continuous outcomes implied the use of ORs (see: Data synthesis). After this integration turned out to be of marginal importance for our analysis, we decided to stick to our protocol to eliminate any reasonable doubt about a postanalysis decision that might inappropriately influence our results.

For the continuous pain scales we calculated standardized mean differences (SMD) between groups.

Dealing with missing data

We checked with the study authors for any missing information and reported data inconsistencies in the table of included studies. Where data could not be obtained, we specified this (see: Characteristics of included studies).

Assessment of heterogeneity

We grouped studies in subgroups based on surgical interventions. Depending on the surgery, chronic postsurgical pain has a different natural history (MacRae 2008). We feel these differences argue against pooling or comparing studies across surgical disciplines (Higgins 2011). We investigated study heterogeneity at the subgroup level using a Chi^2 test and calculation of the I^2 statistic (Higgins 2002). We followed the thresholds suggested in the *Cochrane Handbook for Systematic Reviews of Interventions* for the interpretation of I^2 (Higgins 2011).

Assessment of reporting biases

We contacted authors to request missing data. We countered time lag bias by repeating our search just prior to submission of our work. To prevent language bias, we did not impose a language restriction.

We considered an examination of publication bias using graphical and statistical tests (funnel plot, Egger's test).

Data synthesis

We did not pool the data across different surgical disciplines. Instead, we grouped studies in broad surgical categories (thoracotomy, limb amputation, breast cancer surgery, laparotomy and other) based on the different natural history of chronic pain after each surgery.

We used the inverse-variance approach, adjusting study weights based on the extent of variation, or heterogeneity, among the varying intervention effects (Higgins 2011). By choosing the more conservative random-effects model, CIs for the average intervention effect will be wider; this accounts for any potential between study heterogeneity and results in a more cautious estimate of any treatment effect (DerSimonian 1986).

We pooled treatment effects following the random-effects meta-analysis using the statistical software RevMan 5.1 provided by The Cochrane Collaboration, as detailed in Chapter 8.6 of the

Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011). Following the process of GRADE assessment (GRADE Working Group 2004), we generated summary of findings tables using the computer software GRADEpro provided by The Cochrane Collaboration, as detailed in Chapter 11.5 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Pooling groups with different timing of regional anaesthesia interventions

For studies with several groups using local or regional anaesthesia albeit with different timing, we pooled all groups employing local or regional anaesthesia and compared them against the comparator. If the first group received a regional anaesthesia intervention before incision and the second group received it after incision, we pooled the (first and second) groups employing local anaesthetics against the (third) control groups not employing any local anaesthetics (that is using only conventional pain control instead).
If follow-up varied only by weeks to one month, we pooled the results, for example data at 24 weeks or at five months with data at six months.

Subgroup analysis and investigation of heterogeneity

Where there were enough studies in one group, we calculated the I^2 statistic. We followed the thresholds suggested in the *Cochrane Handbook for Systematic Reviews of Interventions* for the interpretation of I^2 (Higgins 2011).
Studies employing adjuvant therapy, using different regional anaesthesia modalities and studies providing continuous postoperative regional anaesthesia were investigated as a subgroup.

Sensitivity analysis

We tested the sensitivity of our results to our model assumptions and calculated the effect estimates for our pooled subgroups (breast cancer surgery and thoracotomy) for the random effects model versus the fixed effect model).

RESULTS

Description of studies

Results of the search

The original searches were undertaken in February and March 2008 and rerun between February and August 2010 and again between April and May 2012. The search and selection process is illustrated in a flow sheet (Figure 1).

Electronic search

The electronic search yielded a total of 4481 references matching the predefined search parameters, 2047 in MEDLINE, 1185 in EMBASE, 991 in CENTRAL, 258 in CINAHL; among them were 1184 duplicates. The review authors (MHA and DAA) screened these and excluded 4337 references as irrelevant or not RCTs.

Handsearch

In our handsearch of the conference proceedings, we looked at 2101 references. We found 372 references in the reference lists of included studies or review articles, or by following links in PubMed and Google to other relevant studies. This resulted in a total of 2473 references; 175 were duplicates and 2293 were excluded as irrelevant or not RCTs.

Unpublished data

In spite of the great efforts to avoid publication bias, we were not able to include any unpublished data. We identified one unpublished study, but the follow-up was at 18 months (Katz 1996). We had defined our outcomes at six and 12 months and therefore could not include his data.

Selection process

One review author (MHA) obtained full text copies of 144 articles for further assessment (see: Figure 1). We (MHA and DAA) selected 23 studies for inclusion in this review (see: Characteristics of included studies). We found six ongoing trials for assessment upon completion (Albi-Feldzer 2007; Bollag 2009; Honigmann 2007; Offner 2007; Sessler 2009; Wylde 2011).

Data extraction

One study report was only available as a conference abstract. We could not identify any follow-up report and obtained no additional data (Katsuly-Liapis1996). The review authors were able to resolve all disagreements with regard to data extraction, study inclusion and quality assessment by informal discussion.

Incomplete and raw data

In spite of contacting authors, we were unable to obtain appropriate or adequate data for six studies (Bain 2001; Burney 2004; Haythornthwaite 1998; Pinzur 1996).

Included studies

We identified 23 RCTs studying regional anaesthesia or local anaesthetics for the prevention of chronic pain after surgery (see: Characteristics of included studies). The surgical operations, type of anaesthesia, timing of intervention, adjuvant therapy and outcomes of the included studies are summarized in an additional table for quick orientation (Appendix 7). Seven studies reported their results in several published manuscripts (Haythornthwaite 1998; Kairaluoma 2006, Katz 1996; Katz 2004; Singh 2007). When two manuscripts were published by the same authors and reported the same participant numbers, we judged them to be reporting on just one and the same trial; we used this data set only once. We reviewed in full or included studies reported in many languages, including Danish (Bach 1988), Mandarin (Lu 2008), Japanese (Hirakawa 1996), German (Weihrauch 2005), French (Baudry 2008; Mounir 2010), Spanish (Ibarra 2011) and English.

Descriptive characteristics of participants

We pooled the data of 250 participants after thoracotomy and of 89 women after breast cancer surgery with outcomes at six months. A breakdown by surgery is provided in Appendix 8. Only adults (> 18 years) were studied; the youngest population had a mean age in the experimental group of 26.2 years ± a standard deviation of 5.2 years (Shahin 2010).

Patient characteristics

Reflecting the diversity of surgical interventions, the patients' age, sex and comorbidities varied widely and were sparsely reported. Breast surgery studies included only female participants. Studies on limb amputation included predominantly male patients.

Types of surgery

We listed the surgical interventions studied (shoulder surgery, thoracotomy, limb amputation, breast cancer surgery, cosmetic breast surgery, laparotomy, iliac crest bone graft, inguinal hernia repair, caesarean section, prostatectomy and vasectomy) in a table (Appendix 7). We grouped studies in broad categories (thoracotomy, limb amputation, breast surgery, laparotomy and other) with similar characteristics. We reported breast cancer surgery (Baudry 2008; Fassoulaki 2005; Ibarra 2011; Kairaluoma 2006) and cosmetic breast surgery (Bell 2001) in the same subgroup, but pooled them separately.

Characteristics of regional anaesthesia interventions

Regional anaesthesia modalities and timing of perioperative blockade

Epidural anaesthesia was used in all thoracotomy studies (Ju 2008; Lu 2008; Senturk 2002) and paravertebral block was used in two studies on breast cancer surgery (Ibarra 2011; Kairaluoma 2006). For other surgical interventions, studies investigated a variety of regional anaesthesia techniques (Appendix 7):

- spinal anaesthesia (Burney 2004);
- epidural anaesthesia (Haythornthwaite 1998; Ju 2008; Karanikolas 2006; Katsuly-Liapis1996; Katz 2004; Lavand'homme 2005; Lu 2008; Senturk 2002);
- plexus block (Bain 2001);
- nerve block and nerve sheath irrigation (Pinzur 1996; Reuben 2006);
- vas deferens injection (Paxton 1995);
- topical application, local infiltration and wound or situs irrigation (Bell 2001; Baudry 2008; Fassoulaki 2005; Lavand'homme 2007; Shahin 2010; Singh 2007).

Intravenous local anaesthetics were used as control in one study (Lavand'homme 2005). Dermal patches, Bier block, ultra long-acting or slow release local anaesthetic compounds were not studied.

Seven studies compared single shot interventions (Baudry 2008; Bell 2001; Burney 2004; Ibarra 2011; Kairaluoma 2006; Katz 2004; Reuben 2006) whereas eight studies compared comprehensive perioperative regional anaesthesia (Fassoulaki 2005; Karanikolas 2006, Katsuly-Liapis1996; Lavand'homme 2005; Lavand'homme 2007; Lu 2008; Pinzur 1996; Singh 2007) to conventional pain control. Two studies tested the hypothesis that blocking ischaemic limb pain prior to amputation prevents the central sensitization that might otherwise lead to persistent pain afterwards (Karanikolas 2006; Katsuly-Liapis1996). The latter comparison was not planned in our protocol and hence these data are not presented.

Primary outcomes

As a prerequisite for inclusion, studies employed an instrument to subjectively measure patient discomfort (Appendix 7). The study authors primarily used a dichotomous outcome, that is presence or absence of (phantom) pain. Several continuous pain scales were also used (verbal rating scale (VRS), numeric rating scale (NRS), VAS). Three studies did not record pain as a dichotomous outcome but rather with continuous pain scales (Bain 2001; Burney 2004; Kairaluoma 2006). Only five studies (Burney 2004; Karanikolas 2006; Katz 2004; Lavand'homme 2005; Pinzur 1996) reported continuous complex outcome instruments, like the McGill questionnaire or the SF-36, which are recommended in consensus statements for the assessment of chronic pain (Turk 2006).

Duration of follow-up

A minimum of five to six months follow-up was required for inclusion. Most studies focused on, and most patient data were collected at, six months follow-up (Appendix 7).

Secondary outcomes

Allodynia and hyperalgesia and other outcome measures

Three studies investigated allodynia and hyperalgesia (Bell 2001; Haythornthwaite 1998; Ju 2008; Lavand'homme 2005). The heterogeneity of surgical interventions precluded any evidence synthesis. Seven studies used other (additional) outcome measures, like overall satisfaction, McGill questionnaire, SF-36 , "interference with life", and orthopaedic functional score mental health inventory (Bain 2001; Burney 2004; Karanikolas 2006; Katz 2004; Lavand'homme 2005; Pinzur 1996; Singh 2007).

Reporting of adverse effects

Most reporting on adverse effects was sparse, sporadic and anecdotal, rather than prospective and systematic. Two RCTs investigated the risk of parturients developing backache after epidural anaesthesia during labour as primary outcome (Howell 2001; Loughnan 2002) but did not meet the inclusion criteria of the main analysis.

Risk factors and pre-existing pain

The included studies did not elicit or compare the known risk factors for the development of persistent (chronic) between the experimental and control groups. We are therefore unable to comment on to what degree a difference between the groups may have introduced bias (Fassoulaki 2008). As patients who present for thoracotomy and breast cancer are usually pain free, pre-existing pain is unlikely to be a confounder for these pooled subgroups (Gottschalk 2006). This may be very different for patient undergoing limb amputation; they may have suffered from prolonged and excruciating ischaemic pain prior to surgery.

Excluded studies

A summary of the excluded studies can be found in the table entitled Characteristics of excluded studies. We excluded 28 studies with a follow-up of less than five months and listed them in (Appendix 9). No study was excluded exclusively for lack of observer blinding. Three studies were excluded for pseudo-randomization (Bach 1988; da Costa 2011; Nikolajsen 1997). One study (da Costa 2011) also failed other inclusion criteria.

Risk of bias in included studies

The risk of bias is detailed in the risk of bias tables (Characteristics of included studies), the risk of bias graph (Figure 2) and is summarized in the methodological quality summary (Figure 3).

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

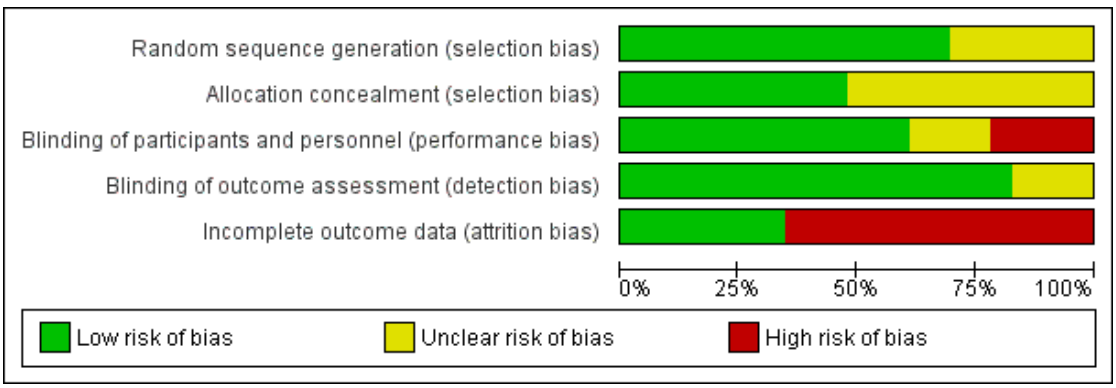
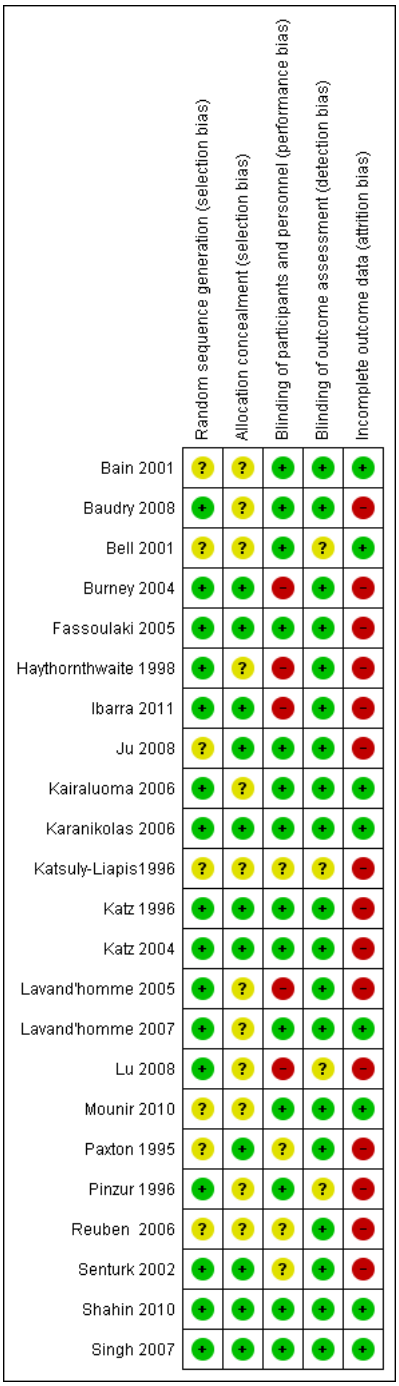


Figure 3. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.



Allocation

Sequence generation

Six studies did not detail the process of sequence generation (Bain 2001; Bell 2001; Haythornthwaite 1998; Ju 2008; Kairaluoma 2006; Katsuly-Liapis1996). Study authors' responses provided additional unpublished information for some studies (Haythornthwaite 1998; Ibarra 2011; Lavand'homme 2007; Senturk 2002). Three studies were excluded for pseudo-randomization (Bach 1988; da Costa 2011; Nikolajsen 1997) (Appendix 10).

Concealment of allocation

Only eight studies described adequate concealment of allocation (Burney 2004; Fassoulaki 2005; Kairaluoma 2006; Karanikolas 2006; Katz 1996; Katz 2004; Paxton 1995; Senturk 2002), using sealed opaque envelopes opened just prior to the regional anaesthesia intervention. Allocation concealment was not detailed in five studies (Bain 2001; Bell 2001; Ju 2008; Katsuly-Liapis1996; Reuben 2006) and was not used on one study (Haythornthwaite 1998).

Blinding

No study was excluded for detection bias, and only outcome assessment blinding was a prerequisite for inclusion. Of all methodological parameters, blinding was best documented and executed (Figure 3). Some authors reported difficulties in keeping the patients and providers blinded due to the need to adjust dosing (Nikolajsen 1997) or the obvious immediate clinical effects of regional anaesthesia, that is numbness of the affected body part and preoperative pain control prior to limb amputation (Bach 1988; Lavand'homme 2005; Senturk 2002). Most patients will note the obvious effects of regional anaesthesia, like motor weakness and sensory loss, and guess their allocation. This made effective blinding of patients and practitioners almost impossible. Many authors detailed efforts to blind study participants, physicians and care givers as well as outcome assessors (Fassoulaki 2005; Kairaluoma 2006; Karanikolas 2006; Katz 1996; Katz 2004; Lavand'homme 2007; Pinzur 1996; Singh 2007). Some reported double blinding but did not provide details (Bell 2001; Paxton 1995; Pinzur 1996). Outcome assessor blinding at least was reported by six studies (Burney 2004; Ju 2008; Lavand'homme 2005; Paxton 1995; Reuben 2006; Senturk 2002), but not described or confirmed in three studies (Bell 2001; Katsuly-Liapis1996; Lu 2008).

Obviously, performance bias may weaken the conclusions of our review. The placebo effect may be particularly strong for pain outcomes and remains unknown for long-term outcomes. Our conclusions are significantly weakened by shortcomings in allocation concealment, considerable attrition and incomplete outcome data. Several studies employed adjuvants (Fassoulaki 2005; Lavand'homme 2005; Reuben 2006) only in the experimental group, potentially introducing bias, but this did not affect the results for the breast cancer surgery subgroup and was not pertinent for the thoracotomy subgroup.

Incomplete outcome data

With the exception of six mostly recent studies (Bain 2001; Kairaluoma 2006; Karanikolas 2006; Mounir 2010; Shahin 2010; Singh 2007), most studies did not adequately address incomplete outcome data. Authors reported high attrition rates, due to loss to follow-up as well as the high mortality of the patient groups studied. This potentially introduces bias. One study excluded randomized patients that the surgeon deemed inoperable intraoperatively, but did not consider an intention-to-treat analysis (Senturk 2002). A formal intention-to-treat analysis was performed only in three studies (Bain 2001; Kairaluoma 2006; Singh 2007).

Selective reporting

We contacted the study authors of 23 included studies for clarification of study methodology or to obtain further unpublished data. We found no contact information for the author of one study (Katsuly-Liapis1996).

Selective reporting was a concern regarding adverse effects. Two studies reporting adverse effects as 'none' did not detail how and which side effects were elicited (Bain 2001; Pinzur 1996). Where reported, information on adverse effects in the included studies was mostly anecdotal and not reported separately by group (Haythornthwaite 1998; Kairaluoma 2006; Katz 2004; Lavand'homme 2007; Paxton 1995; Singh 2007).

