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Epidural analgesia versus patient-controlled intravenous analgesia for pain following intra-abdominal surgery in adults (Review)

Salicath JH, Yeoh ECY, Bennett MH

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[Intervention Review]

Epidural analgesia versus patient-controlled intravenous analgesia for pain following intra-abdominal surgery in adults

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ABSTRACT

Background

Intravenous patient-controlled analgesia (IVPCA) with opioids and epidural analgesia (EA) using either continuous epidural administration (CEA) or patient-controlled (PCEA) techniques are popular approaches for analgesia following intra-abdominal surgery. Despite several attempts to compare the risks and benefits, the optimal form of analgesia for these procedures remains the subject of debate.

Objectives

The objective of this review was to update and expand a previously published Cochrane Review on IVPCA versus CEA for pain after intra-abdominal surgery with the addition of the comparator PCEA. We have compared both forms of EA to IVPCA. Where appropriate we have performed subgroup analysis for CEA versus PCEA.

Search methods

We searched the following electronic databases for relevant studies: Cochrane Central Register of Controlled Trials (CENTRAL) (2017; Issue 8), MEDLINE (OvidSP) (1966 to September 2017), and Embase (OvidSP) (1988 to September 2017) using a combination of MeSH and text words. We searched the following trial registries: Australian New Zealand Clinical Trials Registry, ClinicalTrials.gov, and the EU Clinical Trials Register in September 2017, together with reference checking and citation searching to identify additional studies.

We included only randomized controlled trials and used no language restrictions.

Selection criteria

We included all parallel and cross-over randomized controlled trials (RCTs) comparing CEA or PCEA (or both) with IVPCA for postoperative pain relief in adults following intra-abdominal surgery.

Data collection and analysis

Two review authors (JS and EY) independently identified studies for eligibility and performed data extraction using a data extraction form. In cases of disagreement (three occasions) a third review author (MB) was consulted. We appraised each included study to assess the risk of bias as outlined in Section 8.5 of the *Cochrane Handbook for Systematic Reviews of Interventions*. We used GRADE to assess the quality of the evidence.

Main results

We included 32 studies (1716 participants) in our review. There are 10 studies awaiting classification and one ongoing study. A total of 869 participants (51%) received EA and 847 (49%) received IVPCA. The EA trials included 16 trials with CEA (418 participants) and 16 trials with PCEA (451 participants). The studies included a broad range of surgical procedures (including hysterectomies, radical prostatectomies, Caesarean sections, colorectal and upper gastrointestinal procedures), a wide range of adult ages, and were performed in several different countries.

Our pooled analyses suggested a benefit with regard to pain scores (using a visual analogue scale between 0 and 100) in favour of EA techniques at rest. The mean pain reduction at rest from waking to six hours after operation was 5.7 points (95% confidence interval (CI) 1.9 to 9.5; 7 trials, 384 participants; moderate-quality evidence). From seven to 24 hours, the mean pain reduction was 9.0 points (95% CI 4.6 to 13.4; 11 trials, 558 participants; moderate-quality evidence). From 24 hours the mean pain reduction was 5.1 points (95% CI 0.9 to 9.4; 7 trials, 393 participants; moderate-quality evidence). Due to high statistical heterogeneity, no pooled analysis was possible for the estimation of pain on movement at any time. Two single studies (one using CEA and one PCEA) reported lower pain scores with EA compared to IVPCA at 0 to 6 hours and 7 to 24 hours. At > 24 hours the results from 2 studies (both CEA) were conflicting.

We found no difference in mortality between EA and IVPCA, although the only deaths reported were in the EA group (5/287, 1.7%). The risk ratio (RR) of death with EA compared to using IVPCA was 3.37 (95% CI 0.72 to 15.88; 9 trials, 560 participants; low-quality evidence).

A single study suggested that the use of EA may result in fewer episodes of respiratory depression, with an RR of 0.47 (95% CI 0.04 to 5.69; 1 trial; low-quality evidence). The successful placement of an epidural catheter can be technically challenging. The improvements in pain scores above were accompanied by an increase in the risk of failure of the analgesic technique with EA (RR 2.48, 95% CI 1.13 to 5.45; 10 trials, 678 participants; moderate-quality evidence); the occurrence of pruritus (RR 2.36, 95% CI 1.67 to 3.35; 8 trials, 492 participants; moderate-quality evidence); and episodes of hypotension requiring intervention (RR 7.13, 95% CI 2.87 to 17.75; 6 trials, 479 participants; moderate-quality evidence). There was no clear evidence of an advantage of one technique over another for other adverse effects considered in this review (Venous thromboembolism with EA (RR 0.32, 95% CI 0.03 to 2.95; 2 trials, 101 participants; low-quality evidence); nausea and vomiting (RR 0.94, 95% CI 0.69 to 1.27; 10 trials, 645 participants; moderate-quality evidence); sedation requiring intervention (RR 0.87, 95% CI 0.40 to 1.87; 4 trials, 223 participants; moderate-quality evidence); or episodes of desaturation to less than 90% (RR 1.29, 95% CI 0.71 to 2.37; 5 trials, 328 participants; moderate-quality evidence)).

Authors' conclusions

The additional pain reduction at rest associated with the use of EA rather than IVPCA is modest and unlikely to be clinically important. Single-trial estimates provide low-quality evidence that there may be an additional reduction in pain on movement, which is clinically important. Any improvement needs to be interpreted with the understanding that the use of EA is also associated with an increased chance of failure to successfully institute analgesia, and an increased likelihood of episodes of hypotension requiring intervention and pruritus. We have rated the evidence as of moderate quality given study limitations in most of the contributing studies. Further large RCTs are required to determine the ideal analgesic technique. The 10 studies awaiting classification may alter the conclusions of the review once assessed.

PLAIN LANGUAGE SUMMARY

Patient-controlled intravenous pain relief compared to pain relief into the epidural space following abdominal surgery in adults

Review question

This review examined pain relief after abdominal surgery. We compared the self administration of pain-relieving drugs such as morphine using a machine connected to an intravenous drip (IVPCA) versus pain relief administered into the tissue around the spine cord within the spinal canal (epidural) using either self administration with a programmable pump (PCEA) or a pre-programmed continuous pump (CEA). The epidurals used morphine-like drugs or local anaesthetics, or both. We assessed how effective these methods were at reducing pain and the likelihood of unwanted effects.

Background

Adequate pain relief is essential for good postoperative recovery and improves the ability to take deep breaths and get out of bed soon after surgery. Patients with poorly controlled pain are at increased risk of serious complications such as chest infections and blood clots to the lungs. At the same time, pain relief can produce side effects and complications. Two of the most common and most effective pain relief alternatives are opioids (such as morphine) injected into an intravenous drip each time the patient presses a button (IVPCA) and epidural pain relief, in which medications are administered to the epidural space around the spinal cord. Previous systematic reviews have suggested that the epidural technique might provide better pain relief than IVPCA.

Search date

We thoroughly searched the major electronic databases and trial registries for randomized trials (a type of study in which participants are assigned to a treatment group using a random method) comparing IVPCA with epidural techniques. We also searched the reference lists of relevant studies for further eligible trials. The evidence is current to September 2017.

Review characteristics

We included 32 studies (1716 participants). A total of 869 participants received epidural analgesia and 847 received intravenous analgesia. The epidural studies included 16 studies with CEA (418 participants) and 16 studies with PCEA (451 participants). All participants were adults undergoing intra-abdominal surgery in a hospital setting.

Key results

Our review suggests that an epidural technique provides better pain relief than IVPCA; however, at rest the difference is small (between 5 and 9 points on a 100-point scale) and may not be important to patients. On movement the difference was larger and may be important. However, there was a higher chance of failure to successfully establish the analgesic technique with the epidural, and of episodes of both low blood pressure that required treatment and itching when using the epidural approach. The death rate in the included studies was so low that we could not conclude whether death is more likely with one or the other approach.

Quality of the evidence

We considered the overall methodological quality of the included studies to be moderate or low, which was due partly to the lack of any attempt to conceal the technique used from the participants and researchers in most studies, and partly because many studies were small, and the results were not precise.

Conclusion

There is a small additional benefit in terms of pain relief when using an epidural technique. The relatively small benefit needs to be balanced against potential risks of inserting an epidural catheter, in particular the failure to put the catheter in the correct place to get good pain relief and the occurrence of low blood pressure and itch needing treatment.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Epidural analgesia versus intravenous patient-controlled analgesia for pain following intra-abdominal surgery in adults

Epidural analgesia (EA) versus intravenous patient-controlled analgesia (IVPCA) for pain following intra-abdominal surgery in adults

Patient or population: adults undergoing intra-abdominal surgery (including hysterectomies, radical prostatectomies, Caesarean sections, colorectal and upper gastrointestinal procedures)

Setting: hospitals in Europe, North America, Scandinavia, Australia, and China

Intervention: epidural analgesia (both delivered as a continuous infusion (CEA) or as an on-demand intermittent dose (PCEA)). Commonly used agents included bupivacaine, ropivacaine, fentanyl, and morphine.

Comparison: IVPCA. Commonly used agents included morphine and fentanyl.

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	N° of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with IVPCA	Risk with epidural analgesia				
Pain score at rest assessed with VAS from 0 to 100 (higher score indicates more pain)	0 to 6 hours		-	384 (7 RCTs)	⊕⊕⊕⊖ Moderate ¹	
	The mean pain score ranged across the control groups from 19 to 54.	5.7 points lower with EA than IVPCA (1.9 to 9.5)				
	7 to 24 hours		-	558 (11 RCTs)	⊕⊕⊕⊖ Moderate ¹	
	The mean pain score ranged across the control groups from 17 to 38.	9.0 points lower with EA than IVPCA (4.6 to 13.4)				
	> 24 hours		-	393 (7 RCTs)	⊕⊕⊕⊖ Moderate ¹	
	The mean pain score ranged across the control groups from 8 to 30.	5.1 points lower with EA than IVPCA (0.9 to 9.4)				
Pain score on movement assessed with VAS from 0 to 100 (higher score indicates more pain)	0 to 6 hours		-	80 (2 RCTs)	⊕⊕⊖⊖ Low ²	No pooled data available for analysis, as only a single trial reported mean and SD
	Both trials reported lower pain scores using an epidural technique compared with IVPCA. Pain scores were 7.0 to 8.0 points lower with epidural analgesia in these trials (mean scores with IVPCA 34 and 53, respectively).					

	7 to 24 hours	-	103 (2 RCTs)	⊕⊕⊕⊖ Low ²	No pooled data available for analysis
	Both trials reported lower pain scores using an epidural technique compared with IVPCA. Pain scores were 10 points lower using PCEA (mean IVPCA score 38) (Aydogan 2015), and 26 points lower using CEA (mean IVPCA score 51) (Carli 2002).				
	> 24 hours	-	102 (2 RCTs)	⊕⊕⊕⊖ Low ²	No pooled data available for analysis, as only a single trial reported mean and SD
	The trials drew different conclusions. 1 trial reported a 16-point lower pain score using CEA (mean in IVPCA group of 39), and 1 trial reported a small 3-point difference in favour of IVPCA (mean of 25 points).				
All-cause mortality rate at 30 days	Study population ³	RR 3.37 (0.72 to 15.88)	560 (9 RCTs)	⊕⊕⊕⊖ Low ²	Due to lack of events in IVPCA arms, the risk with EA was derived by summing the events and sample sizes from EA treatment arms across the studies.
	0 per 1000 17 per 1000 (2 to 32)				
Failure of analgesic technique requiring alternative approach (assessed at any time)	Study population ³	RR 2.48 (1.13 to 5.45)	678 (10 RCTs)	⊕⊕⊕⊖ Moderate ¹	
	34 per 1000 120 per 1000 (55 to 175)				
Adverse events (assessed at any time during follow-up)	Venous thromboembolism	RR 0.32 (0.03 to 2.95)	101 (2 RCTs)	⊕⊕⊕⊖ Low ²	
	Study population				
	41 per 1000 13 per 1000 (1 to 59)				
	Pruritus	RR 2.36 (1.67 to 3.35)	492 (8 RCTs)	⊕⊕⊕⊖ Moderate ¹	
	Study population				

127 per 1000	299 per 1000 (211 to 424)				
Nausea and vomiting		RR 0.94 (0.69 to 1.27)	645 (10 RCTs)	⊕⊕⊕⊖ Moderate ¹	
Study population					
352 per 1000	331 per 1000 (243 to 447)				
Sedation		RR 0.87 (0.40 to 1.87)	223 (4 RCTs)	⊕⊕⊕⊖ Moderate ¹	
Study population					
112 per 1000	98 per 1000 (45 to 210)				
Respiratory rate < 10 breaths/minute		RR 0.47 (0.04 to 5.69)	40 (1 RCT)	⊕⊕⊖⊖ Low ²	No pooled data for analysis, as only a single trial gave case numbers for each group (Yosunkaya 2003)
Study population					
100 per 1000	47 per 1000 (4 to 569)				
Oxygen saturation < 90%		RR 1.29 (0.71 to 2.37)	328 (5 RCTs)	⊕⊕⊕⊖ Moderate ¹	
Study population					
86 per 1000	111 per 1000 (61 to 204)				
Hypotension requiring intervention		RR 7.13 (2.87 to 17.75)	479 (6 RCTs)	⊕⊕⊕⊖ Moderate ¹	
Study population					
17 per 1000	120 per 1000 (48 to 300)

***The risk in the intervention group** (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).

CEA: continuous epidural analgesia; **CI:** confidence interval; **EA:** epidural analgesia; **IVPCA:** intravenous patient-controlled analgesia; **PCEA:** patient-controlled epidural analgesia; **RCT:** randomized controlled trial; **RR:** risk ratio; **SD:** standard deviation; **VAS:** visual analogue scale

GRADE Working Group grades of evidence

High quality: We are very confident that the true effect lies close to that of the estimate of the effect.