Other potential sources of bias

Reporting bias

The small numbers of studies found in each subgroup precluded a formal study of publication bias by graphical analysis or the test proposed by Egger 1997. At least 10 studies should be included in the meta-analysis to make a funnel plot or a Egger test useful, because with fewer studies the power of the tests is insufficient to distinguish chance from real asymmetry (Higgins 2011). In

spite of considerable efforts outcome data were not available for some studies, as detailed in the table Characteristics of included studies; this potentially introduced bias in our review and may reflect publication bias.

Assessment of pre-existing pain and risk factors for chronic postsurgical pain

There are risk factors for the development of chronic pain (Kehlet 2006). The severe ischaemic pain prior to limb amputation may be a predictor for chronic pain after amputation (Karanikolas 2006). Most studies did not assess risk factors or baseline pain.

Effects of interventions

See: **Summary of findings for the main comparison** Should thoracic epidural anaesthesia versus conventional pain control be used to prevent persistent (chronic) pain after open thoracotomy; **Summary of findings 2** Paravertebral block compared to conventional pain control for breast cancer surgery

Regional anaesthesia for the prevention of chronic pain six and 12 months after surgery

We report the pooled data in subgroups according to the surgery performed and the endpoint of the pain outcome (Analysis 1.1; Analysis 1.2). We report the pooled data (Analysis 1.1; Analysis 1.2) separately from the data not pooled (Analysis 2.1; Analysis 2.2) for technical reasons inherent in the review software (RevMan). A precis of the number of included patients grouped according to surgery is in Appendix 8. We presented the data in two summary of findings tables (Summary of findings for the main comparison; Summary of findings 2) for outcomes in the thoracotomy and breast cancer surgery subgroups at six months.

1. Thoracotomy

We pooled three studies on regional anaesthesia for the prevention of chronic post-thoracotomy pain in 250 participants, with dichotomous outcomes at six months after thoracotomy (Analysis 1.1). This resulted in an OR of 0.34 (95% CI 0.19 to 0.60) strongly favouring regional anaesthesia (P = 0.0002) (Ju 2008; Lu 2008; Senturk 2002). However, the included studies were of intermediate methodological quality. Cryotherapy can arguably cause neuropathy (Ju 2008; Mustola 2011) and is clinically different from conventional pain therapy. We did not perform a sensitivity analysis excluding Ju 2008 for chronic pain outcomes six months after thoracotomy because there was no evidence of heterogeneity between the effect measures estimated by the included studies (I^2 estimate of 0%). To exclude the one study employing cryotherapy as the control group (Ju 2008) from our data synthesis on studies with outcomes six months after thoracotomy (Analysis 1.1) would not alter the results. Only one study (Ju 2008), an insufficient number for meta-analysis, reported outcomes at 12 months, but results were inconclusive with an OR of 0.56 (95% CI 0.23 to 1.39).

2. Breast cancer surgery

We pooled two studies on paravertebral block for breast cancer surgery (Ibarra 2011; Kairaluoma 2006), but excluded one study on plastic surgery of the breast (Bell 2001) and one study on breast cancer surgery using a multimodal approach (Fassoulaki 2005). The two pooled studies (Ibarra 2011; Kairaluoma 2006) included 89 participants with outcomes at five or six months, respectively. Their evidence synthesis resulted in an OR of 0.37 (95% CI 0.14 to 0.94) favouring regional anaesthesia (P = 0.04). We considered the populations and pathological mechanisms of persistent pain after breast cancer surgery versus after plastic surgery of the breast as too disparate to pool both in one surgical subgroup (Jung 2003; van Elk 2009). We deemed the multimodal pluripotent regional anaesthesia approach in Fassoulaki 2005 too different from the paravertebral block employed in Ibarra 2011 and Kairaluoma 2006 to justify evidence synthesis in a Cochrane review. Fassoulaki 2005 favoured regional anaesthesia with a similar OR of 0.32 (95% CI 0.09 to 1.17) as Ibarra 2011 and Kairaluoma 2006 (Analysis 2.1). The data on breast cancer surgery are reported (Analysis 1.1; Analysis 1.2). One study on plastic surgery of the breast (Bell 2001) (Analysis 2.1) was insufficient for pooling. Bell 2001 found that infiltration of the breast for bilateral mastopexy increased the risk of developing persistent pain afterwards (OR of 1.80), albeit with a CI that crossed the midline (95% CI 0.21 to 15.41).
Including Fassoulaki 2005 and Bell 2001 in the data synthesis on paravertebral block for breast cancer surgery at six months (Analysis 1.1) would not have altered the ORs much (OR of 0.42) but would have slightly improved our confidence in the risk reduction afforded by employing regional anaesthesia (95% CI 0.21 to 0.86; P = 0.02). There was no indication of heterogeneity when pooling all four (Bell 2001; Fassoulaki 2005; Ibarra 2011; Kairaluoma 2006) or only two studies (Ibarra 2011; Kairaluoma 2006) (I^2 = 0% for both analysis; Analysis 1.1).
At 12 months, the study on postsurgical infiltration for breast cancer surgery (Baudry 2008) did not suggest benefit, with an OR of 2.46 and a CI that crossed the midline (95% CI 0.80 to 7.55), while the study on paravertebral block for breast cancer surgery (Kairaluoma 2006) still favoured regional anaesthesia, with an OR of 0.14 (95% CI 0.03 to 0.72).

3. Limb amputation

We did not pool two studies investigating the effect of epidural anaesthesia on chronic pain (phantom limb pain) after limb amputation at six months (Karanikolas 2006; Katsuly-Liapis1996). Timing of nociception may be much more important for phantom limb pain (Karanikolas 2006). Pooling groups of patients receiv-

ing epidural analgesia during different pre-, intra- and postoperative intervals may be seen as arbitrary and controversial. The small number of participants and the high variance would have resulted in a large CI at six months (Analysis 2.1) and at 12 months, also including Reuben 2006 (Analysis 2.2). Inclusion of two studies on pre-amputation epidural analgesia (Bach 1988; Nikolajsen 1997), excluded for pseudo-randomization as discussed in Appendix 10, would not have altered the results.

4. Laparotomy

We did not pool data from two studies with data at six months on 189 laparotomy patients (Analysis 2.1) as an I^2 estimate of 90% suggested marked heterogeneity. The CI for the study on epidural anaesthesia for laparotomy for major gynaecological surgery (Katz 2004) crossed the midline with an OR of 0.81 (95% CI 0.35 to 1.88) at six months, while the study on thoracic epidural anaesthesia for colonic resection (xiphopubic incision) (Lavand'homme 2005) favoured regional anaesthesia with an OR of 0.04 (95% CI 0.01 to 0.22) at six months and OR of 0.08 (95% CI 0.01 to 0.45) at 12 months (Analysis 2.2).

5. Caesarean section

We report on two studies after caesarean section (Pfannenstiel incision), including 414 participants (Lavand'homme 2007; Shahin 2010), but abstained from pooling the data (Analysis 2.1). One used continuous postoperative wound irrigation (Lavand'homme 2007), the other a single shot instillation of local anaesthetic into the peritoneal pelvis (Shahin 2010). Orthodox evidence synthesis would be controversial in the light of this clinical heterogeneity of regional anaesthesia interventions. Both studies favoured regional anaesthesia, with an OR of 0.37 (95% CI 0.08 to 1.58) (Lavand'homme 2007) and 0.46 (95% CI 0.25 to 0.84) (Shahin 2010).

6. Other surgery

We report on three single studies (Mounir 2010; Paxton 1995; Singh 2007) that all favoured regional anaesthesia at six months (Analysis 2.1) or at 12 months (Analysis 2.2), with an OR of 0.01 (95% CI 0.00 to 0.09) for wound infiltration after iliac hernia repair (Mounir 2010), OR of 0.22 (95% CI 0.03 to 1.42) for continuous local infiltration after Iliac crest bone graft harvesting (Singh 2007), and OR of 0.02 (95% CI 0.00 to 0.33) for single shot local bupivacaine after vasectomy (Paxton 1995).

7. Extended perioperative nociception

When we excluded single shot interventions to test if continuous prolonged antinociception was more effective in reducing the risk of persistent pain after surgery, the results were unchanged because either the same or too few studies were left for meta-analysis in each surgical subgroup.

8. Anaesthesia modality

Within most surgical categories, the regional anaesthesia modality was identical. Only epidural anaesthesia was used for thoracotomy, limb amputation and laparotomy. The remaining categories contained too few studies for pooling in this subgroup analysis.

9. Adjuvant therapy

We examined studies employing adjuvant therapy. Because they investigated surgeries of different body parts (Fassoulaki 2005; Lavand'homme 2005; Reuben 2006), we did not pool the data (Data synthesis). A separate Cochrane review on pharmacological interventions to prevent chronic pain after surgery is underway (Gilron 2010).

Adverse effects

Reporting of adverse effects was mostly anecdotal. Three studies systematically compared adverse effects between the experimental and the control groups, but these studies and the collected data sets were too heterogenous for meta-analysis. Details are listed in Appendix 11.

Sensitvity analysis of model assumptions

The effect estimates of our evidence synthesis were similar for both the thoracotomy and the breast cancer surgery subgroups using a fixed-effect model or random-effects model (data not presented).

ADDITIONAL SUMMARY OF FINDINGS *[Explanation]*

paravertebral block compared to conventional pain control for breast cancer surgery

Patient or population: patients with breast cancer surgery
Settings: University Hospital
Intervention: paravertebral block
Comparison: conventional pain control[1]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Conventional pain control	Paravertebral block				
Persistent Pain Six Months after Breast Cancer Surgery telephone interview six months after surgery Follow-up: 5-6 months[2]	**Study population**		**OR 0.37** (0.14 to 0.94)[3]	89 (2 studies)	⊕⊕⊕◯ **moderate**[4,5,6]	
	432 per 1000	**219 per 1000** (96 to 417)				
	Low					
	200 per 1000	**85 per 1000** (34 to 190)				
	High					
	600 per 1000	**357 per 1000** (174 to 585)				
Adverse effects of paravertebral block for breast cancer surgery	**Study population**		Not estimable	0 (0)	See comment	
	See comment	See comment				
	Moderate					

*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; **OR:** Odds ratio;

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] Conventional pain control with opioids and NSAID was the comparator.
[2] There was insufficient data at twelve months after surgery for evidence synthesis. Data at five months was pooled with data at six months.
[3] Paravertebral block may prevent persistent (chronic) pain after breast cancer surgery in one out of every five patients treated.
[4] Conclusions may be significantly weakened by performance bias, shortcomings in allocation concealment, considerable attrition and incomplete outcome data.
[5] There was no evidence of heterogeneity. The effects estimates were homogenous.The results were robust to sensitivity analysis including studies on plastic surgery of the breast and multimodal regional anaesthesia approaches.
[6] The results are based on only two small studies. Meta-analysis results based on small numbers tend to overestimate the effects.

DISCUSSION

Summary of main results

We included data from 23 randomized trials enrolling a total of 1090 patients. Despite this, the clinical heterogeneity between trials prevented pooling and meta-analysis for many of our outcomes. Pooling data from three trials enrolling a total of 250 patients who had undergone a thoracotomy suggested that those receiving an epidural were less likely to develop chronic pain in the six months after surgery than those receiving either intravenous analgesia or cryo-ablation of intercostal nerves (OR 0.34, NNT 4) (Analysis 1.1 and Summary of findings for the main comparison). The three studies were completed in different institutions in different countries and were remarkably homogenous in their estimates of the effect measure (I^2 = 0%). Only one trial reported this outcome in thoracotomy patients at 12 months and there was no evidence of a statistically significant effect (OR 0.56). Pooling data from two trials enrolling a total of 89 patients who had undergone breast cancer surgery also suggested that those receiving a paravertebral block were less likely to have developed chronic pain at six months than women receiving conventional analgesia (OR 0.37, NNT 5) (Analysis 1.1 and Summary of findings 2). The two studies were completed in different institutions in different countries and were homogenous in their estimates of the effect measure (I^2 = 0%). Including data from studies on plastic surgery of the breast or with alternate regional techniques, or both, neither altered the results nor introduced heterogeneity. We did not pool the two trials reporting this outcome in breast cancer surgery patients at 12 months because rather different regional anaesthesia techniques were employed. Six and 12 month outcomes from other operative sites were too sparse and too clinically heterogenous to justify pooling, even though the results consistently favoured regional anaesthesia. We considered subgroup analysis for comparator therapies, adjuvant therapies and immediate postoperative pain control, and to investigate the superiority of extended duration continuous local anaesthetic infusions over single shot interventions, but either data were too sparse or clinical differences between populations and interventions were too important to allow conclusions or justify pooling.

Surgical and anaesthetic complications were too sparsely and inconsistently reported for any conclusions to be drawn from the data included in this review. It is probable that large observational studies would be more suited to accurately estimating these risks, particularly the rare but serious risk of neurological injuries after regional anaesthesia (Brull 2007; Schnabel 2010).

Overall completeness and applicability of evidence

Participants

Most included studies were performed in university settings. Other than this limitation, the inclusion and exclusion criteria did not limit the applicability of the results to patients in the community. We deplore the absence of paediatric trials. On a cautionary note, there is still insufficient evidence to extrapolate the effect of one regional anaesthesia technique to another. For example, with our data on epidural anaesthesia for thoracotomy and on paravertebral block for breast cancer surgery, we cannot conclude that paravertebral blocks prevent chronic pain after thoracotomy.

Interventions

We limited our evidence synthesis to almost identical regional techniques for very similar surgical interventions (epidural anaesthesia for thoracotomy or paravertebral blocks for breast cancer surgery) in Analysis 1.1 and Analysis 1.2. We took this conservative approach because a sceptical reader may consider different regional anaesthesia techniques or different surgical interventions clinically too diverse to justify pooling in a meta-analysis (Higgins 2011). While we found no evidence of statistical heterogeneity within the subgroups we pooled (Effects of interventions), even when we included somewhat different surgeries or regional techniques, this lack of evidence for heterogeneity obviously constitutes no proof for homogeneity.

Comparator

Our review compared local and regional anaesthesia to conventional pain control (Appendix 1). Only one study (Lavand'homme 2005) compared the effects of the localized (for example wound infiltration) versus the systematic (for example intravenous) administration of local anaesthetics on chronic pain after surgery (Strichartz 2008).There is insufficient evidence to support or refute the notion that systemically administered local anaesthetics are equally effective in reducing the risk of persistent pain after surgery (Lavand'homme 2005; Strichartz 2008; Vigneault 2011).

Outcomes

Dichotomous outcomes were reported by most studies. While neither optimal nor comprehensive, dichotomous outcomes are meaningful and easy to understand for patients, payers and physicians alike. Many continuous outcome measures of chronic pain represent not just similar scales measuring the same outcome but rather different dimensions of the human pain experience that hence can not be pooled by frequentist meta-analysis. We acknowledge that the dichotomous outcomes used in our review fall short of a comprehensive assessment of the full impact of chronic postsurgical pain on patients' quality of life (Turk 2006).

The summary statistics extracted from the included studies did not provide the detail required to differentiate between mild and

severe disabling chronic pain six months after surgery. Mild versus severely disabling chronic pain may make an important difference (Kehlet 2006) for the individual. However, persistent pain after thoracotomy can decrease function even at low levels of pain (Gottschalk 2006). Considering the impact of even minor pain on quality of life (Gottschalk 2006; MacRae 2008) we feel that the prevention of minor chronic pain after thoracotomy or breast cancer surgery is clinically meaningful; this is even more so after minor or benign elective interventions like cesarean section, vasectomy, lumpectomy or iliac bone graft harvesting. Similar to responder analysis, the state of the art for the evaluation of interventions for chronic pain (Dworkin 2009), our dichotomous effect measure is also appropriate to investigate if regional anaesthesia reduces the risk of persistent pain after surgery. To judge the clinical meaningfulness of regional anaesthesia we must weigh its risks and costs against short-term benefits (like enhanced recovery and improved immediate pain control) (Dworkin 2009; Gottschalk 2006) plus the reduced risk for persistent postsurgical pain suggested by our evidence synthesis. The risk of regional anaesthesia is deemed very low (Brown 1995; Neal 2008; Schnabel 2010). An overall assessment of the clinical usefulness of regional anaesthesia should probably be reserved for a Cochrane overview.

Quality of the evidence

The risk of bias graph gives an overview of the methodological weaknesses of the included studies (Figure 2), detailed in the methodological quality summary (Figure 3). We noted several important limitations in the quality of the evidence. The nature of the interventions made participant blinding effectively impossible. Hence, performance bias may weaken the conclusions of our review. The placebo effect may be particularly strong for pain outcomes and remains unknown for long-term outcomes. Several studies employed adjuvants only in the experimental group, potentially introducing bias, although this did not affect the pooled results for the breast cancer surgery subgroup and was not pertinent for the thoracotomy subgroup. Our conclusions are significantly weakened by shortcomings in allocation concealment (Hewitt 2005), considerable attrition and incomplete outcome data. We caution that our evidence synthesis is based on only a few small studies.

Potential biases in the review process

Reporting and selection bias

Not all outcome data were available for inclusion (Results of the search; Assessment of reporting biases). This potentially introduced bias in our review and may reflect publication bias. A formal analysis of publication bias by using a funnel plot or the test proposed by Egger 1997 was precluded by the small numbers of studies found in each subgroup.

Predefining subgroups based on surgical interventions effectively eliminated heterogeneity. Our results were robust to sensitivity analysis and were independent of model assumptions. Many more studies on limb amputation, laparotomy, caesarean section and other surgery were deemed clinically too heterogenous for orthodox frequentist data synthesis.

Agreements and disagreements with other studies or reviews

No systematic reviews and meta-analysis of regional anaesthesia for chronic pain after surgery exist, to our knowledge. Two previous narratives reviews were rather sceptical as to the potential of regional anaesthesia for the prevention of chronic pain after surgery (Kehlet 2006; MacRae 2008) but did not quote all the evidence analysed in this review (Ibarra 2011; Ju 2008; Karanikolas 2006; Lu 2008; Senturk 2002). Five major trials are underway on regional anaesthesia for chronic pain after surgery (Albi-Feldzer 2007; Bollag 2009; Honigmann 2007; Offner 2007; Wylde 2011), plus one trial where this is likely to be an important albeit not the primary outcome (Sessler 2009).

AUTHORS' CONCLUSIONS

Implications for practice

Epidural anaesthesia should be considered for patients undergoing open thoracotomy and paravertebral block should be considered for women undergoing breast cancer surgery to reduce their risk of persistent pain six months after surgery. Using epidural anaesthesia may reduce the risk of developing persistent pain six months after thoracotomy in one patient out of every three to four patients treated (Summary of findings for the main comparison); the number needed to treat for paravertebral block for breast cancer surgery is five (Summary of findings 2). Our findings were robust to sensitivity analysis and independent of model assumptions. However, our conclusions may be significantly weakened by performance bias, shortcomings in allocation concealment, considerable attrition and incomplete outcome data. We caution that our evidence synthesis is based on only a few small studies. On a cautionary note, we cannot extend these conclusions to other surgical interventions or regional anaesthesia techniques, for example we cannot conclude that paravertebral block reduces the risk of chronic pain after thoracotomy.

Implications for research

Future clinical trials

Participants

We urgently need RCTs on the effects of regional anaesthesia on chronic pain after surgery in children.

Interventions

We need to study the effects of adjuvant medications and more diverse regional anaesthesia interventions, for example paravertebral blocks for thoracotomy.

Control groups

Studies should compare the experimental regional anaesthesia intervention to a conventional pain control comparator and to an intravenous local anaesthetic control group. The latter would confirm or refute the hypothesis that intravenous local anaesthetics are equally effective, while much easier to administer (Lavand'homme 2005; Strichartz 2008; Vigneault 2011).

Outcomes in clinical studies

Outcomes should include dichotomous pain data, eliciting analgesic consumption and employing complex psychosocial instruments (Turk 2006). Studies should assess the baseline pain prior to surgery, in particular for studies where this is significant enough to warrant regional anaesthesia, as for limb amputation (Bach 1988). Risk factors should be elicited and reported separately for each group (Kehlet 2006).

Research on adverse effects

Studies should include adverse effects, separated by group, as primary outcomes.

Study design

Future studies should employ methods to address patient attrition, for example intention-to-treat analysis.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Bain 2001

Methods	Single (outcome assessor) blinded, randomized controlled clinical trial Sequence generation: not described Follow up: 12 months
Participants	Subjects: 40 adults from several teaching hospitals in Adelaide, Australia Operation: digitally assisted acromioplasty for subacromial impingement 2 groups, size: 20/20 Age (groups 1,2): 45.2 years (range 27-64), 45.1 (range 19-69) Men/women (group 1, 2) 11/9, 11/9
Interventions	Group 1 (preincisional plexus block): preincision interscalene brachial plexus block (Winnie, paraesthesia) with bupivacaine (0.5%, 30 ml), GA (fentanyl (1.5 ug/kg), postop PCA pethidine (dosing not reported) for 24 hrs, PRN paracetamol (500 mg) and codeine phosphate (30mg) Group 2 (control): no block, GA (fentanyl (1.5 ug/kg), postop PCA pethidine (dosing not reported) for 24 hrs, PRN paracetamol (500 mg) and codeine phosphate (30 mg) Adjuvants: none Immediate postop pain control: significantly improved
Outcomes	Dichotomous: none reported. Continuous: VAS 12 months postoperatively, mean analgesic dosages, but no standard deviation reported. American Shoulder and Elbow Surgeons Functional Score and Range of Abduction at 12 months
Notes	No standard deviation was reported for any of the above continuous outcomes. The author, contacted twice at several e-mail addresses for missing information, failed to respond. Therefore the data could not be used

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as "randomized", but no method is given.
Allocation concealment (selection bias)	Unclear risk	Allocation not explained, unclear what time interval between randomization and block/surgery
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Surgeon, patients and anaesthesia provider were not blinded, which is acceptable

Bain 2001 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	"An independent observer (not the surgeon), blinded to the block status of any patient, reviewed all patients." Outcome assessor blinding is adequate and well explained
Incomplete outcome data (attrition bias) All outcomes	Low risk	Withdrawals and loss to follow up were reported as none. Two blocks were reported as failure, but an ITT analysis was performed

Baudry 2008

Methods	Quadruple (patient, provider, surgeon, outcome assessor) blinded, randomized, placebo-controlled clinical trial Sequence generation by random number tables Follow up: one year (effectively, in treatment group: 17 months, control group 15 months)
Participants	Subjects: 96 women included (78 analysed), from one university hospital, Besancon, France Operation: breast cancer surgery (mastectomy and lumpectomy with sentinel node biopsy) 2 groups, size: 40/38 Age (groups 1,2): 52.4 years (SD ± 11.2), 57.7 (SD ± 12.6) Only women
Interventions	Group 1 (postsurgical breast infiltration): GA (sufentanil 0.3 ug/kg), at wound closure single shot local infiltration with ropivacaine (0.475%, 40 ml), postop: paracetamol (1g, intravenously, q6hrs), ketoprofene (100 mg, intravenously, q12hrs) rescue analgesic (if VAS >30/100) nalbuphine 0.2 mg/kg Group 2 (placebo postsurgical breast infiltration): GA (sufentanil 0.3 ug/kg), at wound closure single shot placebo infiltration with normal saline (40 ml), postop: paracetamol (1 g, intravenously, q6hrs), ketoprofene (100 mg, intravenously, q12hrs) rescue analgesic (if VAS >30/100) nalbuphine 0.2 mg/kg Adjuvants: none reported Immediate postop pain control: analgesic rescue medication and VAS were not different between groups
Outcomes	Dichotomous: pain/no pain at one year (effectively at 17 months in the experimental and at 15 months in the control group.) Continuous: McGill Questionaire described, but results not reported Effective regional anaesthesia not reported, and treatment did not reduced the severity of immediate postoperative pain or the consumption of rescue pain medication
Notes	Article in French, extracted by authors.

Risk of bias

Baudry 2008 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were randomized with the use of a "randomization table"
Allocation concealment (selection bias)	Unclear risk	Patients were randomized "after inclusion." Unclear how the allocation was concealed, however
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The anaesthetist in charge, the surgeon, the investigator were blinded." "The anaesthetic was administered with the patients anaesthetized." "The solution was prepared by personnel not taking care of the patient."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"The investigator was blinded." "The solution was prepared by personnel not taking care of the patient."
Incomplete outcome data (attrition bias) All outcomes	High risk	Significant attrition due to post hoc exclusion/lost patients and lost data that is reported but not analysed with ITT. Unclear how many patients were initially randomized to which group? Hence attrition cannot even be assessed by group. Patients initially excluded for missing data were later included for the one year analysis

Bell 2001

Methods	Double (patients, outcome assessors) blinded, placebo controlled, randomized controlled clinical trial Sequence generation randomized but not described Follow up: 6 months
Participants	Subjects: 8 adults in a university setting in Bergen, Norway Operation: bilateral reduction mammoplasty 2 groups, size: 8/8 Age: 28.5 years (range 18-34) Men/women: 0/8 Remarks: body sides, not patients randomized
Interventions	Breast Group 1 (preop infiltration): GA (fentanyl), preincision: infiltration with lidocaine (0.5%, 100 ml with epinephrine 5 ug/ml), postop PRN ketobemidone (po, 5 mg) and paracetamol (1000 mg TID) Breast Group 2 (placebo): GA (fentanyl), preincision: infiltration with normal saline (100 ml with epinephrine 5 ug/ml), postop PRN ketobemidone (po, 5 mg) and paracetamol

Bell 2001 (*Continued*)

	(1000 mg TID) Adjuvants: none Immediate postop pain control: significantly improved in treated breasts
Outcomes	Dichotomous: pain at 6 months Continuous: none reported Secondary: thermal thresholds were reported as tables, touch allodynia or hyperalgesia only graphically
Notes	Some details, reported as graphs, are difficult to compare and extract

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Patients' breasts were randomized to test and control groups", but the method was not described in detail
Allocation concealment (selection bias)	Unclear risk	Efforts to conceal allocation were not described. Bias is rather unlikely, because body sides, not patients were randomized
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The procedure was performed double blind", however blinding of patients and personnel not explicitly described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"The procedure was performed double blind", however outcome assessor blinding not explicitly described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Withdrawals and attrition reported as none, except one patient excluded for drug spillage. With only one withdrawal, body parts randomized not patients, even though no ITT analysis was performed, bias seems unlikely

Burney 2004

Methods	Single (outcome assessor) blinded, randomized controlled clinical trial Sequence generation by random number tables Follow up: 6 months
Participants	Subjects: 34 adults in a university setting in Ann Arbor, Michigan, USA Operation: unilateral inguinal hernia repair 2 groups, size: 15/18 Age: not reported

	Men/women: not reported Remarks: recurrent hernias or bilateral hernias were excluded
Interventions	Group 1 (spinal): spinal with lidocaine (5% with 7.5% dextrose, volume not reported) , postincision: illio-inguinal block with bupivacaine (0.5%, 8-10 ml), postop regimen not reported Group 2 (control): GA (fentanyl), postincision: illio-inguinal block with bupivacaine (0. 5%, 8-10 ml), postop regimen not reported Adjuvants: none Immediate postop pain control: significantly improved
Outcomes	Dichotomous: none reported Continuous: Health status measured by the 36-Item Short-Form Health Survey (SF-36) at 6 months, but without randomization list
Notes	We contacted the author for missing information on SF-36 outcome. He provided original data and comments, but regretted that the randomization list was no longer available. Therefore the data could not be included

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Randomization was carried out using a blocked and balanced random number table."
Allocation concealment (selection bias)	Low risk	"A sealed opaque envelope with the randomization assignment was opened only after the patient had given informed consent for the study." The well described method makes bias is unlikely
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants and care givers were not blinded, but this is acceptable
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessor blinding was not reported, but patients filled out the questionnaire alone. Author responded: "research assistants collecting the data were blinded as to experimental groups during initial data collection. All data collection was by questionnaire. Research assistants were present for early data collection, but at 6 months I think it was only by mail."
Incomplete outcome data (attrition bias) All outcomes	High risk	Loss to follow up reported, but not assigned to groups or outcomes. Initially 34 patients

		were recruited, but only 23 questionnaires were collected at 6 months. Patient erroneously assigned to the wrong group were analysed with ITT. Bias is likely due to the unclear group allocation of patients lost to follow up

Fassoulaki 2005

Methods	Double-blind (patient, outcome assessor), placebo controlled, randomized clinical trial Sequence generation by computer generated random number tables Follow up: 6 months
Participants	Subjects: 50 adults in a university setting in Athens, Greece Operation: breast surgery (modified radical mastectomy and lumpectomy plus axillary dissection) for breast cancer 2 groups, size: 25/25 Age (group 1, 2): 49 years (SD ± 8.4), 48 (SD ± 8.1) Men/women: 0/50
Interventions	Group 1 (multimodal): GA, brachial plexus irrigation with ropivacaine (0.75%, 10 ml), intercostal ropivacaine (0.75%, 3 ml) @ICS 3-5, postop for three days topical (wound, sternum, axilla) EMLA cream (20g, 2.5% lidocaine/ prilocaine), codeine, paracetamol Group 2 (control): GA, brachial plexus irrigation with normal saline, sham intercostal block @ICS 3-5, postop for three days topical (wound and axilla) placebo cream, codeine, paracetamol Adjuvants: Group 1: gabapentin (400 mg, po every 6 hrs starting the night before surgery) for eight days, Group 2: Placebo as above Immediate postop pain control: significantly improved
Outcomes	Dichotomous: pain, analgesic consumption at 6 months Continuous: none reported Adverse effects, withdrawal and attrition were reported with group allocation
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Fifty envelopes, 25 containing odd and 25 containing even numbers, obtained from a computer-generated table, were prepared and sealed...," this is an adequate description of an acceptable randomization technique. Bias is unlikely

Allocation concealment (selection bias)	Low risk	"An independent anesthesiologist, who did not participate in the study or data collection, read the number contained in the envelope and made group assignments." Bias is unlikely
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Except for the independent anesthesiologist, [not involved in the study] no other physician or nursing staff member was aware of the interventions administered to each patient." "Regarding EMLA cream and possible interference with blinding, EMLA or placebo was applied in the morning after pain assessment"... "pain was assessed by an anesthesiologist blinded to group assignment." "Placebo capsules were identical in appearance with the gabapentin capsules. The same number of capsules was packaged in group-specific bottles and coded as bottle A and bottle B for the control and treatment groups, respectively. A white odourless cream was the control treatment corresponding to the EMLA cream. Similarly, cream for each group was kept in boxes labelled as A and B for the control and treatment groups, respectively."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Except for the independent anesthesiologist, [not involved in the study] no other physician or nursing staff member was aware of the interventions administered to each patient." "Pain was assessed by an anesthesiologist blinded to group assignment."
Incomplete outcome data (attrition bias) All outcomes	High risk	Authors provide a good account of attrition, including group allocation, but considered no ITT analysis: Drop outs, patients lost to follow up, failures,.. etc were all excluded

Haythornthwaite 1998

Methods	Single blind (outcome assessor) randomized controlled clinical trial Sequence generation was randomized but not described Follow up: 6 months
Participants	Subjects: 110 adults in a university setting in Baltimore, Maryland, USA Operation: radical retropubic prostatectomy 3 groups, size: 35/36/39 Age (group 1, 2, 3): 63 years (SD ± 1), 61 (SD ± 1), 61 (SD ± 1) Men/women: 110/0
Interventions	Group 1 (epidural): no GA, L3/4/5 epidural bupivacaine (bolus 0.5%, 0.25 ml/kg body weight, infusion 0.125% @0.1 ml/kg titrated), postop epidural fentanyl (100 ug) PCEA bupivacaine (0.0625%, fentanyl 5 ug/ml, basal rate 2 ml/h, demand 4 ml, lock out 10 min) Group 2 (epidural/general): GA (fentanyl), L3/4/5 epidural bupivacaine (bolus 0.5%, 0.2 ml/kg body weight, infusion 0.125% @0.1 ml/kg titrated), postop epidural fentanyl (100 ug), PCEA bupivacaine (0.0625%, fentanyl 5 ug/ml, basal rate 2 ml/h, demand 4 ml, lock out 10 min) Group 1 (GA): GA (morphine), postop L3/4/5 epidural fentanyl (100 ug), PCEA bupivacaine (0.0625%, fentanyl 5 ug/ml, basal rate 2 ml/h, demand 4 ml, lock out 10 min) Adjuvants: none Immediate postop pain control: analgesic consumption significantly less only on POD 2 and 3
Outcomes	Dichotomous: pain at 6 months Continuous: quality of life at 6 months
Notes	The pain data at 6 months was not published. The quality of life data was not published according to the initial group allocation, but as pain versus pain free groups. The author responded with additional information on methodology, but regretted that the requested data were not available. Data could not be included

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	No description of the actual randomization method in any of the three published articles, but detailed as "randomization was carried out using a block size of six (two patients per group) and stratified on the four surgeons..." Patients "were randomly assigned..." The author specified: "Randomization was done in a block size of 6 patients per surgeon, by randomly selecting one of 6 pre-prepared opaque envelops containing each patient's group allocation."

Allocation concealment (selection bias)	Unclear risk	We found no description of concealment of allocation in the three published articles. The author responded: "Allocation could not be concealed from the anesthesiologist-me [the author], I have performed the anesthesia in all but four or five patients. Patients knew about their group allocation as of the night before surgery. Surgeons were not aware of the group allocation, but could know which patients had epidural only and which had general anesthesia."
Blinding of participants and personnel (performance bias) All outcomes	High risk	The author responded: "Patients knew about their group allocation as of the night before surgery. Surgeons ... could know which patients had epidural only and which had general anesthesia."The SF-36 was administered as a questionnaire without the presence of the outcome assessor. Patients were cared for by an investigator "not involved postoperative pain management, data collection and analysis." Lack of blinding during the postoperative period might introduce bias
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessor blinding is not described in the report. The SF-36 was administered as a questionnaire without the presence of the outcome assessor. Lack of blinding during the postoperative period might introduce bias. The author responded: "Outcome assessors had no access to group allocation."
Incomplete outcome data (attrition bias) All outcomes	High risk	One article reports 110, the other 102 participants. "Excluded from the study were patients with epidural catheter failure (due to infection, skin infiltration, or inadvertent withdrawal and kinking)." Withdrawals and loss to follow up are described, but ITT analysis is not reported

Ibarra 2011

Methods	Blinded (Pacu nurses, outcome assessor), controlled, randomized clinical trial Computer generated randomization in blocks of two using sealed opaque envelopes Follow up: 5 months
Participants	Subjects: 40 adults in a university hospital setting in Albacete, Spain Operation: radical mastectomy and conservative breast surgery for breast cancer 2 groups, size: 20/20 Age: not reported Men/women: 0/40
Interventions	Group 1 (preoperative paravertebral block): single shot paravertebral block at T4 with ropivacaine (0.5% without epinephrine, 25-30 ml, doses maximum 150 mg; using nerve stimulations according to Naja but only one single injection), GA (Laryngeal Mask Airway using sevoflurane and remifentanil 0,05-0,1 mcg/kg/min only in the first 20-30 min), postop: intravenous morphine (0.1 mg/kg), dexketoprofen 50 mg iv plus 25 mg every 8 hours PRN for pain and acetaminophen (1 g every six hours) Group 2 (no block): no block, GA (Laryngeal Mask Airway using sevoflurane and remifentanil 0,05- 0,02 mcg/kg/min), postop: intravenous morphine (0.1 mg/kg), dexketoprofen 50 mg iv plus 25 mg every 8 hours PRN for pain and acetaminophen (1 g every six hours) Adjuvants: none Immediate postop pain control: not significantly improved
Outcomes	Dichotomous: number of patients with pain (including detailed number per group on myofascial pain, breast phantom pain or neuropathic pain) at 3 and 5 months per group Continuous: not reported Effective regional anaesthesia: One patient had an unsuccessful block but was NOT excluded, yet paravertebral blocks did not reduced the severity of postoperative pain
Notes	We acknowledge the author's response regarding randomization, allocation concealment and blinding, dosing and attrition

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Computer generated list", "randomization in blocks of two". Low risk of bias
Allocation concealment (selection bias)	Low risk	"Patients were assigned as they arrived in the preoperative clinic", "The anaesthesiologist [enrolling the patient] did not know in which group the patient was going to be enrolled". "The anaesthesiologist [in the OR] did not know the group allocation, until the patient reached the operating room." "The randomization number was included in the chart in a sealed opaque envelope." Low risk of bias

Ibarra 2011 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	High risk	"The recovery room nurses did not know the anaesthetic technique used in each case. " "The surgeon knew" if a block was performed. Patients were not blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"The outcome observer conducting the interview did not know the group allocation. "
Incomplete outcome data (attrition bias) All outcomes	High risk	The numbers excluded in each group for radiotherapy and lost to follow-up, respectively are unclear. Significant attrition with unclear group allocation may have caused bias., but no intention to treat analysis considered

Ju 2008

Methods	Double-blind (patients and outcome assessor), sham epidural controlled, randomized controlled clinical trial Sequence generation was randomized, but not described. Follow up: 12 months.
Participants	Subjects: 114 adults in a university setting in Beijing, China Operation: posterolateral thoracotomy for lung and oesophageal disease 2 groups, size: 57/57 Age (group 1, 2): 61.80 years (SD ±13.78), 61.41 (SD ±11.78) Men/women (group 1, 2): 41/13, 38/15 (completed the protocol) Remarks: 7 patients with dislodged catheters were excluded.
Interventions	Group 1 (preincision epidural): epidural @T6/7/8, preincision epidural ropivacaine (0. 5%, bolus 5-10 ml), GA (fentanyl), postop for 72 hrs PCEA (0.125% bupivacaine + 0. 05 mg/ml morphine + 0.02 mg/ml droperidol, basal 3 ml/h, demand 3 ml, lock out 15 min) Group 2 (control/cryotherapy):sham epidural @T6/7/8, GA (fentanyl), cryoalgesia, postop for 72 hrs PCA through sham epidural (subcutaneous, 1 mg/ml morphine, demand 2 ml, lock-out in 30 min, no basal) Adjuvants: none Immediate postop pain control: not significant
Outcomes	Dichotomous: pain at 6 and 12 months. Continuous: not reported Secondary: allodynia at 6 and 12 months
Notes	
Risk of bias	

Ju 2008 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Patients were stratified by disease sites (lung or oesophagus), and blinded randomized to receive either epidural analgesia (Epidural Group, Group E) or intercostal nerve cryoanalgesia (Cryo Group, Group C), in order to ensure that both groups had comparable operation methods." Randomization method not detailed, but otherwise well documented
Allocation concealment (selection bias)	Low risk	Patients unaware of allocation, concealment of allocation for providers described: "After obtaining ... written informed consent from the prospective patient cases, 114 physical status I or II patients scheduled for posterolateral thoracotomy for lung or oesophagus diseases were enrolled in the study."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Intra-operative anaesthesia providers were not blinded. An effort was made to blind study participants: "In order to make the patients blinded to the analgesic method, subcutaneous infusion catheters were inserted at upper back (T7-8 level) in Group C." This is acceptable, bias is unlikely
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessor "who was blinded to the postoperative pain management, interviewed patients by telephone, using a standard questionnaire."
Incomplete outcome data (attrition bias) All outcomes	High risk	Attrition was reported, but no ITT analysis was considered.