Moderate quality: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low quality: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low quality: There is substantial uncertainty in this estimate: the true effect is likely to be substantially different from the estimate of effect.

¹Downgraded one level for study limitations.

²Downgraded two levels for study limitations (relating to blinding) and imprecision.

³Assumed risk in IVPCA group derived from available trial data in this review.

BACKGROUND

Description of the condition

The experience of postoperative pain is a predictable result of intra-abdominal surgery and can be ameliorated by several alternative classes of drugs and routes of administration. Postoperative analgesia is therefore a routine part of patient management, and postoperative pain is one of the most important problems that confront surgical patients. It affects the cardiovascular, respiratory, and endocrine systems (Kouraklis 2000; Rademaker 1992), and is distressing for the patient. Adequate perioperative analgesia has been shown to improve clinical outcomes, avoid complications, reduce hospital stay (Wickstrom 2005), and improve patient satisfaction (Myles 2000; Sauaia 2005).

Successful analgesia can be a complex clinical problem and difficult to achieve in all cases, whatever the modality chosen. There are limitations regardless of modality due to adverse effects, problems with administration, and variable pharmacokinetics and pharmacodynamics (Miller 2009a). The type of analgesia that a patient receives is dependent on multiple factors. These include type of procedure, comorbidities, institutional factors (including nursing, allied health, and medical expertise) and the surgeon, anaesthetist, and patient preferences (Kehlet 2005).

Description of the intervention

Intravenous patient-controlled analgesia (IVPCA) with opioid drugs (morphine-like) and epidural analgesia (EA) are popular techniques for analgesia following intra-abdominal surgery. The latter may be delivered either by continuous infusion (CEA) or using a patient-controlled device analogous to the intravenous device (PCEA). Both CEA and PCEA can employ epidural local anaesthetic or opioid, or both. The optimal form of analgesia following intra-abdominal surgery remains the subject of debate despite several attempts to compare the risks and benefits.

Intravenous patient-controlled analgesia with opioids was popularized around 1971 (Evans 1976; Keeri-Szanto 1971), and ushered in a new concept of analgesia. The patient was essentially put in control of his or her own analgesia for the first time through the use of an electronic controller. Whenever the patient required more analgesia, he or she could push a button, which would result in a predetermined small dose of opioid being released into the venous line. Patients can consequently titrate the delivery of the opioid to their individual pain levels.

Continuous epidural administration and PCEA involve a catheter advanced percutaneously into the epidural space (Miller 2009b), with subsequent administration of local anaesthetic or an opioid, or a combination of both (Miller 2009a; Wheatley 2001). Continuous epidural administration utilizes a pump to continuously administer the analgesic solution at a rate set by the clinician. Patient-controlled epidural analgesia utilizes a pump with an electronic controller, and the patient can control the administration of a predetermined dose of the analgesic. Patient-controlled epidural analgesia is often combined with a background continuous infusion (Miller 2009a).

How the intervention might work

Systemic modes of opioid administration, such as intramuscular (IM), subcutaneous (SC), and intravenous (IV), act on all parts

of the body that have opioid receptors, especially the central nervous system. Opioids via IVPCA offer improved analgesia compared with nurse-delivered IM or SC opioids, while the risks of sedation, hypoventilation, and nausea are similar (McNicol 2015; Walder 2001). Intravenous patient-controlled analgesia requires less nursing time compared with IM and SC opioids (Chang 2004; Rittenhouse 1999). There have been multiple systematic reviews comparing IVPCA with nurse-administered opioid analgesia in surgical patients (Ballantyne 1993; McNicol 2015; Walder 2001). These confirmed the advantages of IVPCA and found that patients preferred IVPCA over nurse-administered IM and SC opioids. Postoperative continuous IV opioid infusion compared with IVPCA on a general ward causes a significantly increased incidence of respiratory depression (Schug 1993). For the purposes of this review we accept that IVPCA is usually superior to opioid administration by IM or SC injections or continuous IV infusion.

Epidural analgesia by either CEA or PCEA is thought to reduce the sympathetic stress response associated with surgery via a reduction in nociceptive stimulation reaching the central nervous system. The potential benefits of EA include earlier gastrointestinal recovery, Basse 2002; Gendall 2007; Zingg 2009, improved respiratory, Ballantyne 1998; Guay 2016, and cardiovascular function, Beattie 2001; Guay 2016, and reduced immunological suppression, Ahlers 2008; Beilin 2003. The benefits seem to be more pronounced for patients with a high risk of complications, particularly with respect to pulmonary complications, bowel recovery, and postoperative myocardial infarction (Hanna 2009). Epidural analgesia may reduce the risk of venous thromboembolism (Rodgers 2000), however the increased use of routine thromboprophylaxis potentially decreases this beneficial effect of EA.

Why it is important to do this review

Epidural analgesia techniques have been compared to IVPCA, but it remains unclear which technique is the better overall and in which situations (Benzon 1993; Parker 1992). Both techniques use agents with well-established analgesic actions. The purpose of this review was to examine the benefits and harms that may arise from choosing the different routes of administration (IVPCA versus EA) and of choosing a patient-controlled analgesia approach compared to a continuous epidural infusion (CEA versus PCEA and IVPCA).

Epidural analgesia compared with IVPCA may be associated with fewer systemic side effects of the opiates, such as respiratory depression and sedation, while delivering excellent analgesia (Brodnier 2000). However, EA is more time consuming and invasive, requires a high level of technical skills and pharmacological knowledge, and has a significantly higher cost (Bartha 2005; Tilleul 2012). Epidural analgesia also carries the rare but devastating risk of nerve injury or paralysis (Cook 2009; Ruppen 2006). The rates of treatment failure with EA are reported as between 10% and 30% (Bartha 2005; McLeod 2001; McLeod 2006). This is significantly higher than the failure rate of IVPCA, reported at 5% (Bartha 2005).

For all the reasons given, a systematic review of the relative merits of these three techniques may have significant clinical impact in informing the best choice of analgesia for individual patients and procedures.

This review updates and replaces a previously published Cochrane Review comparing the efficacy of IVPCA versus CEA. That review,

published in 2008, was withdrawn in 2013 ([Werawatganon 2013](#)). Werawatganon and colleagues concluded that CEA was superior to IVPCA in relieving postoperative pain for up to 72 hours in participants undergoing intra-abdominal surgery. There was an increased rate of pruritus in the CEA group, but insufficient evidence to draw conclusions on other clinical advantages and disadvantages. This revised review includes PCEA in addition to CEA in order to further identify the best strategy.

OBJECTIVES

The objective of this review was to update and expand a previously published Cochrane Review on IVPCA versus CEA for pain after intra-abdominal surgery with the addition of the comparator PCEA. We have compared both forms of EA to IVPCA. Where appropriate we have performed subgroup analysis for CEA versus PCEA.

METHODS

Criteria for considering studies for this review

Types of studies

We included parallel and cross-over randomized controlled trials (RCTs).

Types of participants

We included adults, aged 16 years and above, undergoing intra-abdominal surgery.

Types of interventions

Intravenous patient-controlled analgesia with opioid compared with epidural analgesia using either CEA or PCEA. The medication for the epidural could be any opioid, local anaesthetic agent, or a combination of these two classes of drugs.

Types of outcome measures

Unless otherwise stated, these outcomes were evaluated at any time during the duration of individual studies.

Primary outcomes

1. Pain score at rest and on movement, by a visual analogue scale (VAS) on a 0-to-100 scale or similar, during the initial 6-hour period (early phase), 6- to 24-hour period (mid-phase), and 24- to 72-hour period (late phase). We considered analysis of the data as continuous (compare mean pain scores between groups).
2. All-cause mortality rate at 30 days

Secondary outcomes

1. Pain on coughing assessed as for primary outcome
2. The number of failures to establish the allocated technique (defined as a clinical decision to use a second analgesic technique, which could be due to multiple reasons such as failure of insertion of epidural, inadequate analgesia, epidural catheter withdrawal or dislodgement, infection, neurological deficit, etc.)
3. Length of hospital stay (days)
4. Time to ambulation (hours)
5. Patient satisfaction, measured by a validated scale as reported
6. Quality of life, measured by a validated scale as reported

Adverse effects

1. Demonstrated venous thromboembolism rate
2. Pruritus
3. Nausea and vomiting
4. Epidural haematoma
5. Sedation
6. Respiratory complications such as respiratory depression (respiratory rate less than 10 per minute or requirement for opioid antagonist), hypoxaemia (defined as SpO₂ < 90% by pulse oximetry)
7. Hypotension requiring treatment

Search methods for identification of studies

Electronic searches

We identified RCTs through literature searching with systematic and sensitive search strategies as outlined in Section 6.4 of the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)). We did not apply restrictions to language or publication status.

We searched the following databases for relevant trials.

1. MEDLINE (Ovid SP, 1966 to 10 September 2017)
2. Embase (Ovid SP, 1988 to 10 September 2017)
3. Cochrane Central Register of Controlled Trials (CENTRAL; 2017, Issue 8)

We developed a subject-specific search strategy in MEDLINE and used that as the basis for the search strategies in the other listed databases. Where appropriate, the search strategy was expanded with search terms for identifying RCTs. Search strategies can be found in [Appendix 1](#), [Appendix 2](#), and [Appendix 3](#).

We developed the search strategy in consultation with the Information Specialist.

Searching other resources

We scanned the following trial registries for ongoing and unpublished trials (10th of September 2017).

1. Australian New Zealand Clinical Trials Registry (www.anzctr.org.au)
2. US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov)
3. EU Clinical Trials Register (www.clinicaltrialsregister.eu)

We searched the reference lists and citations of retrieved articles to identify further relevant trials. When necessary we contacted trial authors for additional information.

Data collection and analysis

Selection of studies

Inclusion criteria

We included all trials that satisfied the following criteria and were not excluded in the next section.

1. RCTs.

2. Studies of adults during the postoperative period after open or laparoscopic intra-abdominal surgery, such as laparotomy, cholecystectomy, Whipple's operation, gastrectomy, splenectomy, hepatectomy, colectomy, low anterior resection, obstetric and pelvic surgery (we do not consider the following to be intra-abdominal procedures: endoscopic surgery such as endoscopic sphincterotomy during endoscopic retrograde cholangiopancreatography, oesophagogastrectomy, fundoplication and retroperitoneal procedures such as nephrectomy, nephrolithotomy, adrenalectomy, abdominal aneurysm repair). We included participants undergoing emergency or elective surgery.
3. Trials that compared the effects of any of the three pain control regimens: opioid via an IVPCA device with or without a background infusion, opioid or local anaesthetic via CEA, or opioid or local anaesthetic via PCEA. For EA, we included all start times (pre- or postoperatively).

Exclusion criteria

We excluded the following:

1. trials in which the patient-controlled analgesia device (IV or epidural) was operated by anyone other than the participant;
2. trials in which the intervention under investigation included receiving EA and opioid analgesia via another route.

Identifying trials

Two review authors (JS and EY) independently evaluated the titles and abstracts of all the studies identified by the search for potential eligibility. Any disagreements were resolved by discussion with a third review author (MB). The review authors were not blinded to the authors and source papers of the studies (we considered that blinding was difficult to achieve, time consuming, and might not substantially alter the results of the review) (Berlin 1997).

Having identified titles and reports, we retrieved the full texts of the potentially relevant reports and linked together multiple reports of the same study. At appropriate times and where required we corresponded with investigators to clarify study eligibility. We then made the final decisions on study inclusion and proceeded to data collection.