Kairaluoma 2006

Methods	Triple blinded (patient, providers, outcome assessor), sham and placebo controlled, randomized clinical trial Sequence generation was not described Follow up: 12 months
Participants	Subjects: 60 adults in a university setting in Helsinki, Finland Operation: conservative breast surgery with sentinel lymph node biopsy for cancer 2 groups, size: 30/30 Age: not reported

	Men/women: 0/60
Interventions	Group 1 (preincision PVB): single shot paravertebral block at T3 with bupivacaine (0.5%, 1.5 ml/kg), GA, postop: per os ibuprofen (10 mg/kg) and acetaminophen (1 g, TID) rescue analgesia: acetaminophen (500 mg with codeine 30 mg) or tramal (50-100 mg) Group 2 (sham PVB): sham paravertebral block at T3 with normal saline, GA, postop: per os ibuprofen (10 mg/kg) and acetaminophen (1 g, TID) rescue analgesia: acetaminophen (500 mg with codeine 30 mg) or tramal (50-100 mg) Adjuvants: none Immediate postop pain control: significantly improved
Outcomes	Dichotomous: NRS larger 3 at 6 and at 12 months, use of pain medication at 6 and 12 months Continuous: Pain at rest and in motion reported as NRS, number of pain descriptors, all at 6 and 12 months Effective regional anaesthesia not reported, but treatment reduced the severity of postoperative pain and oxycodone consumption, postoperatively
Notes	We acknowledge the author's response regarding randomization and allocation concealment

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Patients "were randomly assigned." Sequence generation was "randomized", "performed in a randomized" fashion", but the exact method of randomization was not explained. The author responded "The randomization was done using the opaque sealed envelope method."
Allocation concealment (selection bias)	Unclear risk	Allocation concealment not described in the original report.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The patients and the study anaesthesiologists who performed the analysis remained blinded to the use of PVB with bupivacaine or a sham block throughout the entire study period." " procedure behind a drape curtain" The author responded also that "the patient, the anaesthesiologist providing anaesthesia and the staff taking care of the patient were blinded to the study group. The curtains and drapes were hung so that the block was performed behind the curtains on the back side of the patient while

		the patient's head and front side and her nurse were on the other side of the curtains. The anaesthesiologist and nursing staff giving general anaesthesia were blinded to the study group..."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"The patients and the study anaesthesiologists who performed the analysis remained blinded to the use of PVB with bupivacaine or a sham block throughout the entire study period.", "telephone interviews by a blinded interviewer." "A group-blinded study assistant conducted all telephone interviews." The author responded also that " A non-medical study assistant blinded to the study group performed the follow-up telephone interviews at predestined time points up to 12 months postoperatively. "
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition explained in detail, intention to treat analysis performed

Karanikolas 2006

Methods	Double blind (patients, outcome assessor) placebo controlled randomized clinical trial Sequence generation was randomized Follow up: 6 months
Participants	Subjects: 65 adults in a university setting in Patras, Greece Operation: lower limb amputation with pain score >60/100 VAS 48 hours prior to amputation 5 groups, group size: 13 Age: Group means ranging [69.2 to 74.3] with largest SD 13 Men/women: 35/53
Interventions	Group 1 (Epi/Epi/Epi): preop: lumbar epidural analgesia bupivacaine (0.2%, fentanyl 2 ug/ml @4-8 ml/h) for 48 hrs, GA preincision: epidural bupivacaine (0.5% 10-15 ml, fentanyl 100 ug), postop epidural bupivacaine (0.2%, fentanyl 2 ug/ml @4-8 ml/h) Group 2 (PCA/Epi/Epi): preop: PCA fentanyl (iv, demand 25 ug, lockout 20 minutes) , preincision: epidural bupivacaine (0.5% 10-15 ml, fentanyl 100 ug), postop epidural bupivacaine (0.2%, fentanyl 2 ug/ml @4-8 ml/h) Group 3 (PCA/Epi/PCA): preop: PCA fentanyl (iv, demand 25 ug, lockout 20 minutes) , preincision: epidural bupivacaine (0.5% 10-15 ml, fentanyl 100 ug), postop PCA fentanyl (iv, demand 25 ug, lockout 20 minutes) Group 4 (PCA/GA/PCA): preop: PCA fentanyl (iv, demand 25 ug, lockout 20 minutes) , General Anaesthesia with LMA, sevoflurane and remifentanil infusion, postop PCA fentanyl (iv, demand 25 ug, lockout 20 minutes)

	Group 5 (Control/GA/control): preop: meperidine (50 mg four to six times per day IM) Acetaminophen/Codeine 30/500 mg per os plus PRN intravenous acetaminophen 650 mg three times per day and parecoxib 40 mg twice daily, General Anaesthesia with LMA, sevoflurane and remifentanil infusion, postop: meperidine (IM) Acetaminophen/ Codeine 30/500 mg per os plus PRN intravenous acetaminophen 650 mg three times per day and parecoxib 40 mg twice daily Adjuvants: none Immediate pain control: significantly improved preop and postop
Outcomes	Dichotomous: Phantom limb pain (PLP) at 6 months Continuous: VAS and McGill PRI(R) and PLP frequency scores for phantom and stump pain at 6 months Effective regional anaesthesia not reported, but interventions reduced the severity of pain pre- and postoperatively
Notes	There are minor discrepancies regarding the dosing described between the preliminary report of the ongoing registered trial (Karanikolas 2008) and the final report. We reported the treatment according to the latest publication. We contacted the author for confirmation and additional information, but received no response. Hence, we could only use the data extracted from the publications and the information provided on clinicaltrials.gov

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Described as "prospective, randomized, clinical trial", with "computer generated blocks with five treatment groups and 13 patients per group."
Allocation concealment (selection bias)	Low risk	"sequentially numbered sealed envelope... concealed until after consent was obtain." Recruitment, outcome assessment and protocol management clearly separated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The trial is described as "double-blind" in the title. Detailed description of blinding procedures. "Control group patients had an epidural catheter placed subcutaneously. " D.A. i.e. the person "responsible for adjusting the epidural..." may not have been blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Detailed description of blinding procedures. "A second blinded investigator interviewed all patients." "A third blinded investigator conducted all interviews during the analgesic protocol."

Karanikolas 2006 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Only minor attrition is reported, and attributed to groups. Seemingly, attrition affects mainly the control groups. ITT analysis is reported. PP or ITT analysis did not change results

Katsuly-Liapis1996

Methods	Randomized controlled clinical trial Sequence generation randomized, but not described Follow up: one year
Participants	Subjects: 45 adults in a university setting in Athens, Greece Operation: lower limb amputation 3 groups, size: 15/12/18 Age: not reported Men/women: not reported
Interventions	Group 1 (pre-operative epidural): for 72 hrs preop: bupivacaine (0.25% and morphine) via epidural catheter [level not specified], [intraop anaesthesia not specified], postop for 72 hrs epidural bupivacaine infusion [not specified] Group 2 (postop epidural): for 72 hrs preop: opiods and NSAIDs [not specified], [intraop anaesthesia not specified], postop for 72 hrs epidural bupivacaine infusion [not specified] Group 3 (control): for 72 hrs preop: opiods and NSAID [not specified], [intraop anaesthesia not specified], postop opioids and NSAIDs [not specified] Adjuvants: none Immediate postop pain control: not reported, phantom pain risk not significantly reduced for the first three days
Outcomes	Dichotomous: phantom limb pain at 6 and 12 months Continuous: none reported
Notes	We were unable to find the contact information for any of the authors using Google and PubMed or the institution and therefore no additional information beyond the abstract could be obtained or extracted

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Patients were "randomly allocated", but the exact method was not explained
Allocation concealment (selection bias)	Unclear risk	Concealment of allocation was not reported.

Katsuly-Liapis1996 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Blinding was not reported in the abstract.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinding was not reported in the abstract.
Incomplete outcome data (attrition bias) All outcomes	High risk	Attrition is not reported. ITT analysis is not mentioned.

Katz 1996

Methods	Triple-blind (patients, providers, outcome assessors), sham/placebo controlled, randomized clinical trial Sequence generation was by random number tables Follow up: 18 months
Participants	Subjects: 30 adults in a university setting in Toronto, Ontario, Canada Operation: lateral thoracotomy for pulmonary or oesophageal disease 2 groups, size: 15/15 Age (group 1, 2): 54.6 years (range 19-75), 58.9 (range 46-72) Men/women (group 1, 2): 5/10, 8/7
Interventions	Group 1 (preincision intercostal block): placebo rectal suppository, intramuscular midazolam (0.05 per kg), GA (fentanyl 1 ug/kg), preincision intercostal nerve block with bupivacaine (0.5% with epinephrine (1:200.000), 3 ml/interspace) two spaces above and below planned incision, postop for 72 hrs PCA morphine (demand 1.5-2 mg, lockout 6 min, max dose 30 mg/ 4 hrs) Group 2 (sham/placebo block): intramuscular morphine (0.15 mg/kg) and perphenazine (0.03 mg/kg), indomethacin (100 mg, rectal suppository), GA (fentanyl 1 ug/kg), preincision sham intercostal nerve block with normal saline (3 ml/level) two spaces above and below planned incision, postop for 72 hrs PCA morphine (demand 1.5-2 mg, lockout 6 min, max dose 30 mg/4hrs) Adjuvants: none Immediate postop pain control: initial analgesic consumption reduced
Outcomes	Dichotomous: pain and analgesic consumption at 18 months Continuous: verbal rating scale at 18 months Secondary: allodynia at 6 and 12 months
Notes	We contacted the author for missing information. He provided a data table with unpublished data from the follow up study to Kavanagh 1994

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Katz 1996 (*Continued*)

Random sequence generation (selection bias)	Low risk	"A table of random numbers was used to allocate patients."
Allocation concealment (selection bias)	Low risk	"..investigator (who had no further involvement with that patient) who administered the medications in accordance with the instructions in the envelope..."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The patients and all other personnel involved in subsequent patient management and assessment were completely blinded as to group allocation...,thus maintain the blind and [patients] also received a placebo rectal suppository."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"other personnel involved in subsequent patient management and assessment were completely blinded as to group allocation. ..,thus maintain the blind..."
Incomplete outcome data (attrition bias) All outcomes	High risk	Attrition was described with regards to group allocation. Per patient analysis was performed, with no intention to treat analysis considered. Bias is unlikely, as an ITT analysis would not alter the lack of the statistical significance

Katz 2004

Methods	Double-blinded, placebo/sham controlled, randomized clinical trial Sequence generation by computer generated random numbers Follow up: 6 months
Participants	Subjects: 152 adults in a university setting in Toronto, Canada Operation: laparotomy for major gynaecological surgery 3 groups, size: 49/56/47 Age: 44 years (SD ± 8.9), 47 (SD ± 10.6), 44 (SD ± 9.6) Men/women: women only
Interventions	Group 1 (preincisional epidural): epidural catheter at L2/3/4 tested, GA, preincision: lidocaine (2% with epinephrine (1:200,000), 12 ml plus 0.8 ml for each inch of height above 60 inch**,** plus 4 ug/kg fentanyl), 40 min after incision epidural normal saline (12 ml), postop morphine PCA (loading dose 4 mg, then bolus 1.0 to 1.5 mg, lockout time 5 min, max 40 mg in 4 hrs, no basal rate) Group 2 (postincision epidural): epidural catheter at L2/3/4 tested, GA, preincision: epidural normal saline (12 ml), 40 min after incision: lidocaine (2% with epinephrine (1:200,000), 12 ml plus 0.8 ml for each inch of height above 60 inch**,** plus 4 ug/kg fentanyl), postop morphine PCA (loading dose 4 mg, then bolus 1.0 to 1.5 mg, lockout

	time 5 min, max 40 mg in 4 hrs, no basal rate) Group 3 (sham epidural): sham epidural catheter at L2/3/4 tested, GA (fentanyl (1 ug/kg)), preincision: epidural normal saline (12 ml), 40 min after incision epidural normal saline (12 ml), postop morphine PCA (loading dose 4 mg, then bolus 1.0 to 1.5 mg, lockout time 5 min, max 40 mg in 4 hrs, no basal rate) Adjuvants: none Immediate postop pain control: not significant
Outcomes	Dichotomous: pain at 6 months, analgesic consumption at 6 months Continuous: Pain Disability Index, Mental Health Inventory-18 and McGill Pain Questionnaire at 6 months Secondary: allodynia/hyperalgesia
Notes	.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"A randomization schedule was computer generated by a biostatistician."
Allocation concealment (selection bias)	Low risk	"An opaque envelope containing the patient number and group assignment was prepared, sealed, and numbered for each patient by the hospital pharmacist, not involved in the study otherwise...All patients and personnel involved in patient management and data collection were unaware of the group to which the patient had been allocated. The anesthesiologist in charge of the case was aware of group allocation for control group patients and was not involved in postoperative management or data collection."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"All patients and personnel involved in patient management and data collection were unaware of the group to which the patient had been allocated. The anaesthesiologist in charge of the case was aware of group allocation for control group patients and was not involved in postoperative management or data collection." but the anaesthesiologist in charge of the case was aware of group allocation for control group patients

Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Neither the person conducting the interview nor the patient was aware of the group to which the patient had been assigned," "personnel involved in ... data collection were unaware of the group to which the patient had been allocated."
Incomplete outcome data (attrition bias) All outcomes	High risk	"Both an intention to treat analysis and a protocol-compliant analysis were performed." "There was no appreciable difference in the results of the intention-to-treat analyses and the protocol compliant analyses. Data and results of significance tests reported below are therefore based on the intention to treat analyses." But ITT was only done for early outcomes, not for questionnaire data at 6 months, when significant attrition occurred

Lavand'homme 2005

Methods	Double-blinded (patient, outcome assessor), placebo/sham controlled, randomized clinical trial Sequence generation by computer generated random numbers Follow up for 12 months
Participants	Subjects: 85 adults in a university setting in Brussels, Belgium Operation: colonic resection (xiphopubic incision) of rectal adenocarcinoma 4 groups, size: 20/20/20/20 Age (group 1,2,3,4): 53 years (SD ± 8), 54 (SD ± 8), 55 (SD ± 8), 53 (SD ± 10) Men/women (total: group 1, 2, 3, 4): 49/31:12/8, 13/7, 12/8, 12/8 Remarks: Intraoperative discovery of an extended tumour resulted in patients exclusion from the study
Interventions	Group 1 (intravenous/intravenous): epidural catheter @T8, GA (sufentanil 2.5 ug) intravenous (lidocaine 2 mg/kg + 0.5 mg/kg/h, clonidine 4 ug/kg + 1 ug/kg/h, sufentanil 0.1 ug/kg + 0.07 ug/kg/h) Postop intravenous PCA (lidocaine bolus per request 7.5 mg, clonidine bolus per request 15 ug, morphine bolus per request 1.3 mg) (0.75 ml solution per demand, lockout time 7 min, max 15 ml per 4 h) Group 2 (intravenous/epidural): epidural catheter @T8, GA (sufentanil 2.5 ug); intravenous (lidocaine 2 mg/kg + 0.5 mg/kg/h, clonidine 4 ug/kg + 1 ug/kg/h, sufentanil 0.1 ug/kg + 0.07 ug/kg/h), before recovery (epidural bolus 7 ml bupivacaine 0.5%, clonidine 1 ug/kg, sufentanil 0.03 ug/kg) postop epidural PCEA (bupivacaine 5 ml 0.0675% + 5 ml/h 0.0675%, clonidine 3.5 ug +3.5 ug/kg/h, sufentanil 0.05 ug + 0.05 ug/h) (continuous infusion of 5 ml and bolus of 5 ml on request, 40 min lockout time) Group 3 (epidural/epidural): epidural catheter @T8, GA (sufentanil 2.5 ug), preincision epidural (bupivacaine 7 ml 0.5% + 5 ml/h 0.125%, clonidine 1 ug/kg + 0.5 ug/kg/h, sufentanil 0.03 ug/kg + sufentanil 0.015 g/kg/h) postop epidural PCEA (bupivacaine 5

	ml 0.0675% + 5 ml/h 0.0675%, clonidine 3.5 ug +3.5 ug/kg/h, sufentanil 0.05 ug + 0.05 ug/h) (continuous infusion of 5 ml and bolus of 5 ml on request, 40 min lockout time) Group 4 (epidural/intravenous): epidural catheter @T8, GA (sufentanil 2.5 ug), preincision epidural (bupivacaine 7 ml 0.5% + 5 ml/h 0.125%, clonidine 1 ug/kg + 0.5 ug/kg/h, sufentanil 0.03 ug/kg + sufentanil 0.015 g/kg/h), Postop intravenous PCA (lidocaine bolus per request 7.5 mg, clonidine bolus per request 15 ug, morphine bolus per request 1.3 mg) (0.75 ml solution per demand, lockout time 7 min, max 15 ml per 4 h) Adjuvants: ketamine from skin incision to the end of surgery (0.5 mg/kg bolus followed by continuous infusion at 0.25 mg/kg/hrs), clonidine as detailed above Immediate postop pain control: significantly improved
Outcomes	Dichotomous: pain at 6 and 12 months. Continuous: Pain Disability Index at 6 months, Mental Health Inventory-18 at 6 months Secondary: Punctuate wound hyperalgesia was reported for the first 72hrs
Notes	The author was contacted for missing data and responded, but with some data inconsistencies that could not be verified or corrected. The authors reported an unusually high success rate of epidural analgesia with only two failures in 60 patients

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"According to a computer-generated table of random number assignments, each patient was assigned to one of four double-blinded groups." Bias is unlikely
Allocation concealment (selection bias)	Unclear risk	The timing of allocation and concealment not detailed. Risk of bias is unclear
Blinding of participants and personnel (performance bias) All outcomes	High risk	"All of the analgesic solutions were prepared by an anesthesiologist who was not involved in the patients' care." Testing the epidural in the PACU "prevented a true double blinding in the postoperative period."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	However, "postoperative parameters were recorded by an anesthesiologist who was not aware of the intraoperative treatment administered to the patient", "mobilization assessed by a blinded observer", telephone interviews were "performed by the research nurse." The Author responded: " the research nurse [outcome assessor] was blinded to the group allocation ..." as there was no random code on questionnaire. Bias

Lavand'homme 2005 (*Continued*)

		is unlikely
Incomplete outcome data (attrition bias) All outcomes	High risk	Adverse effects and attrition were reported with group allocation. "Absence of thermoanalgesia level as well as intraoperative discovery of an extended tumor resulted in the patient's exclusion from the study. " "One was excluded during surgery after discovery of widespread neoplastic disease, and two other patients were excluded for postoperative early dislocation of epidural catheter (before 72-h follow-up)." "... one who died of a cardiac arrest at home 2 months" before completion. Results reported on a per patient basis, with no ITT analysis considered

Lavand'homme 2007

Methods	Triple blinded (patients, provider, outcome assessor), placebo/sham controlled, randomized clinical trial Sequence generation by computer generated random numbers Follow up: 6 months
Participants	Subjects: 92 adults in a university setting in Brussels, Belgium Operation: elective caesarean section (Pfannenstiel incision) 3 groups, size: 30/30/30 Age (group 1,2,3): 33 years (SD ± 5), 31 (SD ± 5), 31 (SD ± 6) Men/women: 0/92 Remarks: no previous caesarean delivery
Interventions	Group 1 (ropivacaine): spinal bupivacaine (1.8-2 ml hyperbaric 0.5%, sufentanil 1 ug/kg), postop for 48 hrs continuous wound irrigation [ropivacaine (0.2%, 5 ml/h), every 12 hrs diclofenac (75 mg in 50 ml/ 20 min)], PCA (morphine, no basal rate, demand 1 mg, lockout 5 min, max 25 mg/ 4hrs), PRN acetaminophen (1 g/ 6hrs) Group 2 (diclofenac): spinal bupivacaine (1.8-2 ml hyperbaric 0.5%, sufentanil 1 ug/kg), postop for 48 hrs continuous wound irrigation [diclofenac (300mg in 240 ml, 5 ml/h) iv saline 50 ml/20 min every 12 hrs], PCA (morphine, no basal rate, demand 1 mg, lockout 5 min, max 25 mg/4 hrs), PRN acetaminophen (1 g/ 6 hrs) Group 3 (saline): spinal bupivacaine (1.8-2 ml hyperbaric 0.5%, sufentanil 1 ug/kg), postop for 48 hrs continuous wound irrigation [saline (5 ml/h), every 12 hrs diclofenac (75 mg in 50 ml/ 20 min)], PCA (morphine, no basal rate, demand 1mg, lockout 5 min, max 25 mg/ 4 hrs), PRN acetaminophen (1 g/ 6hrs) Adjuvants: none Immediate postop pain control: pain and analgesic consumption significantly improved
Outcomes	Dichotomous: pain and analgesic consumption at 6 months Continuous: none reported

	Secondary: Punctuate wound hyperalgesia for the first 48hrs. Wound healing and complications such as hypotension, nausea or vomiting
Notes	The author responded to our request for clarification, but with information differing from the published data

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"...according to a randomized, prospective, blinded protocol...The parturients were randomly assigned using computer-generated random numbers..."
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not explicitly described.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The patient, the person in charge of perioperative management,... were not aware of the patient group assignment."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"the staff involved in data collection were not aware of the patient group assignment. " The author responded to our inquiry that "the research nurse was blinded to the group allocation- there was no code on the questionnaire, she used."
Incomplete outcome data (attrition bias) All outcomes	Low risk	A per patient analysis was performed, with no attrition reported. But the author responded: "patients were excluded from the data analysis (intraoperative failure of intrathecal anaesthesia and intra-wound catheter out, which did not allow a 48h postoperative follow up). We continued the inclusion of patients following the randomisation and at the end of the random list, we add 1 patient in ropivacaine group and 1 patient in diclofenac group (in the same order than those patients were excluded from the study)." Even though no formal ITT analysis was performed, only two out of 90 patients were excluded, reducing the likelihood of bias

Lu 2008

Methods	Placebo controlled, randomized clinical trial Sequence generation was randomized. Follow up: 6 months.
Participants	Subjects: 105 adults in a university setting in Guangdong, China Operation: thoracotomy for tumour resection 3 groups, size randomized(completed): 36(32)/36(30)/33(28) Age (median group 1,2,3): 57, 55, 59 years Men/women (group 1, 2, 3): 24/8, 18/12, 20/8 Remarks: 2 patients excluded intraop, 13 patients excluded postop with group allocation not specified
Interventions	Group 1 (preincision epidural): epidural @T7/8, 3 ml 1% Lidocaine (test dose), preincision 10 ml ropivacaine (0.25%, with morphine 0.2 mg/ml) epidurally, GA, postop 2 ml per hour (0.15% ropivacaine and 1.5 ug/kg/ml morphine) epidurally for 48hrs, additional analgesics and rescue medication not described Group 2 (postop epidural): epidural @T7/8, 3 ml 1% Lidocaine (test dose), GA, postop 2 ml per hour (0.15% ropivacaine and 1.5 ug/kg/ml morphine) epidurally for 48hrs, additional analgesics and rescue medication not described Group 3 (control): GA (0.1 mg fentanyl), postop iv fentanyl (0.25 ug/kg/ml @basal 2 ml/hr + 0.05 mg/ml demand) for 48 hrs, additional analgesics and rescue medication not described Adjuvants: none Immediate postop pain control: significantly improved
Outcomes	Dichotomous: pain at 6 months Continuous: not reported
Notes	Article published in Mandarin. Data extracted from the abstract and tables, methodological information extracted with the help of a Madarin speaking statistician

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	the allocation was by "random numbers generation". Bias is unlikely
Allocation concealment (selection bias)	Unclear risk	Allocation concealment was not described. Bias is possible, but unclear
Blinding of participants and personnel (performance bias) All outcomes	High risk	"The attending physician called the patient". No detail provided neither in the English abstract nor the Mandarin methods section
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"The attending physician called the patient". No detail provided neither in the English abstract nor the Mandarin meth-

		ods section
Incomplete outcome data (attrition bias) All outcomes	High risk	Attrition was described with reasons, but it is unclear what the reasons for the attrition were in each group. Attrition was larger in control group. No intention to treat analysis described. Bias is likely

Mounir 2010

Methods	Double blinded (patient/outcome assessor), placebo controlled, randomized clinical trial Sequence generation unclear Follow up: 6 months
Participants	Subjects: men in a military teaching hospital in Rabat, Marroco Operation: inguinal hernia repair groups, size: 20/22 Age: years (range): 46 ± 5; 40 ± 4 Men/women (group 1, 2): 20/0; 22/0 Comorbidities (group 1/2/3): none reported Remarks: only ASA I and II
Interventions	Group 1 (bupivacaine wound infiltration): spinal (12.5 mg hyperbaric bupivacaine +25 ug fentanyl, intrathecally), post incision subcutaneous infiltration of the skin with bupivacaine (0.5%, 20 ml), post op 1 g acetaminophen, ketoprofene (100 mg), morphine 3 mg PRN for breakthrough pain Group 2 (saline/placebo wound infiltration): spinal (12.5 mg hyperbaric bupivacaine +25 ug fentanyl, intrathecally), post incision subcutaneous infiltration of the skin with saline (0.9%, 20 ml), post op 1 g acetaminophen, ketoprofene (100 mg), morphine 3 mg PRN for breakthrough pain Adjuvants: none Immediate postop pain control: significantly improved
Outcomes	Dichotomous: pain/no pain at 6 months, (pain differentiated in mild, moderate and severe) Continuous: none Secondary:
Notes	The report leaves it unclear if postoperative analgesics were given intravenously or orally. The author was contacted for clarification of randomisation, allocation and blinding methods, but did not respond

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"etude prospective randomisee", [prospective randomized trial] "La randomisation

		etait realise au cours de la visite preanesethesique par envelopes cachetees et numerotees..." [the randomization was realized during the preoperative visit with numbered and sealed envelopes] Even so the study is reportedly "randomized", the randomization method is not explained, hence bias is possible
Allocation concealment (selection bias)	Unclear risk	"La randomisation etait realise au cours de la visite preanesethesique par envelopes cachetees et numerotees..." It is unclear if and how and how long the allocation was concealed to the person enrolling the participants or to the anaesthesia provider. Bias is therefore possible
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"l' anesthesiste remettait au chirurgien une seringue", "le chirurgien, qui ignorait la solution de infiltration", [The anesthesiologist passed a syringe to the surgeon, ... the surgeon did not know the solutions to be infiltrated] Possibly no blinding of the anaesthesia providers, but patient and surgeon were blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	" a six mois" "evaluee grace a un questionnaire rempli par tous les patients lors de leur consultation de chirurgie de controle?". [at six months ... evaluated by a questionnaire filled out by all patients during their surgical follow up visit] The "Outcome observer (surgeon) was blinded and the outcome was reported with the use of a questionnaire
Incomplete outcome data (attrition bias) All outcomes	Low risk	The uneven numbers of 22 and 20 in both groups leaves open the possibility of an error in the allocation process, cross over, attrition or incorrect randomisation and this is not addressed in the report. Bias seems still unlikely, due to the low attrition

Paxton 1995

Methods	Double-blind, placebo controlled, randomized clinical trial Sequence generation "at random", but not described. Follow up: 12 months.
Participants	Subjects: 70 adults from a university setting in Belfast, Northern Ireland Operation: vasectomy for contraception 2 groups, size: 70 total, (group size not given) Age: years (range): 35 years (range 26-45), 34 years (28-45) Men/women: 70/0 Remarks: in the intervention group, body sides were randomized to receive treatment or placebo
Interventions	Group 1a (intervention, body side treated): GA, intraop: bupivacaine (0.5% 1 ml) injected into the lumen of the vas deferens, postop NSAID Group 1b (intervention, placebo body side): GA, intraop: normal saline injected into the lumen of the vas deferens, postop NSAID Group 2 (control, both sides): GA, intraop: no injection, postop NSAID Adjuvants: none Immediate postop pain control: significantly improved
Outcomes	Dichotomous: testicular discomfort at 12 months Continuous: duration of testicular discomfort Secondary: none
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomly....at random..," but exact method of sequence generation not reported. Still, with excellent description of allocation concealment and blinding, we judge that bias is unlikely
Allocation concealment (selection bias)	Low risk	Allocation was done after education and enrolment, (it remains unclear when the vas deferens side was randomized, but this is unlikely to cause bias.) Bias is unlikely
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Bias during operation by non-blinded providers possible, e.g. by administering additional fentanyl, but not very likely
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"All the replies were analysed by one of the authors who was unaware of the treatment"

Paxton 1995 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	High risk	"The questionnaire was valid for 61 (91%) patients only." Six patients did not respond and "...three were excluded because of development of wound infection and scrotal hematoma." A per patient analysis was performed, withdrawals and attrition were reported, but allocation to groups or subgroup was not reported. Bias is likely, but unlikely to change the result of the study

Pinzur 1996

Methods	Double, possibly triple blind (patient, provider and possibly outcome assessor), placebo/ sham controlled randomized clinical trial Sequence generation "with use of a table of random numbers" Follow up: 6 months
Participants	Subjects: 21 adults, at a university setting, Chicago, Illinois, USA Operation: lower limb amputation because of ischaemic necrosis secondary to peripheral vascular disease 2 groups, size: 11/10 Age: 68.3 years (SD ± 12.96) Men/women: 10/11 Comorbidities: diabetes mellitus in 9 subjects
Interventions	Group 1 (treatment): GA or spinal, postop nerve sheath irrigation (Bupivacaine 0.5%, 1 ml/h) and PCA (morphine, no basal rate, demand 2 mg, lockout 15 min, max 30 mg/ 4 h) for 72 h Group 2 (placebo): GA or spinal, postop nerve sheath irrigation (normal saline, 1 ml/ h) and PCA (morphine, no basal rate, demand 2 mg, lockout 15 min, max 30 mg/ 4 h) for 72 h Adjuvants: none Immediate postop pain control: significantly improved analgesic consumption
Outcomes	Dichotomous: pain at 6 months Continuous: McGill Pain Questionnaire at 6 months Secondary: None
Notes	Reported data not allocated to groups. No graphics that report data. We contacted the author for missing information and outcome data. He responded that the data were not accessible. Hence, outcome data could not be included

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Pinzur 1996 (*Continued*)

Random sequence generation (selection bias)	Low risk	Patients were 'divided into two groups with use of a table of random numbers."
Allocation concealment (selection bias)	Unclear risk	Concealment of allocation not reported.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The patients and the staff were blinded to the contents of the bag, which were known only to the research pharmacist."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Outcome assessor blinding was not described, but "The patients and the staff were blinded to the contents of the bag, which were known only to the research pharmacist."
Incomplete outcome data (attrition bias) All outcomes	High risk	The authors report on attrition, (two patients died, five did not participate in the questionnaire), but did neither allocate it to groups nor consider an ITT analysis. It remains unclear based on what numbers the difference in phantom pain was not significant. ITT analysis would likely only have confirmed the lack of significance, however

Reuben 2006

Methods	Double blinded (patient and outcome assessor), placebo controlled, randomized clinical trial Sequence generation randomized Follow up: 12 months
Participants	Subjects: 80 adults, at a teaching hospital, Springfield, MA, USA Operation: lower limb amputation because of ischaemic necrosis, secondary to peripheral vascular disease 2 groups, size: 40/40 Age (group 1, 2): 68 years (SD ± 12), 65 years (SD ± 17) Men/women (group 1, 2): 23/17, 25/15 Comorbidities (group 1, 2): BKA:AKA ratio 29:11, 26:14
Interventions	Group 1 (treatment): GA (fentanyl), intraop perineural injection of bupivacaine 10 mL 0.25% and clonidine 100 mcg, postop morphine iv and acetaminophen/ oxycodon po Group 2 (placebo): GA (fentanyl), intraop perineural injection of placebo, postop morphine iv & acteaminophen/ oxycodon po Adjuvants: Clonidine perineurally Immediate postop pain control: significantly reduced analgesic consumption

Reuben 2006 (*Continued*)

Outcomes	Dichotomous: phantom limb pain and stump pain at 12 months. Continuous: not reported Secondary: not reported
Notes	The sciatic nerve was infiltrated for above the knee amputation (AKA)) or the posterior tibial nerve for below the knee amputation (BKA) We could not make sense of some numbers reported on attrition As reported Jan 22nd 2009, SS Reuben has been accused of fraudulent data. Up to 22 papers have been or will be retracted by the journals in which they have been published. This article, however, is not among the retracted manuscripts. [Retraction notice Anesthesia and Analgesia Feb 20th 2009]

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The study is described as "randomized", but the method of sequence generation is not reported
Allocation concealment (selection bias)	Unclear risk	Concealment of allocation is not explained.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"... double-blind study." Patient blinding is not explained, but single blinding would be acceptable
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"... double-blind study." Data collected "by telephone by a blinded investigator (SR), who was unaware of analgesic technique."
Incomplete outcome data (attrition bias) All outcomes	High risk	No comparison was done on demographics or other differences between included patients and those lost or deceased. No ITT analysis is considered. Attrition was reported in detail also with respect to group assignments. But attrition numbers for control group do not add up. Adverse effects were not reported

Senturk 2002

Methods	Single-blind (outcome assessor), randomized controlled clinical trial Sequence generation was random, but not described Follow up: 6 months.
Participants	Subjects: 112 adults at a university setting in Istanbul, Turkey Operation: open thoracotomy for a mix of lung resections

	3 groups, size: 28/29/28 Age (group 1,2,3): 49 (SD 9), 52 (SD 11), 50 (SD 11) years Men/women: 56/13 (reported at end of study) Comorbidities: not reported
Interventions	Group 1 (preincision):epidural @T7-8, preincision bupivacaine bolus 10 ml, 7 mL/h infusion (0.1% + 0.1 mg/mL morphine), GA, postop 48 hrs PCEA (0.1% bupivacaine + 0.05 mg/ml morphine, basal rate 5 ml/h, demand 3 ml, lockout 30 min) Group 2 (postsurgery): epidural @T7-8, GA (fentanyl), postsurgical bupivacaine bolus 10 ml (0.1% + 0.1 mg/mL morphine), postop 48 hrs PCEA (0.1% bupivacaine + 0.05 mg/ml morphine, basal rate 5 ml/h, demand 3 ml, lock time 30 min) Group 3 (control): GA (fentanyl), PCA (morphine, bolus 5 mg, no basal rate, demand 2 mg, lockout 15 min) Adjuvants: none Immediate postop pain control: significantly improved
Outcomes	Dichotomous: pain at 6 months, pain affecting daily life at 6 months Continuous: NRS at 6 months Secondary: none
Notes	Regional anaesthesia catheter placement was verified under fluoroscopy. The author responded and provided additional information regarding randomization and allocation concealment

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Patients were "randomly divided into three groups", "using sealed envelopes technique."
Allocation concealment (selection bias)	Low risk	"Randomization was performed at the first presentation of the patient to our department, i.e. 5-7 days before the operation (just before the anaesthetic evaluation). The result of the randomization was "hidden" by the secretary of the department until the operation date."
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"Patients were not blinded to group", anaesthesia providers aware of allocation at least during treatment."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors " were blinded to the analgesic method." Blinding of only outcome assessors is acceptable

Senturk 2002 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	High risk	Allocation of excluded patients is not reported, no ITT analysis was considered. Considerable attrition prior to, during and after intervention make bias likely. Adverse effects were not, but attrition was described albeit without group allocation 27 participants were excluded preoperatively, 6 intraoperatively, and 10 postoperatively, without specification of their group allocation. Comorbidities were the preoperative, inoperability the intraoperative and recurrence of pain due to metastasis & reoperation were the postoperative exclusion criteria