Data extraction and management

We constructed and pilot tested a data extraction form with five included studies. We modified the form based on its effectiveness as required (see Appendix 4). Two review authors (JS and EY) then independently entered the data onto the form for each study. Any disagreements were resolved by discussion with a third review author (MB).

When data from the same study were published in multiple reports, we collated these data onto a single data extraction form. We contacted the authors of individual studies where we could not extract data that were likely to exist.

We only included data from cross-over RCTs prior to cross-over due to concerns with potential carry-over effects.

Assessment of risk of bias in included studies

We appraised each included study to assess the risk of bias as outlined in Section 8.5 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

We scored each included study according to the seven criteria outlined in the *Cochrane Handbook* and 'Risk of bias' tables. We rated all studies as at 'low risk', 'unclear risk', or 'high risk' of bias for each criterion.

We considered cross-over RCTs as at unclear risk of bias for the 'other potential sources of bias' criterion, as we could only use pre-cross-over data for analysis in the review.

Measures of treatment effect

Dichotomous data

For proportions (dichotomous outcomes), we calculated the risk ratio (RR) with 95% confidence interval (CI). Where possible, all analyses were made on an intention-to-treat basis; where this was not possible, this was clearly stated. Where the 95% CI for the absolute risk difference did not cross zero, we calculated the number needed to treat for an additional beneficial outcome (NNTB) to avoid each additional outcome using the superior method of analgesia. We calculated the 95% CI from the 95% CI of the risk difference between the groups. We undertook sensitivity analyses to include participants (events) potentially lost to follow-up (see *Dealing with missing data*).

We included the following dichotomous outcomes.

1. All-cause mortality rate at 30 days.
2. Venous thromboembolism rate.
3. The number of failures to establish the allocated technique.
4. Adverse events.

Continuous data

For any continuous outcomes measured in the same way across trials, we reported a mean difference (MD) with 95% CI. We used the standardized mean difference (SMD) where trials measured the same outcome using different methods. We included the following continuous outcomes.

1. Mean pain score on VAS.

Unit of analysis issues

We dealt with unit of analysis issues as outlined in the relevant sections of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). If an included study had more than two arms, we allocated the control group between study arms in order to avoid double counting of control cases. If any included studies were cluster randomized, we intended to seek statistical advice as to the best approach to use.

We utilized the method outlined in Section 7.7.3.8 of the *Cochrane Handbook for Systematic Reviews of Interventions* to enable combining of means for our statistical analysis (Higgins 2011).

Dealing with missing data

For any trials indicating missing data on allocated participants, we used the 'best-case' and 'worst-case' scenario methods as cited

in Section 16.2 of the *Cochrane Handbook for Systematic Reviews of Interventions* to assess any effect of allocation of that missing data (Higgins 2011). In the 'best-case' scenario, all participants with missing outcomes in the experimental intervention group had good outcomes, and all those with missing outcomes in the control intervention group had poor outcomes. The 'worst-case' scenario is the converse.

Assessment of heterogeneity

We examined clinical heterogeneity and considered the appropriateness of meta-analysis. We used the I^2 statistic to measure statistical heterogeneity among the trials in each analysis. If we identified substantial heterogeneity, we explored it by prespecified subgroup analysis. The I^2 statistic describes the percentage of total variation across trials that is due to heterogeneity rather than sampling error. We considered there to be significant statistical heterogeneity if I^2 was greater than 50% (Higgins 2011).

If prespecified subgroup analyses did not explain the statistical heterogeneity, we planned to perform a sensitivity analysis by exclusion of poor-quality studies.

Assessment of reporting biases

If there were sufficient included trials for any outcome (more than 10 RCTs), we planned to assess whether the review was subject to publication bias by using a funnel plot to graphically illustrate variability between trials. If we detected asymmetry, we explored causes other than publication bias.

Data synthesis

We undertook analysis for statistical pooling using Review Manager 5 software (Review Manager 2014). For all meta-analyses using continuous outcomes, we applied a random-effects model with inverse variance method, and for binary outcomes we used the random-effects with Mantel-Haenszel method. If the I^2 was greater than 70%, we did not conduct a pooled analysis. As an estimate of the clinical relevance of any difference between the experimental intervention and control intervention, we calculated the NNTB with 95% CI when there was evidence of a difference between groups.

Subgroup analysis and investigation of heterogeneity

We considered heterogeneity from both a clinical perspective and through statistical testing using the I^2 statistic. In the absence of clear clinical heterogeneity, we considered the wisdom of conducting a pooled analysis by interpretation of the I^2 statistic as outlined in data synthesis. We considered performing subgroup analysis by analgesic technique (comparing IVPCA versus CEA and IVPCA versus PCEA), analgesic start time (pre- or postincision), drugs employed, drug doses, the use of thromboprophylaxis, open versus laparoscopic surgery, and region of surgery (e.g. pelvic versus intraperitoneal). However, we could only undertake subgroup analysis for the two different epidural techniques.

Sensitivity analysis

We performed sensitivity analysis by study quality (defined as more than two 'Risk of bias' domains rated as high risk) and missing data. For the latter, we assumed a best-case versus worst-case analysis for the allocation of any missing data.

Presentation of results

We have adjusted all VAS numbers to a zero (no pain) to 100 (maximum possible pain) scale. We analysed pain at three time points. When there was more than one estimate in a time period, we chose the latest pain score relevant to each phase. We have presented all differences between interventions as positive values to make the direction of benefit clear and to avoid the presentation of a 'negative benefit'.

To assess the clinical significance of differences in pain scores we used as a guide the article 'Measuring acute postoperative pain using the visual analogue scale: the minimal clinically important difference and patient acceptable symptom state' (Myles 2017). The minimal clinically important difference (MCID) is 9.9 mm on the VAS scale. Any analgesic interventions with a change of 10 mm or more out of 100 mm on the VAS scale signify a clinically significant difference.

'Summary of findings' table and GRADE

We used the principles of the GRADE system to assess the quality of the body of evidence associated with the specific outcomes of pain scores at rest and on movement, all-cause mortality rate, failure to establish the chosen technique, and the adverse events of hypotension requiring intervention, pruritus, the occurrence of venous thromboembolism, nausea and vomiting, sedation, and low arterial oxygen saturation below 90% (Guyatt 2008). We constructed a 'Summary of findings' table using the GRADE software (GRADEpro GDT). The GRADE approach appraises the quality of a body of evidence based on the extent to which one can be confident that an estimate of effect or association reflects the item being assessed. Quality of a body of evidence involves consideration of within-study risk of bias (methodologic quality), directness of evidence, heterogeneity of the data, precision of effect estimates, and risk of publication bias. Problems identified in any of these five domains resulted in downgrading the quality of the evidence one level for each problem.

RESULTS

Description of studies

Results of the search

The results of all literature searches up to September 2017 are presented in a PRISMA study flow diagram (Figure 1). The electronic literature search identified 1649 records. We identified an additional 979 potential trials through trial registry searches and 652 articles by handsearching reference lists of included publications and other review articles on the topic, for a total of 3280 records.

Figure 1. Study flow diagram.

Figure 1. (Continued)

After identification and removal of duplicate records, the total number of records was 2383. Two review authors (EY and JS) independently screened the abstracts of these records for eligibility and excluded 2268 abstracts found to be ineligible. We assigned 10 records as 'awaiting classification' and found one ongoing study. Two review authors (EY and JS) evaluated 104 full-text articles for eligibility. If there was insufficient information to enable us make a judgement, we attempted to contact the authors of the article for further information. Any disagreements regarding inclusion or exclusion of an article were resolved by consulting a third review author (MB). We excluded 72 full-text articles, and included 32 studies in the qualitative synthesis and 25 studies in the meta-analysis.

Of the 104 full-text articles reviewed, 97 were published in English, three in Chinese, two in German, one in Italian, and one in Russian. We organized clinicians fluent in the above languages to evaluate these studies. Of the 32 included studies, 31 were published in English, and one was published in Chinese.

Included studies

We included 32 trials in this review. A detailed description of the included trials can be found in the [Characteristics of included studies](#). Thirty of the 32 included studies were parallel-group randomized trials. The remaining two trials were cross-over randomized trials (Ngan 1997; Paech 1994); we included only the results prior to cross-over in this review.

Thirty-one of the included studies reported outcomes of interest for this review. One study met the inclusion criteria but did not report outcomes in a form relevant to this review (Schricker 2000).

Participants

The 32 included trials enrolled a total of 1797 participants, however 81 of these participants were excluded after randomization, leaving 1716 participants for analysis in our review. In two trials it was unclear how and when participants were lost (10 participants missing in Parker 1992 and seven participants missing in Steinberg 2002). The smallest trials had 16 participants each (Donatelli 2006; Liu 1995; Schricker 2000). The largest studies had 117 and 111 participants (Hübner 2015; Schumann 2003). Of the 1716 participants, 869 (51%) were allocated to EA and 847 (49%) to IVPCA. The EA trials included 16 trials with CEA (418 participants) and 16 trials with PCEA (451 participants). Details are given in [Appendix 5](#).

The included trials enrolled 942 females and 597 males; however, this does not equal the total number of enrolled participants, as four studies did not specify the gender of participants (Aceto 2002; Kowalski 1992; Madej 1992; Zutshi 2005). Five studies included only female participants (Ngan 1997; Paech 1994; Parker 1992; Tsui 1997; Wang 2004). Two studies included only male participants (Gupta 2006; Liu 1995).

The trials were mainly conducted in Europe and North America, with 11 European trials, Aceto 2002; Chauvin 1993; Gupta 2006; Heurich 2007; Hübner 2015; Jayr 1998; Madej 1992; Mann 2000; Motamed 1998; Taqi 2007; Welchew 1991, and 10 North American trials (Carli 2001; Carli 2002; Donatelli 2006; Kowalski 1992; Liu 1995; Parker 1992; Schricker 2000; Schumann 2003; Steinberg 2002; Zutshi 2005). Three trials were Middle Eastern (Aydogan 2015; Elkaradawy 2011; Yosunkaya 2003); six were Chinese (three from Hong Kong (Chen 2001; Ngan 1997; Tsui 1997), and three from mainland China (Chen 2015a; Wang 2004; Zeng 2003)); and two were Australian (Barratt 2002; Paech 1994).

Surgical procedure

The trials included a variety of intra-abdominal surgical procedures. In six studies the surgical procedures were heterogeneous (Chauvin 1993; Heurich 2007; Jayr 1998; Mann 2000; Motamed 1998; Zeng 2003). In three studies the procedure was exclusively elective Caesarean section (Ngan 1997; Paech 1994; Parker 1992); in two studies the procedures were hysterectomies (Madej 1992; Wang 2004); and in one study the procedure was gynaecological lower abdominal surgery through a vertical midline incision (Tsui 1997).

Ten studies enrolled colorectal procedures (Aceto 2002; Carli 2001; Carli 2002; Chen 2015a; Donatelli 2006; Hübner 2015; Schricker 2000; Steinberg 2002; Taqi 2007; Zutshi 2005), of which two specifically identified themselves as laparoscopic surgery (Hübner 2015; Taqi 2007).

In seven studies the procedures were upper abdominal surgery (Barratt 2002; Chen 2001; Elkaradawy 2011; Kowalski 1992; Schumann 2003; Welchew 1991; Yosunkaya 2003). Of the remaining three studies, two studies were radical prostatectomies (Gupta 2006; Liu 1995), and in one study the procedure was donation for liver transplantation (Aydogan 2015).

Types of anaesthesia and analgesia

The methods of surgical anaesthesia and postoperative analgesia of the included trials are summarized in [Appendix 6](#). Five trials had more than two treatment groups ([Ngan 1997](#); [Parker 1992](#); [Schumann 2003](#); [Wang 2004](#); [Zeng 2003](#)). The remaining studies had two treatment groups: one group received postoperative epidural analgesia (intervention group), and the other group received postoperative systemic opioid analgesia (control group).

In all studies except five participants who received postoperative epidural analgesia also received epidural anaesthesia during surgery. In one of the five trials ([Aydogan 2015](#)), the epidural was commenced 15 minutes before the completion of surgery, and for the remaining four ([Chauvin 1993](#); [Jayr 1998](#); [Motamed 1998](#); [Welchew 1991](#)), the epidural infusion was commenced after surgery. In eight studies participants who received postoperative IVPCA received epidural anaesthesia during surgery ([Gupta 2006](#); [Kowalski 1992](#); [Liu 1995](#); [Madej 1992](#); [Ngan 1997](#); [Paech 1994](#); [Parker 1992](#); [Tsui 1997](#)).