Shahin 2010

Methods	Double blinded (patient/outcome assessor), placebo/sham controlled, randomized clinical trial Sequence generation by computer generated random numbers Follow up: 8 months
Participants	Subjects: parturients in a university setting in Assiut, Egypt Operation: caesarean section for delivery groups, size: 185/185 Age: 25 years (SD ± 1.5) Men/women (group 1, 2): 0/185, 0/185 Comorbidities (group 1/2/3): none reported Remarks:
Interventions	Group 1 (intraperitoneal lidocaine instillation): spinal (details not reported), post incision, preperitoneal closure single shot instillation of peritoneal lidocaine (2%, 10 ml) into the pelvis, postop acetaminophen 1g intravenously every 6 hours for 36 hours, rectal suppository of 10mg followed by oral 400 mg ibuprofen for 72 hours, plus intravenous morphine 2 mg for breakthrough pain Group 2 (intraperitoneal placebo/saline instillation): spinal (details not reported), post incision, preperitoneal closure single shot instillation of peritoneal saline (0.9%, 10 ml) into the pelvis, postop acetaminophen 1 g intravenously every 6 hours for 36 hours, rectal suppository of 10 mg followed by oral 400 mg ibuprofen for 72 hours, plus intravenous morphine 2 mg for breakthrough pain Adjuvants: none Immediate postop pain control: significantly improved
Outcomes	Dichotomous: overall pain/no pain at 8 months, differentiated also in wound and epigastric pain Continuous: at 8 months: NRS
Notes	

Shahin 2010 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer based random allocation...
Allocation concealment (selection bias)	Low risk	Placed in sealed opaque consecutively numbered envelopes... just after providing consent the women were given the next number on the random list..., [allocation] was concealed from the residents and caregivers..
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The surgeon involved complied with the instruction but was not further involved" data "collection sheets with corresponding codes,.. a number of syringes equal in size;" "preparation and administration of the medication was carried out by a nurse not involved in the management of the patient", "access to randomization code was only available to the secretary of the statistics department", "randomization code was not broken until the completion of the study"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Access to randomization code was only available to the secretary of the statistics department", "randomization code was not broken until the completion of the study"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Analysis was per protocol, not intention to treat, but the low number of subjects lost to follow up with almost equal attrition in both groups and the similar demographics in both groups make bias unlikely

Singh 2007

Methods	Triple-blind (patient/provider/outcome assessor), placebo controlled, randomized controlled clinical trial Sequence generation by a computer based random numbers generator Follow up: mean of 4.7 years (range 4.5-5.4 years)
Participants	Subjects: 26 adults in a university setting, Houston, Texas, USA Operation: Iliac Crest Bone Graft (ICBG) harvesting for spinal arthrodesis

	2 groups, size: 11/14 Age (all, 1, 2): 64 (range 34-84), 66, 63 years Sex: not reported. Comorbidities: not reported Remarks: 11 anterior ICBG included in the initial stage were later excluded
Interventions	Group 1 (treatment): GA, at closure continuous wound irrigation (Marcaine 0.5% 2 ml/hr) for 48 hrs postop + PCA (Dilaudid) (basal, bolus and lock-out time not specified) Group 2 (control): GA, at closure continuous wound irrigation (normal saline, 2 ml/hr) for 48 hrs postop + PCA (Dilaudid) (basal, bolus and lock-out time not specified) Adjuvants: none Immediate postop pain control: significantly improved
Outcomes	Dichotomous: Graft Site Pain at around 55 months Continuous: VAS at around 55 months Secondary: pain frequency in days, functional activity score, overall satisfaction with the surgical procedure at around 55 months
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"The method used to generate the randomization consisted of a computer-based number generator. Moreover, to account for the size of the sample groups, randomization attempted to balance baseline characteristics by stratification, such as age."
Allocation concealment (selection bias)	Low risk	"The participants were randomized and allocated by a different individual than the one who enrolled the patient." "Randomization and allocation to group type was concealed and not made public to the individual enrolling the patients, the treating physician, or to the nursing staff." "Patients were assigned to receive either one or the other [treatment] solutions at the time of surgery based on a coded sequence enclosed within an envelope."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Blinded and identical in appearance, solutions of saline and Marcaine were prepared. " "Physicians, patients, nursing staff, and research personnel conducting the statistical analyses were blinded to the infusion so-

		lution until the end of the study to minimize potential for performance and detection bias.“
Blinding of outcome assessment (detection bias) All outcomes	Low risk	”The physician conducting the telephone interview as well as recording the data were blinded to the treatment group “Research personnel conducting the statistical analyses were blinded to the infusion solution until the end of the study to minimize potential for performance and detection bias.”
Incomplete outcome data (attrition bias) All outcomes	Low risk	Authors report details of attrition with reference to the groups subjects were randomized to. “An intent-to-treat analysis was considered to preserve randomization and to offer the best representation of the clinical population.” “Even if we assume that any treatment patient that was lost to follow-up (n = 6 patients) was considered to be a failure (chronic dysesthesias, an ICBG VAS score of 8, 15 days of narcotic usage/mo, functional activity score of 4, and an overall dissatisfaction with the procedure), a statistical difference was still noted in the 2 groups (p= 0.05).”

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

Study	Reason for exclusion
Abdel-Salam 1975	Study comparing different epidural local anaesthetic mixtures for analgesic effect, two days after surgery. No long-term outcomes recorded
Aguilar 1994	Follow up only 3 months.
Aguirre 2012	Follow up only after three months; randomized controlled clinical trial investigating epicapsular ropivacaine infusion for total hip replacement
Bach 1988	Pseudo-randomized controlled clinical trial (Sequence generation by means of patients' year of birth) investigating epidural analgesia before limb amputation for chronic phantom pain with a follow up of 12 months
Baguneid 1997	Follow up only 3 months.

(*Continued*)

Batoz 2009	Follow up only two months in this randomized controlled trial of scalp infiltration for craniotomy
Blumenthal 2005	Follow up only 3 months.
Blumenthal 2011	Comparing regional technique against combination of regional techniques
Borgeat 2001	Outcome: regional anaesthesia complications associated with interscalene block
Borghi 2010	non-randomized prospective trial of perineural catheter for phantom limb pain
Brown 2004	Follow up only 3 months.
Cerfolio 2003	preincision epidural anaesthesia versus none for thoracotomy, but no control (as both groups had postop epidural anaesthesia)
Chelly 2011	All patients received local wound infiltration and there was no control group without application of local or regional anaesthesia
Chiu 2008	RCT comparing wound infiltration with bupivacaine versus saline in thoracotomy for minimally invasive cardiac surgery with chronic pain outcomes at three months
Coghlan 2008	Outcome is orthopedic function at four months: randomized controlled trial on continuous infusion of ropivacaine in the subacromial space versus placebo for arthroscopic subacromial decompression
da Costa 2011	Excluded for pseudo-randomization, this prospective trial investigated different anaesthetic techniques for the prevention of regional pain syndrome after carpal tunnel release
De Kock 2001	Comparing intravenous ketamine to epidural ketamine to control as adjuvant therapy; all patients receiving local anaesthetics via epidural catheter
Doyle 1998	Comparing pre- verus postoperative epidural anaesthesia for thoracotomy
Elman 1989	Comparing different doses of bupivacaine intrapleurally, no long-term pain outcome assessed
Fassoulaki 2000	Follow up only 3 months.
Fassoulaki 2001	Follow up only 3 months.
Gottschalk 1998	Follow up only 9.5 weeks, in a double-blind randomized controlled clinical trials of 100 patients undergoing elective radical retropubic prostatectomy for the treatment of prostate cancer. Epidural bupivacaine, epidural fentanyl, or no epidural drug was administered prior to induction of anaesthesia and throughout the entire operation resulting in more pain free patients at 9.5 weeks
Gundes 2000	Follow up only 3 months.
Hirakawa 1996	RCT comparing preincicsional versus postoperative thoracic epidural anaesthesia for thoracotomy and median sternotomy. Outcome recorded was only pain after 3 months. (This article is written in Japanese)

(*Continued*)

Hivelin 2011	Not a randomized trial but only a prospective blinded study of transabdominal plane block in breast reconstruction
Howell 2001	Outcome: difference in backache as complication/adverse effect of labour epidural, no chronic postsurgical (site) pain outcome measure
Ilfeld 2004	Not a randomized controlled clinical trial, but only case reports on three paediatric patients with continuous regional anaesthesia catheters, two patients with pain outcomes at 3 months
Iohom 2006	Follow up only 3 months, (chronic postsurgical pain not primary outcome)
Jahangiri 1994	Prospective, but not randomized study of preoperative epidural anaesthesia for phantom pain after limb amputation
Jarvela 2008	Outcome is orthopedic function: randomized controlled trial on continuous infusion of ropivacaine in the subacromial space versus placebo for arthroscopic subacromial decompression
Jirarattanaphochai 2007	Follow up only 3 months.
Jorgensen 1982	Intervention does not include local anaesthetics.
Kairaluoma 2010	Comparing paravertebral block against local infiltration for hernia repair under spinal anaesthesia
King 2006	Follow up only 3 months.
Lambert 2001	Comparing regional against regional technique: randomized controlled clinical trial comparing preoperative epidural versus postoperative perineural catheter for risk reduction of phantom pain after limb amputation
Lebreux 2007	Not comparing regional versus non regional anaesthesia. 20 healthy parturients undergoing elective caesarean section under spinal anaesthesia were randomized to receive spinal clonidine. Outcome was pain up to 6 months and hyperalgesia
Loane 2012	Randomized controlled trial comparing Tap (trans abdominal plane) block versus intrathecal morphine with all patients receiving a spinal anaesthetic with three months follow up
Loughnan 2002	Controlled clinical trial without chronic postsurgical (site) pain outcome measure, but instead difference in backache as complication/adverse effect of labour epidural
Miguel 1993	Follow up only 3 months.
Milligan 2002	Follow up only 3 months and comparison of local anaesthetic versus local anaesthetic
Morin 2005	RCT comparing different regional blocks for knee surgery; no control group without local anaesthetic
Nikolajsen 1997	Study excluded for pseudo-randomization as discussed in (Appendix 10). Double blinded (patients and outcome assessors) pseudo-randomized (Sequence generation was by "the toss of a coin") controlled clinical

(*Continued*)

	trial on preoperative epidural analgesia for limb amputation with a follow up of 12 months including 60 adults in a university setting in Aarhus, Denmark
O'Neill 2012	Only 3 months follow up after wound infiltration following caesarean section
Obata 1999	Comparing preincisional versus postincisional epidural anaesthesia for thoracotomy
Ochroch 2006	Comparing preincisional versus postincisional epidural anaesthesia for thoracotomy
Ouaki 2009	RCT comparing continuous ropivacaine through an iliac crest catheter versus placebo for iliac crest bone graft in children, but with follow up of only three months
Panos 1990	RCT comparing intravenous versus epidural fentanyl, not local anaesthetic versus control
Perniola 2009	Follow up only 3 months, in this RCT of intraabdominal local anaesthetic for abdominal hysterectomy
Popova 1990	Follow up less than 6 months. (Article written in Bulgarian)
Royse 2007	Outcome is a depression score not chronic postsurgical pain.
Saber 2009	Follow up only 2 months.
Salengros 2010	RCT investigating pre- versus post operative epidural anaesthesia after thoracotomy
Schaller 2005	Follow up less than 6 months
Schley 2007	Study on effect of adjuvants for local anaesthetics to prevent chronic postsurgical pain. All 19 participants received a continuous brachial plexus block for one week after the amputation of an upper extremity. In addition they were treated with the NMDA antagonist memantine or placebo for 4 weeks
Shir 1994	No pain assessed at 6 month follow up.
Sim 2012	Randomized trial investigating pre- versus postincisional pre-emptive thoracic epidural analgesia for thoracotomy with outcomes at six month, but with no control group without regional anaesthesia
Sprung 2006	Follow up only 3 months.
Suvikapakornkul 2009	Follow up only three months.
Suzuki 2006	Studying the adjuvant effect of intravenous ketamine versus placebo in 49 thoracotomy patients, all participants receiving ropivacaine with morphine via epidural analgesia for 2 days
Vigneau 2011	Only two month follow up in this randomized clinical trial on would infiltration after breast surgery
Weihrauch 2005	Comparing block versus block with no pain outcome.

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

Albi-Feldzer 2007

Trial name or title	Efficacy of infiltration of chlorhydrate of ropivacaine in the prevention of chronic breast pain after surgery for breast cancer
Methods	Treatment, randomized, single-blind, placebo control, parallel assignment, efficacy study
Participants	Breast cancer patients treated by conservative surgery with axillary node dissection or treated by mastectomy with or without axillary node dissection or sentinel lymph node biopsy Ages eligible for study: 18 to 85 years Genders eligible for study: female Estimated enrolment: 230
Interventions	The aim of the study is to evaluate the effect of local anaesthetic (chlorhydrate of ropivacaine) to prevent chronic pain after breast surgery for cancer Patients will be randomized between: infiltration with chlorhydrate of ropivacaine at the time of breast surgery for cancer versus placebo. Intra-operative analgesia will be standardized as well as peri-operative pain management
Outcomes	Primary outcome measures: Comparing the frequencies of chronic breast pain three months after breast surgery evaluated by the brief pain inventory in the two groups Secondary outcome measures: Visual analogue scale (VAS), patient satisfaction with analgesic, consumption, neuropathic pain and depression/anxiety rating scale
Starting date	September 2006
Contact information	Aline H Albi-Feldzer, MD, Centre René Huguenin, Saint-Cloud, 92210 France
Notes	Study ID Numbers: (CRH 05353A), EudraCT 2005-005691-32 This study is ongoing, but not recruiting participants. Follow up may be only 3 months

Bollag 2009

Trial name or title	Transversus abdominis Plane (TAP) block for caesarean section (CLOTAP)
Methods	Prevention, randomized, double-blind, placebo control, parallel assignment, safety/efficacy study The purpose of this randomized, double-blinded study is to evaluate the ability of an established anaesthetic technique called the transversus abdominis plane (TAP) block to reduce the amount of hyperalgesia women develop around their incision after caesarean section
Participants	Ages eligible for study: aged between 18 and 45 years Genders eligible for Study: females only Estimated enrolment: 90

Bollag 2009 (*Continued*)

Interventions	Participants are randomized to three groups; all receive a bilateral transverse abdominis plane block: 1) Placebo/sham with normal saline 2) TAP (150 mg bupivacaine) 3) Clo-TAP (150 mg bupivacaine + 150 µg clonidine)
Outcomes	Short-form McGill pain questionnaire 2 (SF-MPQ-2) but this is a secondary outcome only. Primary outcome is postoperative area of hyperalgesia 48 hrs after the start of the caesarean section
Starting date	November 16, 2009
Contact information	Jake C Kraft, BSc, Tel: +1 206-543-7859, e-mail: kraft@uw.edu Lisa Y Flint, BSc, Tel +1 206-543-7817, e-mail: lyflint@uw.edu
Notes	Contact: Lisa Y Flint, BSc

Honigmann 2007

Trial name or title	Investigating the effect of intra-operative infiltration with local anaesthesia on the development of chronic postoperative pain after inguinal hernia repair. A randomized placebo controlled triple blinded and group sequential study design
Methods	Prevention, randomized, double-blind, placebo control, parallel assignment, safety/efficacy study
Participants	Ages eligible for study: 18 years and older Genders eligible for study: both Estimated enrolment: 264
Interventions	264 patients scheduled for an inguinal hernia repair using one of three procedures (Lichtenstein, Barwell and TEP = total extraperitoneal hernioplasty) are being randomly allocated intra-operatively into two groups. Group I patients receive a local injection of 20 ml Carbostesin® 0.25% at the end of the operation according to a standardised procedure. Group II patients get a 20 ml placebo (0.9% Saline) injection. We use pre-filled identically looking syringes for blinded injection, i.e. the patient, the surgeon and the examinator who performs the postoperative clinical follow-ups remain unaware of group allocation. The primary outcome of the study is the occurrence of developing chronic pain (defined as persistent pain at three months FU) measured by VAS and Pain Matcher® device (Cefar Medical AB, Lund, Sweden) In addition to a sample size re-evaluation three interim analyses are planned after 120, 180 and 240 patients had finished their three-months follow-up to allow for early study termination
Outcomes	Primary outcome measures: occurrence of chronic pain at three months Secondary outcome measures: Level of pain: pain matcher®,VAS; areas of hyperalgesia, hypnaesthesia; hospitalization:Length of stay (days); ASA-classification; beginning of mobilization (days); return to work or normal activity (days and %); quality of life (SF36) at one year
Starting date	July 2006

Contact information	Jürg Metzger, PD Dr. med. Tel: +41 41 205 48 60 e-mail: juerg.metzger@ksl.ch Philipp Honigmann, Dr. med. Tel: +41 41 205 16 16 e-mail: philipp.honigmann@ksl.ch
Notes	

Offner 2007

Trial name or title	Prospective, randomized, single-blinded, monocentric clinical study to compare postoperative analgesia and outcome after combined paravertebral and intrathecal versus thoracic epidural analgesia for thoracotomy
Methods	Treatment, randomized, single-blind, active control, parallel assignment, safety/efficacy study
Participants	Ages eligible for study: 18 years to 75 years Genders eligible for study: both Estimated enrolment: 200
Interventions	Intrathecal opioids and thoracic paravertebral analgesia versus thoracic epidural analgesia Timing is unclear, as is the inclusion of a non-regional control group The hypothesis is that combining intrathecal sufentanil and morphine with an application of thoracic paravertebral ropivacaine would provide equal analgesia compared to thoracic epidural analgesia with ropivacaine and sufentanil. The authors further speculate that this new regimen would have a lower risk for the typical side effects due to TEA, such as block failure, hypotension or urinary retention
Outcomes	Primary outcome measures: The primary outcome measures used are pain at rest, at coughing, and on movement at each time point, as reported by the patient using a standard visual analogue score (VAS). [Time frame: within the first three days] Secondary outcome measures: event rate of side-effects (nausea, vomiting, sedation score, respiratory depression, hypotension, pruritus, urinary retention), total number of doses of piritramide administered, patient satisfaction, and risk of chronic pain. [Time frame: within one year]
Starting date	June 2007
Contact information	Torsten Loop, MD Tel: +49761-2702306 e-mail: torsten.loop@uniklinik-freiburg.de
Notes	

Sessler 2009

Trial name or title	Regional anesthesia and breast cancer recurrence: prospective, randomized, double-blinded, multicenter clinical trial to compare postoperative analgesia and cancer outcome after combined paravertebral versus thoracic epidural v general anaesthesia for breast cancer surgery
Methods	Prevention, randomized, open label, active control, parallel assignment, efficacy study
Participants	Ages eligible for study: 18 to 85 years Genders eligible for study: women only Estimated enrolment: 1100 Patients undergoing mastectomies or isolated lumpectomy with axillary node dissection
Interventions	Combined paravertebral versus thoracic epidural versus general anaesthesia
Outcomes	Cancer recurrence, chronic pain among others, with a follow up of five years
Starting date	Jan 2007
Contact information	Nancy Graham, RN Tel: +1216-445-7530 e-mail: grahamn@ccf.org
Notes	

Wylde 2011

Trial name or title	Arthroplasty Pain Experience (APEX) Study
Methods	Single-centre double-blind randomized controlled clinical trial
Participants	300 participants after total knee replacement (TKR) and 300 participants after total hip replacement (THR) for OA patients are being recruited
Interventions	Participants randomized to the interventional arm of the trial will receive a local wound infiltration, in addition to the standard anaesthetic regimen during surgery. The local anaesthetic mixture will consist of 60 ml of 0.25% bupivacaine with 1 in 200,000 adrenaline
Outcomes	Participants are assessed for the severity of joint pain on the first 5 days postoperative, and then at 3-months, 6-months and 12-months. The primary outcome is the WOMAC Pain Scale, a validated measure of joint pain at 12 months
Starting date	25/11/2009
Contact information	Miss Vicky Wylde Bristol Implant Research Centre Southmead Hospital Southmead Road Westbury-On-Trym email: helen.lewis@nbt.nhs.uk

Notes	Funded by the National Institute for Health Research (NIHR) (UK) - Central Commissioning Facility (CCF)

DATA AND ANALYSES

Comparison 1. Local anaesthetics and regional anaesthesia for persistent pain after surgery (pooled)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Dichotomous pain outcomes at six months	5		Odds Ratio (IV, Random, 95% CI)	Subtotals only
1.1 Thoracotomy (epidural analgesia))	3	250	Odds Ratio (IV, Random, 95% CI)	0.34 [0.19, 0.60]
1.2 Breast cancer surgery (paravertebral block)	2	89	Odds Ratio (IV, Random, 95% CI)	0.37 [0.14, 0.94]
2 Dichotomous pain outcomes at twelve months	3		Odds Ratio (IV, Random, 95% CI)	Totals not selected
2.1 Thoracotomy (epidural analgesia)	1		Odds Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 Breast cancer surgery (paravertebral block)	2		Odds Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]

Comparison 2. Local anaesthetics and regional anaesthesia for persistent pain after surgery (not-pooled)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Dichotomous pain outcomes at six months	9		Odds Ratio (IV, Random, 95% CI)	Totals not selected
1.1 Plastic surgery of the breast (local infiltration)	1		Odds Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 Breast Cancer Surgery (multimodal pain therapy)	1		Odds Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
1.3 Limb amputation (epidural analgesia)	2		Odds Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
1.4 Laparotomy (epidural analgesia)	2		Odds Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
1.5 Cesarean section (wound/pelvic irrigation)	2		Odds Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
1.6 Other surgery	1		Odds Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
2 Dichtotmous pain outcomes at twelve months	5		Odds Ratio (IV, Random, 95% CI)	Totals not selected
2.1 Limb amputation (various)	2		Odds Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
2.2 Laparotomy	1		Odds Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
2.3 Other surgery	2		Odds Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]

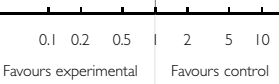
Analysis 1.1. Comparison 1 Local anaesthetics and regional anaesthesia for persistent pain after surgery (pooled), Outcome 1 Dichotomous pain outcomes at six months.

Review: Local anaesthetics and regional anaesthesia for preventing chronic pain after surgery

Comparison: 1 Local anaesthetics and regional anaesthesia for persistent pain after surgery (pooled)

Outcome: 1 Dichotomous pain outcomes at six months

Study or subgroup	Favours regional n/N	Conventional Pain Control n/N	Odds Ratio IV,Random,95% CI	Weight	Odds Ratio IV,Random,95% CI
1 Thoracotomy (epidural analgesia))					
Ju 2008	26/48	31/43		43.4 %	0.46 [0.19, 1.10]
Lu 2008	9/62	12/28		31.4 %	0.23 [0.08, 0.63]
Senturk 2002	25/46	18/23		25.2 %	0.33 [0.10, 1.04]
Subtotal (95% CI)	**156**	**94**		**100.0 %**	**0.34 [0.19, 0.60]**
Total events: 60 (Favours regional), 61 (Conventional Pain Control)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.04$, df = 2 (P = 0.59); $I^2 = 0.0\%$					
Test for overall effect: Z = 3.69 (P = 0.00023)					
2 Breast cancer surgery (paravertebral block)					
Ibarra 2011	5/15	7/14		39.3 %	0.50 [0.11, 2.24]
Kairaluoma 2006	5/30	12/30		60.7 %	0.30 [0.09, 1.00]
Subtotal (95% CI)	**45**	**44**		**100.0 %**	**0.37 [0.14, 0.94]**
Total events: 10 (Favours regional), 19 (Conventional Pain Control)					
Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.27$, df = 1 (P = 0.60); $I^2 = 0.0\%$					
Test for overall effect: Z = 2.09 (P = 0.036)					



Analysis 1.2. Comparison 1 Local anaesthetics and regional anaesthesia for persistent pain after surgery (pooled), Outcome 2 Dichotomous pain outcomes at twelve months.

Review: Local anaesthetics and regional anaesthesia for preventing chronic pain after surgery

Comparison: 1 Local anaesthetics and regional anaesthesia for persistent pain after surgery (pooled)

Outcome: 2 Dichotomous pain outcomes at twelve months

Study or subgroup	Regional Anaesthesia n/N	Conventional Pain Control n/N	Odds Ratio IV,Random,95% CI	Odds Ratio IV,Random,95% CI
1 Thoracotomy (epidural analgesia)				
Ju 2008	16/38	22/39		0.56 [0.23, 1.39]
2 Breast cancer surgery (paravertebral block)				
Baudry 2008	16/29	8/24		2.46 [0.80, 7.55]
Kairaluoma 2006	2/30	10/30		0.14 [0.03, 0.72]

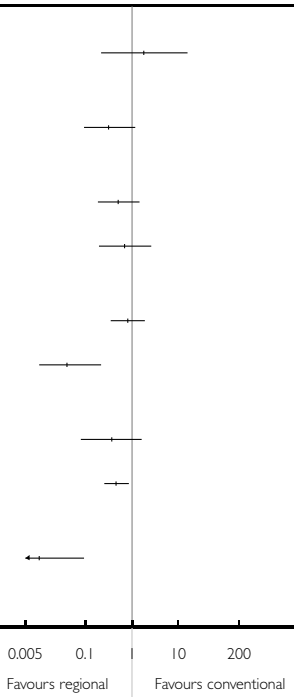
Analysis 2.1. Comparison 2 Local anaesthetics and regional anaesthesia for persistent pain after surgery (not-pooled), Outcome 1 Dichotomous pain outcomes at six months.

Review: Local anaesthetics and regional anaesthesia for preventing chronic pain after surgery

Comparison: 2 Local anaesthetics and regional anaesthesia for persistent pain after surgery (not-pooled)

Outcome: 1 Dichotomous pain outcomes at six months

Study or subgroup	Favours regional n/N	Conventional Pain Control n/N	Odds Ratio IV,Random,95% CI	Odds Ratio IV,Random,95% CI
1 Plastic surgery of the breast (local infiltration)				
Bell 2001	3/8	2/8		1.80 [0.21, 15.41]
2 Breast Cancer Surgery (multimodal pain therapy)				
Fassoulaki 2005	6/20	12/21		0.32 [0.09, 1.17]
3 Limb amputation (epidural analgesia)				
Karanikolas 2006	12/38	12/25		0.50 [0.18, 1.42]
Katsuly-Liapis1996	7/27	6/18		0.70 [0.19, 2.58]
4 Laparotomy (epidural analgesia)				
Katz 2004	22/72	13/37		0.81 [0.35, 1.88]
Lavand'homme 2005	2/60	9/20		0.04 [0.01, 0.22]
5 Cesarean section (wound/pelvic irrigation)				
Lavand'homme 2007	3/30	7/30		0.37 [0.08, 1.58]
Shahin 2010	19/176	37/178		0.46 [0.25, 0.84]
6 Other surgery				
Mounir 2010	2/20	20/22		0.01 [0.00, 0.09]



Analysis 2.2. Comparison 2 Local anaesthetics and regional anaesthesia for persistent pain after surgery (not-pooled), Outcome 2 Dichtotmous pain outcomes at twelve months.

Review: Local anaesthetics and regional anaesthesia for preventing chronic pain after surgery

Comparison: 2 Local anaesthetics and regional anaesthesia for persistent pain after surgery (not-pooled)

Outcome: 2 Dichtotmous pain outcomes at twelve months

Study or subgroup	Regional Anaesthesia n/N	Conventional Pain Control n/N	Odds Ratio IV,Random,95% CI	Odds Ratio IV,Random,95% CI
1 Limb amputation (various)				
Katsuly-Liapis1996	2/27	2/18		0.64 [0.08, 5.01]
Reuben 2006	25/29	23/28		1.36 [0.32, 5.69]
2 Laparotomy				
Lavand'homme 2005	2/59	6/20		0.08 [0.01, 0.45]
3 Other surgery				
Paxton 1995	0/30	14/30		0.02 [0.00, 0.33]
Singh 2007	0/9	7/11		0.03 [0.00, 0.68]

APPENDICES

Appendix 1. Lay explanation of intervention and comparator: regional anaesthesia versus conventional analgesia

Conventional analgesia

Drugs used to treat pain are called analgesics or painkillers. They act on receptors of the peripheral and central nervous systems. Painkillers are mainly divided in opioids and non-opioids. Non-opioids include paracetamol (acetaminophen in the US) and the non-steroidal anti-inflammatory drugs (NSAIDs), a well-known example being aspirin. Opioids include weaker opioids like codeine and stronger ones like morphine and fentanyl.

A disadvantage is that painkillers work systemically, in other words in the entire body not just locally where the pain is felt. Painkillers have adverse and side effects. NSAIDs' typical side effects range from mild stomach upset to severe gastrointestinal bleeding. Ketorolac, the only intravenous NSAID approved in the US, is used with caution as it potentially can cause kidney damage. In higher doses all NSAIDs can damage the kidney. Newer (COX-2 antagonists) and older NSAIDs except aspirin, may increase the risk of myocardial infarction and stroke. Opioids often cause nausea and vomiting, drowsiness and constipation. In the elderly in particular they can cause delirium and hallucinations. At higher doses opioids can cause potentially dangerous respiratory depression, in other words causing

patients to stop breathing. Patients often describe that opioids take the edge off the pain and make it bearable, but do not completely suppress the pain.
The WHO pain ladder is often used to titrate the painkillers to effect: Mild pain is treated ideally with just NSAIDs. Stronger pain is treated with a combination of NSAID and mild or stronger opioids as needed. After surgery patients sometimes cannot eat right way; hence medication cannot be administered orally, but has to be given intravenously. Opioids are sometimes administered by patient controlled analgesia (PCA). A PCA machine administers intravenous opioids when the patient presses a button. This allows the patient to titrate the medication to meet his or her individual needs better. The PCA machine is programmed such that the patient cannot overdose by pressing the PCA button too often. In spite of the ubiquitous availability and the relatively low price for conventional painkillers in the industrialized world, many patients find their pain under-treated.

Local anaesthetics and regional anaesthesia

Local anaesthetics block nerve conduction if applied close to nerves. We included studies that applied local anaesthetics close to peripheral nerves (nerve block), close to a nerve plexus (plexus block) or in the spinal canal (spinal or epidural anaesthesia). We also included studies that irrigated the operative field with local anaesthetics or infused local anaesthetics in the wound, or localised local anaesthetics by tourniquet to the operated limb an extremity (Bier Block). We include the intravenous delivery of local anaesthetics (IVRA) as local anaesthetics might also have beneficial anti-hyperalgesic (Strichartz 2008) and anti-inflammatory properties (Herroeder 2007), even if administered systemically.
We included studies where local anaesthetics were given as a single shot or as a continuous infusion through catheters or controlled-release preparations, dermal patches etc.
Adjuvants like ketamine may enhance the effect of local anaesthetics. They act through different receptors on the nerves. We included studies regardless if they also employed adjuvants or opioids, either locally or systemically in the experimental and/or in the control groups. We included studies that employed local or regional analgesia for any length of time during the perioperative period, for example only for the 24 hours preceding the operation or only for postoperative pain control.
We compared if local anaesthetics work better than conventional pain control in reducing the event rate of persistent pain after surgery. Hence, we excluded studies that only compared different regional anaesthesia techniques or varying dose regimens of local anaesthetics during the same perioperative time span and studies using local anaesthetics for other than anaesthetic or analgesic purposes (for example as anti-arrhythmics).

Appendix 2. MEDLINE search strategy via PubMed

#01 “Anesthesia, Conduction”[MeSH]
#02 “Anesthesia, Spinal”[MeSH]
#03 “Analgesia, Epidural”[MeSH]
#04 “Anesthesia, Epidural”[MeSH] OR “Anesthesia, Caudal”[MeSH]
#05 “Nerve Block”[MeSH]
#06 regional anaesthesia[Text Word] OR regional anesthesia[Text Word]
#07 “conduction anesthesia”[Text Word]
#08 spinal block[Text Word]
#09 epidural block*
#10 epidural anesthesia[Text Word] OR epidural anaesthesia[Text Word]
#11 plexus block*
#12 plexus[All Fields] AND block[All Fields]
#13 bier[All Fields] AND block[All Fields]
#14 Ropivacaine
#15 Lidocaine
#16 Bupivacaine
#17 Tetracaine
#18 Mepivacaine
#19 Prilocaine
#20 levobupivacaine
#21 “Anesthetics, Local”[MeSH] OR “Anesthetics, Local”[Pharmacological Action] OR “Anesthesia, Local”[MeSH]

#22 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21
#23 phantom limb[MeSH Terms]
#24 phantom limb[Text Word]
#25 "mastectomy"[MeSH Terms]
#26 mastectomy[Text Word]
#27 "thoracotomy"[MeSH Terms]
#28 thoracotomy[Text Word]
#29 postsurgical[All Fields]
#30 "pain"[MeSH Terms]
#31 pain[Text Word]
#32 (#23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29) AND (#30 OR #31)
#33 hyperalgesia
#34 allodynia
#35 "pain, postoperative"[MeSH Terms]
#36 Postoperative pain[Text Word]
#37 "Phantom Limb/prevention and control"[MeSH] OR "Pain, Postoperative/prevention and control"[MeSH]
#38 preventive analgesia[All Fields] OR ((preventive analg*)) OR ((pre-emptive analg*)) OR ((preemptive analg*))
#39 #32 OR #33 OR #34 OR #35 OR #36 OR #36 OR #37 OR #38
#40 chronic[All Fields] OR weeks[All Fields] OR months[All Fields]
#41 #39 AND #22
#42 #39 AND #22 Limits: only items with abstracts
#43 #41 NOT #42
#44 #42 AND #40
#45 #44 OR #43
#46 (randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized controlled trials[mh] OR random allocation[mh] OR single-blind method[mh] OR double blind method[mh] OR clinical trial[pt] OR clinical trials[mh] OR "clinical trial"[tw] OR ((singl* [tw] OR doubl*[tw] OR trebl*[tw] OR tripl*[tw]) AND (mask*[tw] OR blind*[tw])) OR placebos [mh] OR placebo*[tw] OR random*[tw] OR re design[mh:noexp] OR comparative study[pt] OR follow-up studies[mh] OR prospective studies[mh] OR control*[tw] OR prospectiv*[tw] OR volunteer*[tw]) NOT (animals[mh] NOT humans[mh])
#47 #45 AND #46
#48 16192774[uid] OR 12411810[uid] OR 10608205[uid] OR 9365449[uid] OR 7979074[uid] OR 3419837[uid]
#49 #48 AND #47
Comments:
#01 through #13 search for anaesthesia interventions employing local anaesthetics
#14 through #21 search for local anaesthetics by text and thesaurus
#22 Sum of all INTERVENTIONS
#23 through #29 search for certain postsurgical conditions
#30 &#31 search for pain
#32 combining certain postoperative conditions AND pain
#33 through #38 for other terms associated with postoperative pain
#39 Sum of all painful postoperative CONDITIONS
#40 search for FOLLOW-UP
#41 CONDITION AND INTERVENTION
#42 and #43 separating the hits into those WITH and WITHOUT abstracts
#44 We limit only those hits WITH abstracts to FOLLOW-UP
#45 RESULTS All hits WITHOUT abstracts are included and added to those WITH abstracts AND FOLLOW-UP
#46 Cochrane highly sensitive strategy
#47 Limiting RESULTS to Cochrane highly sensitive strategy
#48 and #49 Test if all articles quoted in the protocol are found by the strategy strategy

Appendix 3. CINAHL (EBSCOhost) search strategy

S3 S1 and S2 (99)
S2 (TX (thoracotomy or phantom limb or mastectomy or postsurgical) and (MJ Pain or TX pain)) or (MJ pain, postoperative) or (hyperalgesia or allodynia or preventive analgesia or pre-emptive analgesia or preemptive analgesia)
S1 MJ Anesthesia, Caudal or MJ Nerve Block or TX (regional anaesthesia or regional anesthesia or conduction anesthesia) or TX (spinal block* or epidural block* or plexus block* or epidural anesthesia or epidural anaesthesia) or TX (bier and block) or TX (Ropivacaine or Lidocaine or Bupivacaine or Tetracaine or Mepivacaine or Prilocaine or levobupivacaine) or MJ Anesthetics, Local or MJ Anesthesia, Local or (MJ Anesthesia, Conduction or MJ Anesthesia, Spinal or MJ Analgesia, Epidural)
MJ = Word in Major Subject Heading
TX = All text
S1, S2 = #1, #2

Appendix 4. EMBASE (Ovid SP) search strategy

1 regional anesthesia/ or spinal anesthesia/ or epidural anesthesia/ or caudal anesthesia/ or nerve block/ or local anesthesia/ or anesthetic agent/
2 ((an?esthesia adj3 (conduction or regional or epidural)) or (block* adj3 (epidural or spinal or plexus or bier)) or (Ropivacain* or Lidocain* or Bupivacain* or Tetracaine or Mepivacaine or Prilocaine or levobupivacaine)).ti,ab.
3 1 or 2
4 ((pain/ or pain.ti,ab.) and (agnosia/ or mastectomy/ or thoracotomy/ or (postsurgical or (phantom limb or mastectomy or thoracotomy)).ti,ab.)) or ((analg* adj3 (preventive or pre?emptive)) or (postoperative adj3 pain)).ti,ab.
5 hyperalgesia/ or allodynia/ or postoperative-pain/
6 4 or 5
7 3 and 6
8 limit 7 to abstracts
9 7 not 8
10 7 and (chronic or week* or month*).af.
11 9 or 10
12 (randomized-controlled-trial/ or randomization/ or controlled-study/ or multicenter-study/ or phase-3-clinical-trial/ or phase-4-clinical-trial/ or double-blind-procedure/ or single-blind-procedure/ or (random* or cross?over* or factorial* or placebo* or volunteer* or ((singl* or doubl* or trebl* or tripl*) adj3 (blind* or mask*))).ti,ab.) not (animals not (humans and animals)).sh.
13 11 and 12

Appendix 5. CENTRAL search strategy

#1 MeSH descriptor Anesthesia, Conduction explode all trees
#2 MeSH descriptor Anesthesia, Spinal explode all trees
#3 MeSH descriptor Analgesia, Epidural explode all trees
#4 MeSH descriptor Anesthesia, Epidural explode all trees
#5 MeSH descriptor Anesthesia, Caudal explode all trees
#6 MeSH descriptor Nerve Block explode all trees
#7 (regional anaesthesia) or (regional anesthesia)
#8 (conduction anesthesia)
#9 (spinal block)
#10 (epidural block*)
#11 (epidural anaesthesia) or (epidural anesthesia)
#12 (plexus block*)
#13 (plexus) and (block)
#14 (bier) and (block)
#15 ropivacaine
#16 lidocaine

#17 bupivacaine
#18 tetracaine
#19 mepivacaine
#20 prilocaine
#21 levobupivacaine
#22 MeSH descriptor Anesthetics, Local explode all trees
#23 MeSH descriptor Anesthesia, Local explode all trees
#24 ((#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23))
#25 MeSH descriptor Phantom Limb explode all trees
#26 phantom limb
#27 MeSH descriptor Mastectomy explode all trees
#28 mastectomy
#29 MeSH descriptor Thoracotomy explode all trees
#30 thoracotomy
#31 postsurgical
#32 MeSH descriptor Pain explode all trees
#33 pain
#34 ((#25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31) AND (#32 OR #33))
#35 hyperalgesia
#36 allodynia
#37 MeSH descriptor Pain, Postoperative explode all trees
#38 postoperative pain
#39 preventive analg*
#40 pre-emptive analg*
#41 preemptive analg*
#42 (#34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41)
#43 (chronic) or (weeks) or (months)
#44 (#24 AND #42)
Exported only clinical trials

Appendix 6. Data extraction sheet template

Cochrane Anaesthesia Review Group
Study Selection, Quality Assessment & Data Extraction Form
Person Extracting Data: **MHA** DAA AT .....