Most study participants received general anaesthesia during surgery, and anaesthetic agents were similar between the control and intervention groups in each study. Inhalational anaesthetics were the main anaesthetic agent for most trials except for [Zutshi 2005](#), which did not specify the anaesthetic agents used. General anaesthesia was not used in three studies ([Ngan 1997](#); [Paech 1994](#); [Parker 1992](#)), and in group E of [Wang 2004](#).

Level of epidural catheter

See [Appendix 6](#) for details. Twenty trials used thoracic epidural ([Aceto 2002](#); [Barratt 2002](#); [Carli 2001](#); [Carli 2002](#); [Chauvin 1993](#); [Chen 2001](#); [Chen 2015a](#); [Donatelli 2006](#); [Elkaradawy 2011](#); [Gupta 2006](#); [Hübner 2015](#); [Mann 2000](#); [Motamed 1998](#); [Schricker 2000](#); [Schumann 2003](#); [Steinberg 2002](#); [Taqi 2007](#); [Welchew 1991](#); [Yosunkaya 2003](#); [Zutshi 2005](#)), and four used lumbar epidural ([Madej 1992](#); [Ngan 1997](#); [Tsui 1997](#); [Wang 2004](#)). In two other trials, either a low thoracic or upper lumbar epidural was placed, depending on the site of surgery ([Heurich 2007](#); [Zeng 2003](#)).

The level of the epidural catheter placement was not mentioned in the remaining six trials ([Aydogan 2015](#); [Jayr 1998](#); [Kowalski 1992](#); [Liu 1995](#); [Paech 1994](#); [Parker 1992](#)).

Epidural drugs administered postoperatively

The epidural drugs administered postoperatively included local anaesthetic (bupivacaine or ropivacaine) and opioid, opioid only, and local anaesthetic only. The opioids used were morphine, fentanyl, hydromorphone, diamorphine, pethidine, alfentanil, and sufentanil. Details for each trial are given in [Appendix 6](#).

Local anaesthetic and opioid

Bupivacaine and opioid were administered in 16 trials, of which 11 used fentanyl ([Barratt 2002](#); [Carli 2001](#); [Carli 2002](#); [Donatelli 2006](#); [Heurich 2007](#); [Hübner 2015](#); [Schricker 2000](#); [Taqi 2007](#); [Tsui 1997](#); [Wang 2004](#); [Zutshi 2005](#)); two used morphine ([Chen 2015a](#); [Motamed 1998](#)); one used diamorphine ([Madej 1992](#)); one used sufentanil ([Mann 2000](#)); and one used pethidine ([Schumann 2003](#)).

Ropivacaine and opioid were administered in four trials: three used fentanyl ([Elkaradawy 2011](#); [Gupta 2006](#); [Steinberg 2002](#)), and one used sufentanil ([Aceto 2002](#)).

One trial had five different treatment arms, of which three received epidural local anaesthetic and opioid ([Zeng 2003](#)). One arm received ropivacaine and fentanyl; one arm received bupivacaine and fentanyl; and one arm received bupivacaine and morphine.

Opioid only

Opioid only was used in 10 trials, of which morphine was used in two trials ([Aydogan 2015](#); [Yosunkaya 2003](#)), fentanyl in two trials ([Kowalski 1992](#); [Welchew 1991](#)), pethidine in two trials ([Chen 2001](#); [Paech 1994](#)), hydromorphone in two trials ([Liu 1995](#); [Parker 1992](#)), and alfentanil in one trial ([Chauvin 1993](#)). The remaining trial had two EA treatment arms, one using fentanyl and the other pethidine ([Ngan 1997](#)).

Local anaesthetic only

One trial used ropivacaine only ([Jayr 1998](#)).

Drugs used for intravenous patient-controlled analgesia

The following opioids were used for IVPCA: morphine in 21 trials ([Aceto 2002](#); [Aydogan 2015](#); [Carli 2001](#); [Carli 2002](#); [Chen 2015a](#); [Donatelli 2006](#); [Elkaradawy 2011](#); [Gupta 2006](#); [Hübner 2015](#); [Jayr 1998](#); [Kowalski 1992](#); [Mann 2000](#); [Motamed 1998](#); [Schricker 2000](#); [Schumann 2003](#); [Steinberg 2002](#); [Taqi 2007](#); [Tsui 1997](#); [Yosunkaya 2003](#); [Zeng 2003](#); [Zutshi 2005](#)), fentanyl in two trials ([Wang 2004](#); [Welchew 1991](#)), pethidine in two trials ([Chen 2001](#); [Paech 1994](#)), and hydromorphone in two trials ([Liu 1995](#); [Parker 1992](#)). One trial used alfentanil ([Chauvin 1993](#)); one used diamorphine ([Madej 1992](#)); and one used piritramide ([Heurich 2007](#)). In the remaining two trials the participants received one of two opioids: [Barratt 2002](#) used fentanyl and morphine, [Ngan 1997](#) used fentanyl and pethidine.

Duration of postoperative analgesia regimen

The duration of the analgesia protocols studied varied from 12 to 72 hours.

Funding sources

Eight trials received financial support from national funding sources and foundations ([Barratt 2002](#); [Carli 2002](#); [Chen 2015a](#); [Heurich 2007](#); [Mann 2000](#); [Schricker 2000](#); [Schumann 2003](#); [Taqi 2007](#)), and seven received financial support from local universities and hospitals ([Carli 2001](#); [Donatelli 2006](#); [Gupta 2006](#); [Hübner 2015](#); [Ngan 1997](#); [Paech 1994](#); [Taqi 2007](#)). Four trials received funding from pharmaceutical companies ([Jayr 1998](#); [Parker 1992](#); [Schumann 2003](#); [Steinberg 2002](#)), and one further trial used equipment loaned by a pharmaceutical company ([Welchew 1991](#)).

The remaining 14 trials did not declare any funding sources ([Aceto 2002](#); [Aydogan 2015](#); [Chauvin 1993](#); [Chen 2001](#); [Elkaradawy 2011](#); [Kowalski 1992](#); [Liu 1995](#); [Madej 1992](#); [Motamed 1998](#); [Tsui 1997](#); [Wang 2004](#); [Yosunkaya 2003](#); [Zeng 2003](#); [Zutshi 2005](#)).

Excluded studies

After evaluating the full-text articles, we excluded 72 studies. Reasons for exclusion are described in further detail in [Characteristics of excluded studies](#). In summary, 44 studies did not use an appropriate intervention; 12 studies did not include individuals having the appropriate surgical procedure; 11 studies were not RCTs; three contained insufficient information to justify inclusion; and two were retracted.

Studies awaiting classification

There are 10 studies awaiting classification ([Ahn 2015](#); [Aloia 2017](#); [Chen 2015b](#); [Cho 2017](#); [Golubovic 2012](#); [Mohamad 2017](#); [Siekman 2017](#); [Wang 2015](#); [Zhang 2015](#); [Zheng 2016](#)). Two articles were only available as a conference abstracts and could not be classified based on the information provided ([Ahn 2015](#); [Golubovic 2012](#)). Our latest search in September 2017 located eight further studies that

appear to meet our inclusion criteria and are also awaiting final classification.

Ongoing studies

We identified one ongoing study ([Klotz 2016](#)).

Risk of bias in included studies

The quality assessments are graphically summarized in [Figure 2](#) and [Figure 3](#).

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Aceto 2002	?	?	?	?	+	?	+
Aydogan 2015	?	?	?	?	+	?	+
Barratt 2002	+	+	?	?	-	?	+
Carli 2001	?	?	?	?	+	?	+
Carli 2002	?	?	?	?	+	?	+
Chauvin 1993	?	?	-	-	+	?	+
Chen 2001	+	?	+	+	?	?	+
Chen 2015a	+	?	?	?	+	?	+
Donatelli 2006	+	?	?	?	+	?	+
Elkaradawy 2011	?	+	?	?	+	?	+
Gupta 2006	+	+	+	+	+	?	+
Heurich 2007	+	?	?	?	-	?	+
Hübner 2015	+	+	-	-	+	+	+
Jayr 1998	+	?	?	?	?	?	+
Kowalski 1992	?	?	+	+	+	?	+
Liu 1995	?	?	+	+	+	?	+
Madej 1992	+	-	?	?	+	?	+
Mann 2000	+	-	?	?	?	?	+
Motamed 1998	?	?	-	-	+	?	+
Ngan 1997	+	?	+	+	?	?	?

Figure 2. (Continued)

Ngan 1997	+	?	+	+	?	?	?
Paech 1994	+	?	+	+	-	?	?
Parker 1992	?	?	?	?	-	?	+
Schricker 2000	+	?	?	?	+	?	+
Schumann 2003	+	?	-	?	-	?	+
Steinberg 2002	?	?	-	-	?	?	+
Taqi 2007	?	?	-	-	+	?	+
Tsui 1997	?	?	-	-	?	?	+
Wang 2004	?	?	?	?	+	?	+
Welchew 1991	?	?	-	?	+	?	+
Yosunkaya 2003	?	?	?	?	+	?	+
Zeng 2003	+	?	?	?	+	?	+
Zutshi 2005	+	?	?	?	?	?	+

Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Allocation

Random sequence generation

Sixteen trials were at low risk of bias with regard to random sequence generation. Six trials used shuffling of envelopes (Barratt 2002; Chen 2001; Jayr 1998; Ngan 1997; Schumann 2003; Zutshi 2005); four used a table of random numbers (Heurich 2007; Madej 1992; Mann 2000; Zeng 2003); five used a computer-generated randomization schedule (Chen 2015a; Donatelli 2006; Gupta 2006;

Paech 1994; Schricker 2000); and one used an online randomization service (Hübner 2015).

Sixteen trials did not report sufficient information about the sequence generation process and were judged as at unclear risk of bias.

Allocation concealment

Four trials described adequate allocation concealment, of which two reported using opaque and sealed envelopes (Barratt 2002;

Elkaradawy 2011), and two reported using central allocation (Gupta 2006; Hübner 2015). We judged these trials as having a low risk of bias for this domain.

We considered two studies that used an open randomization schedule as at high risk of bias for this domain (Madej 1992; Mann 2000). The remaining 26 trials did not describe the method used for allocation concealment in sufficient detail and were judged as at unclear risk of bias.

Blinding

Blinding of participants and personnel

Six trials reported that participants and personnel were blinded to group allocation (Chen 2001; Gupta 2006; Kowalski 1992; Liu 1995; Ngan 1997; Paech 1994). Four of these trials used a concealed three-way stopcock to direct the flow of the study drug to the correct site (Chen 2001; Kowalski 1992; Liu 1995; Paech 1994). Two of the trials had identical drug infusion syringes or bags, which were prepared by an independent source (Gupta 2006; Ngan 1997). The study drug was allocated as per the randomization schedule. We considered these trials as at low risk of bias for blinding of participants and personnel.

Eight trials explicitly stated that they were either open or not blinded (Chauvin 1993; Hübner 2015; Motamed 1998; Schumann 2003; Steinberg 2002; Taqi 2007; Tsui 1997; Welchew 1991). We classified these studies as at high risk of bias for this domain. The remaining 18 trials did not provide an explicit statement on blinding of participants and personnel and were judged as at unclear risk of bias.

Blinding of outcome assessment

Six trials reported statements that outcome assessors were blinded to participant group allocation (Chen 2001; Gupta 2006; Kowalski 1992; Liu 1995; Ngan 1997; Paech 1994). We classified these studies as at low risk of bias for this domain.

Of the remaining 26 trials, 20 reported insufficient information about blinding and were judged as having an unclear risk of bias for this domain (Aceto 2002; Aydogan 2015; Barratt 2002; Carli 2001; Carli 2002; Chen 2015a; Donatelli 2006; Elkaradawy 2011; Heurich 2007; Jayr 1998; Madej 1992; Mann 2000; Parker 1992; Schricker 2000; Schumann 2003; Wang 2004; Welchew 1991; Yosunkaya 2003; Zeng 2003; Zutshi 2005). The remaining six trials specifically reported that they were not blinded and were assessed as at high risk of bias (Chauvin 1993; Hübner 2015; Motamed 1998; Steinberg 2002; Taqi 2007; Tsui 1997).

Incomplete outcome data

Incomplete outcome data

We judged studies with no missing data or less than 10% missing data in each arm as having a low risk of bias for this domain. If a study was missing 10% to 20% of data or there was no clear information about missing data, we assessed the risk of bias as unclear. We judged a study as at high risk of bias for this domain if more than 20% of data were missing in either arm. In addition, if it was clear that incomplete outcome data had the potential to cause attrition bias, we judged the study as at high risk of bias for this domain.

We assessed 20 studies as having a low risk of attrition bias. Fifteen studies had no missing data (Carli 2001; Chauvin 1993; Chen 2015a; Donatelli 2006; Elkaradawy 2011; Hübner 2015; Kowalski 1992; Liu 1995; Madej 1992; Schricker 2000; Taqi 2007; Wang 2004; Welchew 1991; Yosunkaya 2003; Zeng 2003), and five studies had less than 10% missing data in each arm, and the missing data were generally balanced across the groups (Aceto 2002; Aydogan 2015; Carli 2002; Gupta 2006; Motamed 1998).