ID #	First author	Journal/Conference etc	Proceedings	Year	PMID/Identifier unpublished

Study eligibility

RCT	Local or regional anaesthesia	Chronic postsurgical Pain	Relevant follow up of six to 12 months
Yes / No / Unclear	**Yes** / No / Unclear	**Yes** / No / Unclear	**Yes** / No / Unclear

Do not proceed if any of the above answers are 'No'. If study to be included in 'Excluded studies' section of the review, record below the information/reason to be inserted into 'Table of excluded studies'. Done:

Freehand space for comments on study design and treatment:

References to trial

Check other references identified in searches. If there are further references to this trial link the papers now & list below. All references to a trial should be linked under one *Study ID* in RevMan.

Code each paper	ID#	Author(s)	Journal/Conference Proceedings etc	Year	PMID/Identifier
A		*The paper listed above*			
B		*Further papers*			
C					

Participants and trial characteristics

Trial characteristics	
	Further details
Single centre / multicentre	
Country / Countries and Dates	
Trial design (circle) parallel or _____	preemptive v. postoperative preemptive v. non regional postoperative v. non regional regional (unclear/mixed) v. non regional

(*Continued*)

	three groups (preempt. v. postop v. non regional) __ groups ___ ____ ____ _____	
Participant characteristics		
	Further details	
n		
Age (mean, SD)		
Paediatric Population %	0	
Sex of participants (men/women)		
Exclusion Criteria		
Comorbidities		
Intervention		
Regional anaesthesia	Local/Nerve/Plexus/Paravert. Block/Epidural/Spinal/___	
Local Anaesthetic/intrathecal opioid	Lidocaine/Bupivacaine/ Ropivicaine/_____ Opioid: Y/N	
Duration of Regional Anesthesia	Single shot/catheter technique for __?48hrs ? SD)	
Effective Regional Anaesthesia	reported not reported comment:_____	
Early Postoperative Pain Control	reported not reported comment:_____	
Allodynia - Hyperalgesia Assessment	reported not reported comment:_____	
Adjuvants none reported	Systemic or local Ketamine/ Clonidine/ ____	
Condition		
Surgery	Breast surgery/thoracotomy/amputation/hernia/cholecystectomy/_____ ___	
Comments		

(*Continued*)

Methodological quality (Jü ni 2001)
Grader A/B

Selection bias/Allocation of intervention		
State here method used to generate allocation and reasons for grading	Grade (circle)	Bias likely
Allocation is clearly described. An accepted randomized method is used. Randomization is done at appropriate time point Detail: _____	Adequate (Random)	no
	Inadequate (e.g. alternate)	yes
	Unclear	Unclear

Performance bias/Concealment of allocation **Process used to prevent foreknowledge of group assignment in a RCT, which should be seen as distinct from blinding**		
State here method used to conceal allocation and reasons for grading	Grade (circle)	Bias likely?
Concealment of allocation is explained. Provider and patients are unaware of allocation throughout treatment/observation period, respectively Detail: _____	Adequate	no
	Inadequate	yes
	Unclear	Unclear

Detection bias/Blinding		**Bias likely**	
Person responsible for participants care	Yes / No / Unclear		
Participant	Yes / No / Unclear		
Outcome assessor	Yes / No / Unclear		
Other (please specify) _____	Yes / No / Unclear		

(*Continued*)

Comments:			

Attrition bias/Intention-to-treat An intention-to-treat analysis is one in which all the participants in a trial are analysed according to the intervention to which they were allocated, whether they received it or not	
Loss to follow up?	reported reported as none uncertain/not reported not applicable
ITT Analysis?	reported not reported no uncertain/not reported not applicable
PP Analysis?	reported not reported uncertain/not reported not applicable
Were withdrawals described?	Yes No not clear
How were lost patients/withdraw accounted for:	Last observation carried forward information collected at end of study uncertain/not reported excluded
Comments	
Bias likely	Yes/No/Unclear

Data extraction

Primary Outcome:

Dichotomous Data not reported

Table 1: Comparison @ _ months __ and __versus __	Treatment Group	Comparison Group	Total
Number randomized			
Number analysed ITT			
Number analysed PP			

Table 2: Comparison @ _months_versus _	Treatment Group	Comparison Group	Total
Number randomized			
Number analysed ITT			
Number analysed PP			

Continuous Outcome - difference in symptom score (include +/- or CI if provided)
not reported group numbers as above

Pain Score	Treatment Group	Comparison Group	Between Group Difference
Baseline, preop +/- SD Not reported			
Immediat postop +/- SD not reported			
6 Months +/- SD not reported			
12 Months +/- SD not reported			

Outcomes: not reported (Affecting daily life) (6months)

Outcome/Instrument @6 months _____	Treatment Group	Comparison Group

Table 1: Quality Control: _____	Treatment Group	Comparison Group	Total
Effective Regional			
Failed Regional			
Comment:			

Effective regional anaesthesia quality control: not reported

Withdrawals and adverse events (report number of patients)

not reported

	Treatment Group	Comparison Group
Any adverse event not reported		
Withdrawals due to adverse events		
Withdrawals due to any reason		
Comments:		

Other information which you feel is relevant to the results
Indicate if: any data were obtained from the primary author; if results were estimated from graphs etc; or calculated by you using a formula (this should be stated and the formula given). In general if results not reported in paper(s) are obtained this should be made clear here to be cited in review

***Authors* contacted** once/twice **by** email & letter **Response** Yes/No

Freehand space for writing actions such as contact with study authors and changes

References to other trials/data
Are there any references to published or unpublished data in this article?

Code each paper	Author(s)	Journal/Conference Proceedings etc	Year	PMID/Identifier	Published
A					Yes/No
B					Yes/No
C					Yes/No
D					Yes/N

Appendix 7. Table of surgeries, interventions, timing and outcomes by subgroup

study ID	regional technique	timing of intervention	adjuvants	outcomes	Continuous	Follow up (month)
Plastic Surgery of the Breast Bell 2001	Local infiltration	Single shot, preincision versus control	None	Pain/no pain	Allodynia/ hyperalgesia	6 months
Breast Cancer Surgery Baudry 2008	Local infiltration	Single shot, preincision versus control	None	Pain/no pain	McGill results not reported	18 months
Ibarra 2011	Single shot, paravertebral block	Single shot, preincision versus control	none	myofascial, phantom or neuropathic pain		3 and 5 months
Kairaluoma 2006	Single shot, paravertebral block	Single shot, preincision versus control	None	NRS > 3	Analgesic consumption	12 months
Fassoulaki 2005	Topical application	Postincision, continuous postop versus control	Gabapentin	Pain/no pain	Analgesic consumption	6 months
Caesaeran Section Lavand'homme 2007	Wound irrigation	preincision, continuous postop versus control	None	Pain/no pain	Analgesic consumption	6 months
Shahin 2010	Peritoneal instillation	Postincision, single shot versus placebo	None	Pain/no pain	NRS	8 months
ICBG Singh 2007	Wound irrigation	Postincision, continuous postop versus control	None	Pain/no pain	VAS, pain frequency, functional activity score, overall satisfaction	4.7 years
Hernia repair Burney 2004	Spinal	Single shot, preincision versus control	None	?	SF-36	6 months
Mounir 2010	Wound infiltration	Single shot post incision versus placebo	None	Pain/no pain	none	6 months

(*Continued*)

Laparotomy Lavand'homme 2005	Epidural	Preincision, continuous postop versus control	Ketamine, Clonidine	Pain/no pain	Mental Health Inventory	12 months
Katz 2004	Epidural	Single shot, pre- versus postop versus none	None	Pain/no pain	Pain Disability Index and Mental Health Inventory	6 months
Amputation Karanikolas 2006	Epidural	Pre- v. intra v. post v. all v. none	None	Pain/no pain	VAS,phantom pain frequency, McGill	6 months
Katsuly-Liapis1996	Epidural	Pre- v. postop v. none	None	Pain/no pain		12 months
Pinzur 1996	Nerve sheath irrigation	Intra- & continuous postop versus none	NoneP	Pain/no pain	McGill	6 months
Reuben 2006	Nerve sheath irrigation	Single shot, postincision versus control	Clonidine	Phantom pain, stump pain		12 months
Prostatectomy Haythornthwaite 1998	Epidural	Preincision versus postop	None	Pain/no pain	Allodynia/ hyperalgesia	6 months
Shoulder Bain 2001	Brachial plexus block	Single shot, preincision versus control	None		VAS, mean analgesic dosages, orthopedic functional score	12 months
Thoracatomy Ju 2008	Epidural	Preincision and postop versus control	None	Pain/no pain	Allodynia	12 months
Senturk 2002	Epidural	Preincision versus postop versus control	None	Pain/no pain	NRS, pain affecting daily living	6 months
Lu 2008	Epidural	Preincision versus postop versus control	None	Pain/no pain		6 months
Katz 1996	Intercostal nerve blocks	Single shot, postincision versus control	None	Pain/no pain	VRS, analgesic consumption	18 months

(*Continued*)

Vasectomy Paxton 1995	Local injection Vas deferens	Single shot, postincision versus control	None	Discomfort/no discomfort		12 months

Appendix 8. Table of included patients

Patients included	@6months	@12 months
Thoracotomy	250	77
Amputation	108	102
Breast cancer surgery	89	113
Laparotomy	189	79
Cesarean section	414	0
Other surgery	42	80
Sum	**1092**	**41**

Appendix 9. Table of studies with short follow up

Reference	Follow up
Aguilar 1994	3 months
Aguirre 2012	3 months
Baguneid 1997	3 Months
Batoz 2009	2 months
Blumenthal 2005	3 months
Brown 2004	3 months
Chiu 2008	3 months
Fassoulaki 2000	3 months

(*Continued*)

Fassoulaki 2001	3 months
Gottschalk 1998	9.5 weeks
Gundes 2000	3 months
Hirakawa 1996	3 months
Iohom 2006	3 months
Jirarattanaphochai 2007	3 months
King 2006	3 months
Loane 2012	3 months
Miguel 1993	3 months
Milligan 2002	3 months
O'Neill 2012	3 months
Ouaki 2009	3 months
Perniola 2009	3 months
Popova 1990	3 months
Saber 2009	2 months
Schaller 2005	<6 months
Shir 1994	<6 months
Sprung 2006	3 months
Suvikapakornkul 2009	3 months
Vigneau 2011	2 months

Appendix 10. Pseudo-randomization

One study (Nikolajsen 1997) was excluded for pseudo-randomization, even though the exclusion did not alter our results. This was a double blinded (patients and outcome assessors) pseudo-randomized controlled clinical trial on preoperative epidural analgesia for limb amputation with a follow up of 12 months including 60 adults in a university setting in Aarhus, Denmark.
We detail our risk of bias assessment below:

Randomization: High risk of bias

"We stratified patients into two groups according to the intensity of their preamputation pain." "Patients were assigned to a group 'by the toss of a coin',..." "The next patient ... was assigned to the opposite treatment." "We randomized women and men separately."
Many authors would include this as an acceptable method of randomization. The review authors feel that the "toss of a coin" is not an adequate method of sequence generation, because it is open to tampering and prone to errors. If in doubt, the adequacy of sequence generation should be questioned (Higgins 2011).

Allocation Concealment: High risk of bias

"The first patient who entered the study with a preamputation pain intensity of less than 30 mm on a VAS was assigned to the blockade or control group by the toss of a coin. The next patient with a VAS score of less than 30 mm was assigned to the opposite treatment. We followed this procedure for patients with a preamputation pain intensity of 30 mm or greater on VAS. If the first patient with a VAS of 30 mm or more was assigned to the blockade group by the coin method, the next patient would automatically be assigned to the control group. We randomized women and men separately.
Attempts to concealment were not reported. "The next patient ... was assigned to the opposite treatment." This made allocation predictable. The review authors take the view that this is pseudo-randomisation because the allocation for every second patient is 'pre-ordained' (Higgins 2011).

Blinding of participants and personnel (performance bias): High risk of bias

"SI was responsible for pain treatment before and during the amputation" but also did the randomization. Also the interoperative provider had to know allocation to adjust doses "to epidural pain treatment (blockade group) or not (control group)." Postop, patients could not identify the group they had been allocated to, when "To assess masked conditions among patients, SI asked patients at the 6-month interview what treatment they received before amputation (epidural blockade or oral/intramuscular morphine)."

Blinding of outcome assessment (detection bias): Low risk of bias

"LN was informed about stratification by preamputation pain intensity, but was otherwise unaware of treatment assignment. Staff (apart from the attending nurse anaesthetist who was informed for safety reasons) and patients were not informed about treatment assignment."

Incomplete outcome data (attrition bias): Low risk of bias

"Patients who underwent amputation during follow-up were excluded from further analysis." Attrition was reported in detail also with respect to group assignments, but no intention to treat analysis was considered.

Appendix 11. Adverse effects

Adverse effects

Reporting of adverse effects was mostly anecdotal. Two studies reported no adverse effects (Bain 2001, Pinzur 1996). Several studies reported anecdotal adverse effects. Adverse effects included cardiac arrhythmias (Ochroch 2006a), bleeding duodenal ulcers (Doyle 1998a), chronic backache after epidural analgesia (Lavand'homme 2005), wound or regional anaesthesia catheter infection (Haythornthwaite 1998; Lavand'homme 2007, Nikolajsen 1997; Paxton 1995; Singh 2007), including one subcutaneous infection and a case of meningitis, attributed to the regional anaesthesia catheter (Nikolajsen 1997). Cases of severe intraoperative chest rigidity and severe nausea were reported (Katz 2004). One patient convulsed during regional anaesthesia (Kairaluoma 2006).

Systematic between group comparisons of adverse effects:

Three included studies (Fassoulaki 2005; Ju 2008; Lavand'homme 2005) compared adverse effects between the experimental and the control group, but the studies and the collected data sets were too heterogenous for meta-analysis. (Lavand'homme 2005) compared adverse effects between groups prospectively and found that orthostatic hypotension was significantly less frequent in patients in the control arm, receiving intravenous analgesics. Lavand'homme 2005 reported no adverse psychomimetic effects of adjuvant low dose intravenous ketamine in the same study. (Ju 2008) compared side effects of opioid neuroaxial treatment between groups and found a similar event rate of nausea, vomiting and sedation similar between groups, but pruritus more frequent in the regional anaesthesia arm. (Fassoulaki 2005) reported higher event rates of adverse effects (depression, local inflammation and thrombosis) in the control groups, but deemed them unrelated to the anaesthesia intervention. Two prospective randomized trials on long term adverse effects after labour epidural analgesia did not fulfil the inclusion criteria of this review (Howell 2001; Loughnan 2002).

WHAT'S NEW

Last assessed as up-to-date: 3 April 2012.

Date	Event	Description
2 July 2013	Amended	Journal version of review (Andrea 2013) cited in 'Other published versions of this review'

CONTRIBUTIONS OF AUTHORS

All authors read and approved the manuscript before submission.

Conceiving the review: Andreae MH

Co-ordinating the review: Andreae MH

Undertaking manual searches: Andreae MH and Andreae DA

Screening search results: Andreae MH and Andreae DA

Organizing retrieval of papers: Andreae MH

Screening retrieved papers against inclusion criteria: Andreae MH and Andreae DA

Appraising quality of papers: Andreae MH and Andreae DA,

Abstracting data from papers: Andreae MH and Andreae DA

Writing to authors of papers for additional information: Andreae MH

Providing additional data about papers:

Obtaining and screening data on unpublished studies: Andreae MH

Data management for the review: Andreae MH

Entering data into Review Manager (RevMan 5.1): Andreae MH

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Other statistical analysis not using RevMan: Andreae MH

Double entry of data: Andreae MH and Andreae DA

Interpretation of data: Andreae MH; Andreae DA

Statistical inferences: Andreae MH

Writing the review: Andreae MH

Securing funding for the review: Andreae MH

Performing previous work that was the foundation of the present study:

Guarantor for the review (one author): Andreae MH

Person responsible for reading and checking review before submission: Andreae MH and Andreae DA

DECLARATIONS OF INTEREST

Michael Andreae: none known.

Doerthe A Andreae: none known.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Improved immediate postoperative pain control

We did not perform a planned subgroup analysis on improved pain control defined at the patient and not at the study level, because of the risk of time depended bias.

Timing of local or regional anaesthesia

We focused exclusively on the prevention of the risk of persistent pain by local anaesthetics regardless of the timing of the intervention to improve clarity and prevent confusion about pre-emptive versus preventive analgesia.

Pooling dichotomous and continuous data

We did not pool the dichotomous data with the continuous data by calculating odds ratios based on the standardized mean differences (a secondary analysis detailed in the protocol) as all studies included in our data synthesis reported dichotomous data.

Sensitivity analysis

We had not planned to test the sensitivity of our results to the model assumptions (Sensitivity analysis).

Change in authors

Various review contributors (A. Timmer, R. Ruecker, E. Motschall), who co-authored the protocol changed institution and/or could no longer participate sufficiently to warrant co-authorship. The lead author sought local statistical advice at his new institution as needed.

NOTES

None to date

INDEX TERMS

Medical Subject Headings (MeSH)

*Anesthesia, Conduction; *Anesthetics, Local; Amputation [adverse effects]; Analgesia [*methods]; Breast Neoplasms [surgery]; Cesarean Section [adverse effects]; Chronic Pain [*prevention & control]; Laparotomy [adverse effects]; Nerve Block [methods]; Pain, Postoperative [*prevention & control]; Randomized Controlled Trials as Topic; Thoracotomy [adverse effects]

MeSH check words

Female; Humans; Male; Pregnancy