We classified five studies as at high risk of bias for this domain based on the following characteristics: high numbers of participants were unaccounted for (Schumann 2003); more than 20% of participants did not complete the study protocol (Heurich 2007; Parker 1992); and high withdrawal rate in one of the study arms (almost 25% in PCEA arm in Barratt 2002 and more than 15% withdrawals in one study arm and one of these withdrawals due to pain in Paech 1994).

We judged seven studies as at unclear risk of bias: in two studies no reasons were given for withdrawal of participants (Ngan 1997; Steinberg 2002); in four studies it was unclear whether the withdrawals would change the final outcome (Chen 2001; Jayr 1998; Mann 2000; Zutshi 2005); and one study due to just over 10% dropout in one arm (Tsui 1997).

Selective reporting

Only one study, Hübner 2015, had a study protocol available. All of the study's prespecified outcomes were reported in the prespecified way. We considered this study as at low risk of bias for this domain. The remaining 31 studies did not have a study protocol available and were considered as at unclear risk of bias for selective reporting.

Other potential sources of bias

We considered cross-over RCTs as at unclear risk of bias as only the pre-cross-over data could be used for analysis in the review (Ngan 1997; Paech 1994).

Effects of interventions

See: [Summary of findings for the main comparison Epidural analgesia versus intravenous patient-controlled analgesia for pain following intra-abdominal surgery in adults](#)

Primary outcomes

1. Pain scores at rest and on movement. Comparison 1, outcomes 1.1 to 1.6

One trial reported pain using a method not amenable to our analysis approach (Schricker 2000). This trial reported a pain score as an average of 12 hours, 24 hours, and at the start of postoperative day two. The authors commented that "the average VAS at rest obtained 12 and 24 hours after surgery and at the beginning of the infusion study on the second postoperative day was similar in the two groups (IVPCA group: 14 ± 8 mm; CEA group: 11 ± 6 mm). On the first postoperative day, participants in both groups were able to sit on the bed, but none of the participants could leave the bed for a walk."

Pain score in early phase (zero to six hours). Outcome 1.1

At rest

Twenty-one of the 32 trials reported this outcome, but only seven contributed data to this analysis (Aydogan 2015; Hübner 2015;

Kowalski 1992; Liu 1995; Madej 1992; Mann 2000; Parker 1992). These trials enrolled a total of 384 participants (23% of the total in this review), with 182 (47.4%) allocated to IVPCA and 202 (52.6%) to EA. Participants in the EA group had lower pain scores than the IVPCA group (mean difference (MD) 5.7, 95% confidence interval (CI) 1.9 to 9.5; $I^2 = 0\%$). Of the latter, 173 (85.6%) received PCEA and 29 (14.4%) received CEA. (Test for subgroup differences $P = 0.45$.) We judged the evidence as of moderate quality, downgrading the assessment due to study limitations (Analysis 1.1).

We could not include 14 trials in our pooled analysis. Two of these did not report a standard deviation with the mean VAS score (Aceto 2002; Welchew 1991). Aceto 2002 reported a mean VAS of 10/100 with CEA versus 13/100 with IVPCA, and Welchew 1991 reported a VAS of 15/100 with PCEA versus 20/100 with IVPCA. Eleven trials used the median as the report of central tendency (Barratt 2002; Chen 2001; Gupta 2006; Heurich 2007; Jayr 1998; Motamed 1998; Ngan 1997; Paech 1994; Schumann 2003; Steinberg 2002; Tsui 1997), and nine of these reported lower median pain scores with an epidural technique. The data from Gupta 2006 were unclear and were therefore not included. The median comparisons are summarized in Table 1. Elkaradawy 2011 reported a pain score but it was unclear if the figure reported was a mean or median.

On movement

Two trials reported this outcome (Aceto 2002; Aydogan 2015). These trials reported outcomes in a total of 80 participants (5% of the total

participants in this review). Both reported lower pain scores using an epidural technique compared with IVPCA, but only Aydogan 2015 reported a standard deviation, thus no pooled analysis was possible. Using a 100-point VAS, pain scores were 7.0 to 8.0 points lower with epidural analgesia in these trials (mean scores with IVPCA 34 and 53, respectively).

Pain score mid-phase (seven to 24 hours). Outcomes 1.3, 1.4

At rest

This outcome was reported by 28 of the 32 trials, but only 11 could contribute to the pooled analysis (Aydogan 2015; Carli 2002; Chen 2015a; Donatelli 2006; Hübner 2015; Kowalski 1992; Liu 1995; Madej 1992; Mann 2000; Parker 1992; Zeng 2003). These trials enrolled a total of 558 participants (33.9% of the total) with 264 (47.3%) allocated to IVPCA and 294 (52.7%) to EA. Of the latter, 225 (76.5%) received PCEA and 69 (23.5%) received CEA. Participants in the EA groups had lower pain scores than the IVPCA group (MD 9.0, 95% CI 4.6 to 13.4; $I^2 = 69\%$) (Analysis 1.2). There was weak evidence (test for subgroup difference $P = 0.07$) for a difference between CEA and PCEA subgroups in pain scores compared to the IVPCA group, with a larger pain reduction in the CEA group (MD 15.4, 95% CI 8.0 to 22.9; $I^2 = 0\%$) (Figure 4). We judged the evidence as of moderate quality, downgrading the assessment due to study limitations in most of the included studies.

Figure 4. Forest plot of comparison: 1 Epidural analgesia versus intravenous patient-controlled analgesia, outcome: 1.2 Pain score mid-phase - at rest.

We could not include 17 trials in our pooled analysis. Two of these trials did not report a standard deviation with the mean VAS score (Aceto 2002; Welchew 1991). Aceto 2002 reported a mean VAS of 15/100 with CEA versus 12/100 with IVPCA, and Welchew 1991 reported a mean VAS of 8/100 with PCEA versus 8/100 with IVPCA. Thirteen of these trials used the median as the report of central

tendency (Barratt 2002; Chen 2001; Gupta 2006; Heurich 2007; Jayr 1998; Motamed 1998; Ngan 1997; Paech 1994; Schumann 2003; Steinberg 2002; Taqi 2007; Tsui 1997; Zutshi 2005). The median comparisons are summarized in Table 2, however the data from Gupta 2006 were unclear and were not included. Elkaradawy 2011

reported a pain score, but it was unclear if this was a mean or median, therefore we were unable to use this study in our analysis.

[Chauvin 1993](#) reported pain in a dichotomous fashion, which excluded it from the pooled analysis. This trial reported the proportion of participants with a pain score at rest of greater than 40/100 on a VAS. There was 1 of 16 in the EA group (6%) and 3 of 16 in the IVPCA group (19%). This difference was reported as non-significant.

On movement

This outcome was reported by six of the 32 trials, but only two could be considered for pooled analysis ([Aydogan 2015](#); [Carli 2002](#)). These trials enrolled a total of 103 participants (6.3% of the total in this review), of which 51 (49.5%) were allocated to IVPCA and 52 (50.5%) to EA. We considered a pooled analysis for PCEA and CEA, but the pooled result was subject to high statistical heterogeneity ($I^2 = 78\%$) and is not reported. Both trials reported lower pain scores using an epidural technique compared with IVPCA. Using a 100-point VAS, pain scores were 10 points lower using PCEA in [Aydogan 2015](#) (mean IVPCA score 38) and 26 points lower using CEA in [Carli 2002](#) (mean IVPCA score 51). We judged this evidence as of low quality, downgrading the assessment for imprecision and study limitations.

We could not consider four other trials for pooled analysis. [Aceto 2002](#) did not report standard deviations, and there were no important differences in mean VAS (30 with CEA versus 31 with IVPCA). The remaining studies used the median as the report of central tendency ([Carli 2001](#); [Steinberg 2002](#); [Taqi 2007](#)). The median results are summarized in [Table 3](#).

Pain score in late phase (> 24 hours). Outcomes 1.5, 1.6

At rest

This outcome was reported by 18 of 32 trials, but only seven could contribute to the pooled analysis ([Carli 2002](#); [Donatelli 2006](#); [Hübner 2015](#); [Kowalski 1992](#); [Liu 1995](#); [Mann 2000](#); [Parker 1992](#)). These studies enrolled a total of 393 participants (23.9% of the total in this review) with 191 (48.6%) allocated to the IVPCA group and 202 (51.4%) to EA. Of the latter, 153 (75.7%) received PCEA and 49 (24.3%) received CEA. Participants in the EA group had lower pain scores than those in the IVPCA group (MD 5.1, 95% CI 0.9 to 9.4; $I^2 = 0\%$). Subgroup analysis by epidural delivery technique suggested there was no difference between subgroups (test for subgroup difference $P = 0.74$). We judged the evidence as of moderate quality, downgrading the assessment due to study limitations ([Analysis 1.3](#)).

We could not include 11 trials in the pooled analysis. One trial did not report a standard deviation with the mean VAS score ([Aceto 2002](#)). [Aceto 2002](#) reported a mean VAS of 17/100 with CEA versus 8/100 with IVPCA. The remaining studies used the median as the report of central tendency ([Barratt 2002](#); [Chen 2001](#); [Gupta 2006](#); [Heurich 2007](#); [Motamed 1998](#); [Schumann 2003](#); [Steinberg 2002](#); [Taqi 2007](#); [Tsui 1997](#); [Zutshi 2005](#)). The median comparisons are summarized in [Table 4](#); the data from [Gupta 2006](#) were unclear and were therefore not included in the table.

On movement

This outcome was reported by five of the 32 trials, but only two reported pain scores as a mean ([Aceto 2002](#); [Carli 2002](#)), enrolling a total of 102 participants (6% of the total in this review) with 50

(49%) of participants in the IVPCA group and 52 (51%) in the CEA group. Both studies used CEA. Only [Carli 2002](#) reported a standard deviation, therefore pooled analysis was not possible. The trials drew different conclusions, with [Carli 2002](#) reporting a 16-point lower pain score using CEA on a 100-point VAS (mean in IVPCA group of 39), and [Aceto 2002](#) reporting a small 3-point difference in favour of IVPCA (mean of 25 points).

We could not consider three trials for a pooled analysis, as they used the median as the report of central tendency ([Carli 2001](#); [Steinberg 2002](#); [Taqi 2007](#)). The results are summarized in [Table 5](#).

2. All-cause mortality at 30 days. Comparison 1, outcome 2.1

This outcome was reported by nine of 32 trials ([Barratt 2002](#); [Carli 2001](#); [Chen 2001](#); [Chen 2015a](#); [Gupta 2006](#); [Hübner 2015](#); [Taqi 2007](#); [Tsui 1997](#); [Zutshi 2005](#)), with a total of 560 participants (34.0% of the total in this review). There were 287 (51%) allocated to EA and 273 (49%) to IVPCA. Of the former, 131 (46%) received PCEA and 156 (54%) received CEA. We included all reported mortality up to 30 days postoperatively. Several trials reported mortality only to discharge; where this was the case, we included those deaths in this outcome. We used a random-effects statistical model.

Subgroup analysis by method of EA did not suggest any differences by technique ($P = 0.82$). There were five deaths out of 287 participants (1.7%) in the EA groups, whilst there were no deaths out of 273 participants in the IVPCA group. We are uncertain as to whether EA has an important effect on the risk of mortality because of the low number of events, wide confidence interval, and study limitations (risk ratio (RR) 3.37, 95% CI 0.72 to 15.88; 9 studies, 560 participants; low-quality evidence due to imprecision and study limitations) ([Analysis 1.4](#)).

This analysis was highly sensitive to missing data, with the analysis favouring EA groups in the best-case scenario and favouring the IVPCA group in the worst-case scenario. Twenty-six of 312 (8.3%) participants were missing from the EA groups, and 24 of 297 (8.1%) were missing from the IVPCA group. Best-case: RR of dying with EA was 0.27 (95% CI 0.11 to 0.69; $I^2 = 0\%$); worst-case: RR of dying with EA was 9.05 (95% CI 2.76 to 29.64; $I^2 = 0\%$) ([Analysis 1.5](#); [Analysis 1.6](#)).

Secondary outcomes

1. Pain score on coughing. Comparison 1, outcomes 3.1 to 3.3

Pain score in early phase (zero to six hours) on coughing. Outcome 3.1

Eleven of the 32 trials reported this outcome. Two of these trials could have contributed data to this analysis ([Liu 1995](#); [Mann 2000](#)), but we could not pool results due to unacceptable statistical heterogeneity ($I^2 = 86\%$). These two trials enrolled a total of 80 participants (4% of the total in this review), with 41 (51.2%) allocated to the IVPCA group and 39 (48.8%) to the PCEA group. [Liu 1995](#) reported a pain score only one point lower with PCEA (mean IVPCA score 58), while [Mann 2000](#) reported a pain score 21 points lower with PCEA (mean IVPCA score 48). We rated this evidence as of very low quality due to imprecision, high heterogeneity, and study limitations ([Analysis 1.7](#)).

Nine trials reported the median pain scores and could not be included in our pooled analysis ([Barratt 2002](#); [Chen 2001](#); [Gupta 2006](#); [Heurich 2007](#); [Jayr 1998](#); [Motamed 1998](#); [Ngan 1997](#); [Paech 1994](#); [Steinberg 2002](#); [Tsui 1997](#)). These results are summarized in

Table 6; the data from Gupta 2006 were unclear and were therefore not included in this table.

Pain score in mid-phase (seven to 24 hours) on coughing. Outcome 3.2

Sixteen of the 32 trials reported this outcome. Only five trials contributed data to this pooled analysis (Carli 2002; Chen 2015a;

Donatelli 2006; Liu 1995; Mann 2000). These five studies enrolled a total of 212 participants (13% of the total in the review), with 107 (50.5%) in the IVPCA group and 105 (49.5%) in the EA group. Of the latter, 65 (61.9%) received PCEA and 40 (38.1%) received CEA (Figure 5).

Figure 5. Forest plot of comparison: 1 Epidural analgesia versus intravenous patient-controlled analgesia, outcome: 1.8 Pain score mid-phase - on coughing.

Combined analysis for PCEA and CEA was subject to high statistical heterogeneity, and we did not pool these two epidural groups.

There was a significant difference in pain scores on coughing between epidural delivery techniques ($P = 0.002$); a greater reduction in pain score on coughing was seen in the CEA than the PCEA group relative to IVPCA (CEA: MD 32.2, 95% CI 20.4 to 44.1; $I^2 = 0\%$; PCEA: MD 11.3, 95% CI 5.9 to 16.7; $I^2 = 0\%$) (Analysis 1.8). We judged this evidence as of moderate quality, downgrading the strength of the evidence due to study limitations.

Ten trials reported median pain scores and could not be included in our pooled analysis (Barratt 2002; Chen 2001; Gupta 2006; Heurich 2007; Jayr 1998; Motamed 1998; Paech 1994; Steinberg 2002; Taqi 2007; Tsui 1997). The results are summarized in Table 7; the data from Gupta 2006 were unclear and were therefore not included in this table.

One trial reported the proportion of participants with a VAS score of $> 40/100$ on coughing (Chauvin 1993): 12/16 participants in the EA group (75%) versus 10/16 (63%) in the IVPCA group. This difference was reported as non-significant.

Pain score in late phase (> 24 hours) on coughing. Outcome 3.3

Twelve of the 32 trials reported this outcome. Only four trials contributed data to this analysis (Carli 2002; Donatelli 2006; Liu 1995; Mann 2000). These four studies enrolled a total of 159 participants (10% of the total in the review) with 80 in the IVPCA group and 79 in the EA group. Of the latter, 39 (48.8%) received PCEA and 40 (51.2%) received CEA.

Combined analysis for PCEA and CEA was subject to high statistical heterogeneity, and we did not combine these two epidural groups.

There was a reduction in pain scores on coughing in the CEA group compared to the IVPCA group (MD 21.0, 95% CI 8.9 to 33.0; $I^2 = 0\%$), but not with PCEA (MD 2.7, 95% CI -6.2 to 11.5). We judged this evidence as of low quality, downgrading the assessment due to imprecision and study limitations (Analysis 1.9).

Eight trials reported median pain scores and could not be included in our pooled analysis (Barratt 2002; Chen 2001; Gupta 2006; Heurich 2007; Motamed 1998; Steinberg 2002; Taqi 2007; Tsui 1997). The results are summarized in Table 8; the data from Gupta 2006 were unclear and were therefore not included in this table.

2. The number of failures to successfully establish the allocated technique (defined as a clinical decision for any reason to use a second analgesic technique). Comparison 1, outcome 4.1

Ten of the 32 trials reported this outcome (Aceto 2002; Barratt 2002; Chen 2001; Heurich 2007; Hübner 2015; Parker 1992; Schumann 2003; Taqi 2007; Tsui 1997; Zutshi 2005), with a total of 678 participants (39.5% of the total in this review). There were 321 (47.3%) allocated to IVPCA and 357 (52.7%) to EA. Of the latter, 142 (39.8%) received PCEA and 215 (60.2%) received CEA. Participants in the EA group had a greater risk of failure of the technique than those in the IVPCA group (RR 2.48, 95% CI 1.13 to 5.45; $I^2 = 20\%$; moderate-quality evidence) (Analysis 1.10; Figure 6).

Figure 6. Forest plot of comparison: 1 Epidural analgesia versus intravenous patient-controlled analgesia, outcome: 1.10 Failure of analgesic technique.

Seven of the 10 trials clearly stated that all failures to establish either EA or IVPCA were excluded from analysis, while two trials treated all enrolled participants by the intention-to-treat principle (Hübner 2015; Zutshi 2005). In the remaining trial, Taqi 2007, the epidural was reinserted if it failed. This analysis was somewhat sensitive to the allocation of missing data. There were 15 (4%) missing participants in the EA groups and 16 (5%) in the IVPCA group. While the worst-case scenario confirmed a high chance of failure with EA, the best-case scenario suggested no important difference between groups (best case: RR 1.28, 95% CI 0.65 to 2.53; $I^2 = 33\%$; worst case: RR 3.39, 95% CI 1.54 to 7.47; $I^2 = 26\%$). We judged this evidence as of moderate quality, downgrading our assessment for study limitations (Analysis 1.11; Analysis 1.12).

We excluded Gupta 2006 as the trial design demanded a successful epidural before randomization of participants. There was a failed epidural insertion prior to randomization.

3. Length of hospital stay (days). Comparison 1, outcome 5.1

Thirteen of the 32 trials reported this outcome. However, only three trials contributed data to the pooled analysis (Aceto 2002; Chen 2015a; Parker 1992). These trials enrolled a total of 186 participants (11% of the total in the review) with 91 (49.9%) allocated to IVPCA and 95 (51.1%) to EA. Of the latter, 75 (78.9%) received PCEA and 20 (21.1%) received CEA. Participants in the EA group had a marginally shorter length of stay (days) than those in the IVPCA group (MD 0.34 days, 95% CI 0.05 to 0.64; $I^2 = 0\%$). We judged this evidence as of moderate quality, downgrading for study limitations (Analysis 1.13).

We could not include 10 trials in our pooled analysis, as they used the median as the report of central tendency (Barratt 2002; Carli 2001; Carli 2002; Chen 2001; Gupta 2006; Hübner 2015; Mann 2000; Steinberg 2002; Taqi 2007; Zutshi 2005). The results of individual studies are summarized in Table 9.

4. Time to ambulation (hours). Comparison 1, outcome 6.1

Four of 32 trials reported this outcome (Gupta 2006; Mann 2000; Parker 1992; Steinberg 2002). However, only a single trial reported mean time to ambulation (Parker 1992), while the remaining three trials reported median times, so a pooled analysis was not possible. There was a total of 251 participants (14.6% of the total in the review), of which 131 (52.2%) were allocated to IVPCA and 120 (47.8%) to EA. Parker 1992 included two PCEA groups with different hydromorphone doses, and one hydromorphone IVPCA control group. Parker 1992 reported a mean time to ambulation score of 26 hours, standard deviation (SD) 6 hours with PCEA (higher-dose hydromorphone) ($n = 14$), 16 hours, SD 5 hours, with PCEA (lower-dose hydromorphone) ($n = 35$) versus 20 hours, SD 7 hours, with IVPCA.

The three trials reporting median times are summarized in Table 10. We assessed this evidence as of low quality, downgrading for study limitations and imprecision.

5. Patient satisfaction. Comparison 1, outcome 7.1

This outcome was reported by nine of 32 trials, however only a single trial reported data as mean and SD (Liu 1995), so pooled analysis was not possible. This trial reported no clear difference between PCEA and IVPCA for patient satisfaction, however there

were only eight participants in each arm. (Liu 1995 reported a mean patient satisfaction score of 8.8/10, SD 0.8/10 with PCEA versus 8.9/10, SD 0.7/10 with IVPCA. Quote: "All patients in each group would choose the same method of analgesia again")

Three trials reported patient satisfaction using medians (Chen 2001; Paech 1994; Zutshi 2005); three used a four-point scale (Aceto 2002; Mann 2000; Motamed 1998); and Tsui 1997 used a three-point scale. These results are summarized in Table 11.

Ngan 1997 reported that the participants had a preference for PCEA, but did not provide numerical data.

6. Quality of life, measured by a validated scale as reported. Comparison 1, outcome 8.1

Four of 32 trials reported this outcome. There was a total of 219 participants (12.7% of the total in the review), of which 108 (49.3%) were allocated to IVPCA and 111 (50.7%) to EA. No pooled analysis was possible due to differences in reporting, and one study, Zutshi 2005, used the median as the measure of central tendency and reported no difference in the 36-item Short Form Health Survey (SF-36) at discharge, 10 or 30 days.

The remaining three trials reported conflicting results, with Carli 2002 and Gupta 2006 reporting some improvements using the SF-36 to report on quality of life preoperatively and postoperatively. Both studies reported better scores in the EA group at three weeks to one month postoperatively (Carli 2002 5.5 points better for mental health dimension, mean in IVPCA group of 50.9; Gupta 2006 actual difference not reported). The third trial reported no significant differences between groups at one month (Steinberg 2002).

Adverse effects

7. Venous thromboembolism rate. Comparison 1, outcome 9.1

Two of 32 trials reported this outcome (Carli 2001; Zutshi 2005). There were a total of 101 participants (5.9% of the total in the review), of which 49 (48.5%) were allocated to IVPCA and 52 (51.5%) to EA. Of the latter, 31 (59.6%) received PCEA and 21 (40.4%) received CEA. The EA group had no events from 52 participants, whilst the IVPCA group had two events out of 49 participants (4%). There is uncertainty as to whether EA reduced the risk of venous thromboembolism because of the low number of events and wide confidence interval (RR 0.32, 95% CI 0.03 to 2.95; $I^2 = 0\%$; low-quality evidence) (Analysis 1.14).

8. Pruritus. Comparison 1, outcome 10.1

This outcome was reported by 13 of 32 studies, of which eight contributed data to our pooled analysis (Aceto 2002; Madej 1992; Mann 2000; Parker 1992; Schumann 2003; Steinberg 2002; Tsui 1997; Yosunkaya 2003). These studies enrolled a total of 492 participants (30% of the total in the review), with 237 (48.2%) allocated to IVPCA and 255 (51.8%) to EA. Of the latter, 122 (47.8%) received PCEA and 133 (52.2%) received CEA. Participants in the EA group were more likely to experience pruritus than those in the IVPCA group (81/255 (32%) versus 30/237 (13%), respectively). The risk of pruritus with EA versus IVPCA was 2.36 (95% CI 1.67 to 3.35; $I^2 = 0\%$) (Analysis 1.15). We judged this evidence to be of moderate quality because of study limitations. Although there were 12 missing outcomes in the EA group and 15 in the IVPCA group, sensitivity analysis for the allocation of missing data did not change this conclusion (best case: RR 1.67, 95% CI 1.23 to 2.27;

worst case: RR 2.68, 95% CI 1.91 to 3.76) (Analysis 1.16; Analysis 1.17). The number needed to use IVPCA rather than EA in order to avoid pruritus was 5 (95% CI 4 to 8).

We could not include five trials in our pooled analysis. Three of the five used the median as the report of central tendency (Chen 2001; Ngan 1997; Paech 1994). Kowalski 1992 commented that there was no difference between the two groups with regard to pruritus, while Liu 1995 could not be included in our pooled analysis because pruritus was reported at differing time periods to our study.

9. Nausea and vomiting. Comparison 1, outcome 11.1

This outcome was reported by 18 of 32 studies, of which 10 contributed to our pooled analysis (Aceto 2002; Carli 2001; Jayr 1998; Madej 1992; Mann 2000; Parker 1992; Schumann 2003; Steinberg 2002; Tsui 1997; Yosunkaya 2003). These trials enrolled a total of 645 participants (39% of the total in the review), with 325 (50.4%) allocated to EA and 320 to IVPCA (49.6%). There was no difference in the risk of experiencing nausea and vomiting between groups (EA 111/314 (35%), IVPCA 107/304 (35%); RR 0.94, 95% CI 0.69 to 1.27; $I^2 = 52\%$; moderate-quality evidence). The risk of this adverse event was similar between the EA and IVPCA groups (test for subgroup differences $P = 0.22$) (Analysis 1.18). We could not account for the heterogeneity by subgroup analysis for EA technique, nor was the result sensitive to the allocation of missing data (best case: RR 0.85, 95% CI 0.65 to 1.11; worst case: RR 1.09, 95% CI 0.75 to 1.57). We judged this evidence to be of moderate quality given the study limitations (Analysis 1.19; Analysis 1.20).

Eight other trials reported on nausea and vomiting, however they were not suitable for pooled analysis. Seven of these concluded that there was no significant difference in nausea or vomiting or both between groups (Chen 2001; Gupta 2006; Kowalski 1992; Liu 1995; Ngan 1997; Paech 1994; Welchew 1991). Taqi 2007 reported daily nausea rates and vomiting rates and commented: "Postoperative nausea and vomiting occurred in both groups. However, the incidence of vomiting requiring pharmacologic intervention was significantly greater in the PCA [patient-controlled analgesia] group during the first 2 postoperative days".

10. Epidural haematoma. Comparison 1, outcome 12.1

None of the included trials reported on this outcome.

11. Sedation. Comparison 1, outcome 13.1

This outcome was reported by nine of 32 studies, of which only four could contribute data to our pooled analysis (Chen 2001; Madej 1992; Motamed 1998; Parker 1992). These trials enrolled a total of 223 participants (13% of the total in the review) with 107 (48%) allocated to IVPCA and 116 (52%) to EA. Of the latter, 68 (58.6%) received PCEA and 48 (41.4%) CEA. There was no important difference between EA and IVPCA for incidence of sedation (EA 17/116 (15%), IVPCA 12/107 (11%); RR 0.87, 95% CI 0.40 to 1.87; $I^2 = 19\%$) (Analysis 1.21). This finding was not influenced by the allocation of missing data (best case: RR 0.78, 95% CI 0.33 to 1.83; worst case: RR 1.66, 95% CI 0.62 to 4.46). We judged this evidence to be of moderate quality (Analysis 1.22; Analysis 1.23).

We could not include five trials in our pooled analysis. Ngan 1997 used the median as the report of central tendency. Both Gupta 2006 and Liu 1995 reported the prevalence of sedation at multiple time periods. Kowalski 1992 commented that there was no difference

between the two groups with regard to sedation, but did not provide numerical data. [Welchew 1991](#) reported the mean hourly sedation scores without standard deviations, and commented that "both groups had high initial sedation scores which slowly declined with time after their anaesthetics. The relatively wide scatter on the graph, particularly in the intravenous group, is probably the effect of random short periods of sleep, which is typical of the early postoperative patient. There were no statistically significant differences in hourly sedation scores between the two groups at anytime during the study period."

12. Respiratory complications. Comparison 1, outcomes 14.1, 14.2

Respiratory compromise - respiratory rate < 10/minute. Outcome 14.1

Four of the 32 studies reported this outcome. However, only a single study reported events in either group (1 of 20 participants in the EA group and 2 of 20 in the IVPCA group) ([Yosunkaya 2003](#)), and we could not pool any data. [Yosunkaya 2003](#) concluded that one participant developed respiratory depression in the EA group and two participants in the IVPCA group, with none of the participants requiring treatment other than stopping the infusion for a short time and reducing the demand dose. The remaining three trials reported no cases of respiratory depression ([Aceto 2002](#); [Chen 2001](#); [Tsui 1997](#)).

The four trials enrolled a total of 229 participants (13.3% of the total in the review), of which 113 (49.3%) were allocated to IVPCA and 116 (50.7%) to EA.

Respiratory compromise - Oxygen saturation < 90%. Outcome 14.2

This outcome was reported by 10 of 32 studies, of which five contributed data to our pooled analysis ([Aceto 2002](#); [Jayr 1998](#); [Madej 1992](#); [Mann 2000](#); [Tsui 1997](#)). These studies enrolled a total of 328 participants (20% of the total in the review), with 162 (49.4%) allocated to IVPCA and 166 (50.6%) to EA. Of the latter, 31 (18.7%) received PCEA and 135 (81.3%) received CEA. There was no important difference in the risk of low saturations between EA and IVPCA (EA 19/166 (11%), IVPCA 14/162 (9%); RR 1.29, 95% CI 0.71 to 2.37; $I^2 = 0\%$). We judged this evidence to be of moderate quality because of study limitations ([Analysis 1.24](#)).

Of those trials not contributing to the pooled analysis, [Chauvin 1993](#) reported on the number of participants who spent a percentage of time with certain saturations, and it was not possible to determine the exact number of participants who experienced desaturation from the data presented; [Hübner 2015](#) reported on respiratory complications, but not in the categories chosen for our meta-analysis (there was one participant in each group with a respiratory complication); [Kowalski 1992](#) commented that "no patients had clinically significant respiratory depression"; [Parker 1992](#) stated that four participants in the IVPCA group had oxygen saturations from 87% to 91%, but did not require therapy; and [Zeng 2003](#) commented that "there was no respiratory depression in any patient."

13. Hypotension requiring treatment. Comparison 1, outcome 15.1

Six of 32 studies reported this outcome ([Aceto 2002](#); [Hübner 2015](#); [Jayr 1998](#); [Mann 2000](#); [Tsui 1997](#); [Zutshi 2005](#)). There was a total of 479 participants (27.8% of the total in the review), of which 237 (49.5%) were allocated to IVPCA and 242 (50.5%) to EA. Of

the latter, 127 (52.5%) received PCEA and 115 (47.5%) received CEA. Participants in the EA group were more likely to experience hypotension than those in the IVPCA group (EA 36/242 (14.9%), IVPCA 4/237 (1.7%); RR 7.13, 95% CI 2.87 to 17.75; $I^2 = 0\%$). We judged this evidence to be of moderate quality, downgrading the assessment due to study limitations ([Analysis 1.25](#)). The NNTB when using IVPCA rather than EA in order to avoid one individual who was hypotensive was 8 (95% CI 6 to 12).

DISCUSSION

Summary of main results

Thirty-two studies met our inclusion criteria, together reporting data on 1716 participants, of which 869 (51%) were allocated to EA and 847 (49%) to IVPCA. There were 16 trials with CEA (418 participants) and 16 trials with PCEA (451 participants). The main results are summarized in the [Summary of findings for the main comparison](#).

Our analysis suggests that EA results in a reduction in pain scores at rest and on movement compared with IVPCA. At rest, the magnitude of the difference was small and unlikely to be clinically important ([Myles 2017](#)). The reductions were as follows: up to six hours after operation 5.7 points on a 100-point scale (95% CI 1.9 to 9.5; 7 trials); from seven to 24 hours, 9.0 points (95% CI 4.6 to 13.4; 11 trials); at 24 hours or longer 5.1 points (95% CI 0.9 to 9.4; 7 trials). We rated the quality of evidence for each of these time periods as moderate due to study limitations. On movement, no pooled analysis was possible for any time period. Only two studies ([Aydogan 2015](#); [Carli 2002](#)), reported mean pain scores on movement with standard deviation. In the zero to six hour period [Aydogan 2015](#) compared PCEA to IVPCA and reported a mean improvement of eight points for PCEA (95% CI 2.7 to 13.3; 1 trial). The two studies reporting the period from seven to 24 hours could not be pooled due to unacceptable statistical heterogeneity. [Aydogan 2015](#) compared PCEA to IVPCA and reported a mean improvement of 10 points for PCEA (95% CI 6.9 to 13.1; 1 trial), while [Carli 2002](#) compared CEA to IVPCA and reported a reduction of 26 points for CEA (95% CI 11.7 to 40.3; 1 trial). In the period after 24 hours, [Carli 2002](#) compared CEA to IVPCA and reported a mean improvement of 16 points for CEA (95% CI 2.9 to 29.1; 1 trial). We rated the evidence as low quality due to study limitations and imprecision.

For our second primary outcome of all-cause mortality at 30 days, we found no difference between EA and IVPCA, although the only deaths reported were in the EA group (5/287 or 1.7%). The RR of death with EA compared to IVPCA was 3.37 (95% CI 0.72 to 15.88; 9 trials; low-quality evidence due to study limitations and imprecision).

A single study suggested that the use of EA may result in fewer episodes of respiratory depression, with an RR of 0.47 (95% CI 0.04 to 5.69; 1 trial; low-quality evidence due to study limitations and imprecision) ([Yosunkaya 2003](#)). Any reduction in pain scores was accompanied by an increase in the risk of failure to establish the allocated technique with EA (RR 2.48, 95% CI 1.13 to 5.45; 10 trials); increased episodes of hypotension requiring intervention with EA (RR 7.13, 95% CI 2.87 to 17.75; 6 trials); and an increased risk of pruritus with EA (RR 2.36, 95% CI 1.67 to 3.35; 8 trials). We rated the evidence for these adverse effects as moderate quality due to study limitations. No one technique showed an advantage over another

for the other adverse effects addressed in this review (venous thromboembolism with EA (RR 0.32, 95% CI 0.03 to 2.95; 2 trials; low-quality evidence due to study limitations and imprecision); nausea and vomiting (RR 0.94, 95% CI 0.69 to 1.27; 10 trials; moderate-quality evidence due to study limitations); sedation (RR 0.87, 95% CI 0.40 to 1.87; 4 trials; moderate-quality evidence due to study limitations); or episodes of desaturation (RR 1.29, 95% CI 0.71 to 2.37; 5 trials; moderate-quality evidence due to study limitations)).

In summary, EA appears to offer some reduction in pain scores compared to IVPCA in this broad category of abdominal surgery, however at the cost of increased adverse effects such as analgesic failure, pruritus, and hypotension requiring treatment.

Overall completeness and applicability of evidence

This review included a total 1716 participants undergoing intra-abdominal surgery. Twenty of the included trials used thoracic epidurals; four trials used lumbar epidurals; six did not specify the site; and one used either, depending on the surgical site. The studies included a broad range of surgical procedures (including hysterectomies, radical prostatectomies, Caesarean sections, colorectal and upper gastrointestinal procedures), a wide range of adult ages, and across several different countries. The evidence can therefore be applied to a range of procedures, patient groups, and healthcare models.

The included studies reported data for most of the primary and secondary outcomes. The two primary outcomes of this review were pain scores and mortality. For pain score at rest, we identified more than 1000 participants at all time points, however only data between 432 to 617 participants could be used in the meta-analysis. For pain scores on movement, only two studies could be included in the meta-analysis, [Aydogan 2015](#) and [Carli 2002](#), which enrolled 40 and 63 participants, respectively.

We identified 560 participants for the outcome mortality, but this was such a rare event that our review has not produced a reliable estimate of the risk ratio with different analgesic techniques.

Quality of the evidence

We rated the quality of the available evidence using the GRADE approach ([Guyatt 2008](#)), which we have presented in [Summary of findings for the main comparison](#). We rated the evidence for most of our outcomes as of moderate quality, downgrading one level, most commonly for study limitations including lack of blinding and imprecision as a result of small sample sizes. Although six of the included trials described credible measures to ensure blinding, many other authors felt blinding was both practically and ethically challenging in this area.

We rated the primary outcome of mortality as low quality due to imprecision and study limitations.

No sensitivity analysis by study quality was undertaken as no trials had more than two 'Risk of bias' domains rated as high risk.

Potential biases in the review process

We have attempted to reduce possible bias and to identify all relevant studies by following the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins](#)

[2011](#)). To reduce selection bias, we employed a comprehensive search strategy and considered studies in all languages for eligibility. We believe we have found all relevant randomized trials that have been published or are registered as under way. There was an insufficient number of studies to draw a funnel plot to assess the presence of possible publication bias.

Three studies contained insufficient information to justify inclusion ([Brandt 1976](#); [Noreng 1987](#); [Zhao 2015](#)). These studies did not measure any outcomes of interest, hence there is no potential for outcome reporting bias.

We identified two cross-over RCTs and decided to only use the pre-cross-over data to avoid carry-over effect of the analgesia. Using only the first-period data may have created bias.

Agreements and disagreements with other studies or reviews

Our findings are generally concordant with other systematic reviews comparing epidural analgesia with other forms of analgesia following different types of abdominal surgery. Those reviews included a number of different modes of opioid analgesia as control groups, in contrast to our focus on IVPCA.

[Marret 2007](#) compared postoperative EA and parenteral opioid analgesia and found a 15 mm (95% CI 11 mm to 19 mm) and 18 mm (95% CI 10 mm to 26 mm) difference in pain score in favour of EA at 24 and 48 hours. The magnitude of the difference may reflect the mode of analgesia in the control group, the type of surgery included in the review, as well as how the VAS was derived. We could not determine from the methods in [Marret 2007](#), if the reported VAS is at rest or a composite score that included VAS while coughing or on movement.

[Block 2003](#) compared all types of EA with parenteral opioid analgesia. They included abdominal and pelvic surgery and reported a difference in pain scores in favour of EA compared to parenteral opioid analgesia. The complication rates were similarly concordant with ours.

[Wu 2005](#) compared both postoperative PCEA and CEA with opiate IVPCA and again found similar reductions in pain scores with EA. There were, however, methodological differences in the method of comparing VAS scores. [Wu 2005](#) reported composite pain scores after abdominal and pelvic surgery, which included all time points and rest and incident pain. Wu and colleagues also reported a difference in nausea and vomiting rates between EA and IVPCA of 5.8% ($P = 0.01$) in favour of EA, and a difference in sedation rates between EA and IVPCA of 9.9% ($P = 0.03$) in favour of EA. Our review does not support these findings; the difference might be explained by the difference in surgical site, as intra-abdominal surgery is known to have a high rate of nausea and vomiting.

Of relevance, from a database with 25,000 patients (not all of whom had epidural analgesia), the failure rate of epidural analgesia was 27% in lumbar epidurals and 32% in thoracic epidurals ([Ready 1999](#)). However, the true incidence is probably unknown ([Rawal 2012](#)). In our review, epidural analgesia failed in 12% of participants.

AUTHORS' CONCLUSIONS

Implications for practice

The risks and benefits of an epidural technique for postoperative pain following abdominal procedures need to be balanced. While we found a small improvement in pain scores in the postoperative phase, there was also an increased rate of failure to establish the allocated technique successfully, pruritus, and hypotension when using an epidural. At rest, the reduction in pain scores is modest and unlikely to be clinically important. On movement, the reduction in pain scores with epidural analgesia is greater and might have clinical importance. The 10 studies categorized as 'awaiting classification' may alter the conclusions of the review once they are assessed.

Implications for research

While this review demonstrated a benefit with regard to pain scores for epidural analgesia over intravenous patient-controlled analgesia, relatively little information is reported on pain scores on movement. It is also unclear if patient-controlled epidural analgesia is superior to continuous epidural analgesia. More randomized controlled trials answering these questions would be beneficial. Such trials should be of adequate power to demonstrate any clinically important differences in pain scores and quality of

recovery, and preferably involve a blinded comparison between groups with respect to participants and outcome assessors.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Aceto 2002

Methods	Randomized controlled trial, parallel group
Participants	N = 40, IVPCA 20 and CEA 20 participants, age 28 to 70, ASA 1 to 3, undergoing general anaesthesia for colorectal surgery Italian study
Interventions	1. IVPCA group: morphine IVPCA started postop, 0.6 mg bolus with 7 min lockout. Tramadol (6.25 mg/mL) and ketorolac (1.875 mg/mL) infusion at 2 mL/h started at end of surgery and continued for 48 hours. Morphine loading in recovery if VAS > 40 mm, 1 mg every 10 min. 2. Epidural group: thoracic CEA place preop, used intra-op. Postoperatively an epidural infusion was commenced: 5 mL/h of 0.2% ropivacaine with 0.75 µg/mL of sufentanil for 72 hours.

Aceto 2002 (Continued)

Both groups had general anaesthetics that were similar in nature, except the IVPCA group had IV fentanyl boluses, and the CEA group had 0.2% ropivacaine epidural boluses as required.

Outcomes	<ol style="list-style-type: none"> 1. Pain scores by VAS at rest and during movement for 72 hours 2. Satisfaction questionnaire 3. Pruritus 4. Nausea and vomiting 5. Respiratory complications 6. Hypotension
Notes	No funding sources declared. No conflicts of interest declared.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No description of randomization method in text. Quote: "patients were randomly divided into two groups of 20: epidural group (group B) and GA/IVPCA group (Group A)"
Allocation concealment (selection bias)	Unclear risk	No description of allocation concealment in text
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No description of blinding of investigators or participants
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No description of blinding of outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "one patient in group A was excluded due to failure of IVPCA device." Unlikely for this to be related to true outcome, unlikely to have a clinically relevant impact on the outcome
Selective reporting (reporting bias)	Unclear risk	No study protocol available
Other bias	Low risk	No indication of other bias

Aydogan 2015

Methods	Randomized controlled trial, parallel group
Participants	<p>N = 42, 2 participants excluded, PCEA = 20, IVPCA = 20, 28 males, 12 females, age 18 to 65, ASA 1 and 2, undergoing right hepatectomy surgery for donation under general anaesthesia between August 2012 and January 2013</p> <p>Turkish study</p>
Interventions	<ol style="list-style-type: none"> 1. IVPCA group. IV morphine 5 mg administered 15 minutes before estimated surgical completion time. IVPCA with morphine, bolus 1 mg, lockout of 15 minutes, 4-hour limit of 20 mg, and no continuous infusion

Aydogan 2015 (Continued)

2. PCEA group. Epidural morphine 2 mg administered 15 minutes before estimated surgical completion time. PCEA with morphine, bolus 0.5 mg, lockout of 30 minutes, 4-hour limit of 10 mg, and no continuous infusion

If analgesia was felt to be inadequate at any time during the study, the lockout time was shortened to 5 minutes for both groups.

Outcomes	1. Pain scores by VAS (0 to 100 mm) at rest and during movement for 24 hours
Notes	1 participant in each group was excluded from the study because of problems with the infusion device (IVPCA group) and sudden bleeding during surgery (PCEA group). No funding sources declared. No conflicts of interest declared.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No description of randomization method in the text. Quote: "forty-two patients were included in the study and randomly divided into 2 groups in a double-blinded manner"
Allocation concealment (selection bias)	Unclear risk	No description of allocation concealment in text
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The article states that the randomization is double-blinded, however there is no description of how blinding was done. It does not appear that participants or personnel were blinded with regard to the route of administration of analgesia. Quote: "forty-two patients were included in the study and randomly divided into 2 groups in a double-blinded manner"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The study states that the nurses evaluating the pain scores were blinded to the study protocol, but does not say if the nurses were blinded to the type of analgesia the participants were receiving or how this blinding was performed. Quote: "Pain scores were evaluated by study nurses who were blinded to the study protocol"
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 participant in each group was excluded. Unlikely to affect outcome
Selective reporting (reporting bias)	Unclear risk	No study protocol
Other bias	Low risk	No indication of other bias

Barratt 2002

Methods	Randomized controlled trial, parallel group
Participants	57 participants randomized, 10 excluded, CEA = 25, IVPCA = 22, adults, median age in the different groups ranged from 57 to 63 years, 27 males, 20 females, undergoing upper abdominal surgery not involving the diaphragm or thorax, under general anaesthesia. Australian study
Interventions	1. 2 IVPCA groups, 1 with TPN, 1 without TPN. These participants received either fentanyl with 10 to 20 µg boluses or morphine with 1 to 2 mg boluses, both with 5 minutes lockout

Barratt 2002 (Continued)

2. 2 CEA groups, 1 with TPN, 1 without TPN. Thoracic epidurals T7 to T10. Postoperatively these participants received 0.25% bupivacaine with 2.5 µg/mL fentanyl at 5 to 10 mL/h. In addition, the CEA groups received intramuscular ketorolac 6 hourly for 24 hours. The epidural was commenced preoperatively.

Outcomes	<ol style="list-style-type: none"> 1. Pain score by VAS (0 to 100 mm) at rest and on coughing at 6, 24, and 48 hours 2. Mortality (number of participants during hospital admission) 3. Failed epidurals (number of participants, these participants were excluded from the trial) 4. Duration of hospital stay (days)
Notes	<p>Supported by the National Health and Medical Research Council of Australia and the Australian and New Zealand College of Anaesthetists</p> <p>The 10 excluded participants were excluded for the following reasons. 1 participant randomized to the CEA + TPN group had a total pancreatectomy that was significantly more extensive than the remaining participants and developed hypotensive sepsis in the second postoperative week. 3 participants had failed epidurals; 1 was randomized to the CEA group and the others to the CEA + TPN group. The other 6 participants withdrew consent for the study (3 CEA + TPN, 1 IVPCA + TPN, 2 IVPCA).</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Allocation by randomly allocated cards in sealed envelopes
Allocation concealment (selection bias)	Low risk	Sealed envelopes not opened until after initial measurements were made before start of anaesthesia.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No description of blinding of investigators or participants
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No description of blinding of outcome assessors
Incomplete outcome data (attrition bias) All outcomes	High risk	57 participants were randomized into the study, but 10 were subsequently excluded, 7 from the CEA groups and 3 from the IVPCA groups. 3 of these were due to epidural failure; 1 was due to sepsis (an exclusion criterion in this study); and 6 participants withdrew consent. As about 25% of participants in the CEA group were withdrawn (more than 10% all participants), we judged this study as at high risk of attrition bias.
Selective reporting (reporting bias)	Unclear risk	No study protocol
Other bias	Low risk	No indication of other bias

Carli 2001

Methods	Randomized controlled trial, parallel group
Participants	Participants N = 42, CEA = 21, IVPCA = 21, 20 males, 22 females, ASA 1 to 3, adults, mean age IVPCA group 64 (+/-11), CEA group 68 (+/-8), undergoing general anaesthesia for open colorectal surgery. Study conducted from March 1998 to July 1999.

Carli 2001 (Continued)

Canadian study

Interventions	<ol style="list-style-type: none"> 1. IVPCA group: morphine IVPCA started in recovery postoperatively 1 to 2 mg every 5 to 10 minutes with no background infusion. The morphine was increased by 0.5 to 1 mg until adequate analgesia was reached, VAS < 50 mm. 2. CEA group: thoracic epidural (T8 to T9), block to T4/T5 dermatome before induction of general anaesthesia with 0.5% bupivacaine 15 to 20 mL, then maintained intraoperatively with 5 mL 0.5% bupivacaine every hour. Epidural infusion started postoperatively with 0.1% bupivacaine and 2 µg/mL of fentanyl at 8 to 12 mL/h. If VAS > 50 mm, a bolus of 0.25% bupivacaine was administered. <p>Both groups had 500 mg naproxen orally or per rectum twice a day for 5 days.</p> <p>Both analgesic regimens were changed on day 4 to paracetamol and codeine as required.</p>
Outcomes	<ol style="list-style-type: none"> 1. Pain scores by VAS (0 to 100 mm) at rest, on coughing, and on ambulation on day 1 to 4 (reports 1 cumulative VAS value for rest and coughing and a daily pain score for pain on ambulation) 2. Mortality (number of participants during hospital admission) 3. DVT (number of participants during hospital admission) 4. Duration of hospital stay (days) 5. Nausea and vomiting
Notes	Supported by research funds from the Royal Victoria Hospital Research Institute and the Departments of Anaesthesia and Surgery at McGill University Health Centre. No reported declarations of interest

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No description of randomization method in the text. Quote: "On the day of surgery patients were allocated at random to one of two groups..."
Allocation concealment (selection bias)	Unclear risk	Participants were enrolled and consented 2 weeks prior to randomization, which occurred on the day of surgery. No description of actual concealment of allocation sequence in the paper
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No description of blinding of investigators or participants
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No description of blinding of outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Unclear risk	No study protocol available
Other bias	Low risk	No indication of other bias

Carli 2002

Methods	Randomized controlled trial, parallel group
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Carli 2002 (Continued)

Participants	Participants N = 64, 1 participant excluded, CEA = 32, IVPCA = 31, adults, mean age CEA group 59 (+/- 12), IVPCA group 62 (+/- 12), 33 males, 31 females, ASA 1 to 3, undergoing elective colorectal surgery for non-metastatic conditions, study conducted from April 1998 to April 2002, Canadian study
Interventions	<ol style="list-style-type: none"> 1. IVPCA group: morphine IVPCA started at the end of surgery and continued for 4 days. 1 to 2 mg bolus every 5 minutes with no background. Bolus was increased if VAS (0 to 100 mm) was greater than 50 mm. IVPCA was ceased on day 3 to 4 if VAS on movement was less than 30 mm. 2. Epidural group: thoracic epidural (T8/T9) commenced preoperatively with 0.5% bupivacaine 15 to 20 mL for T4 to S5 block, and maintained with 5 mL 0.5% bupivacaine hourly, intraoperatively. Postoperatively: CEA of 0.1% bupivacaine and 2 µg/mL fentanyl at a rate of 4 to 15 mL/h. Infusion rate adjusted to keep sensory block between T7 to L3. If VAS greater than 50 mm, the rate was increased to max 15 mL/h or concentration increased to 0.2% bupivacaine (with max rate of 8 mL/h). Epidural was ceased on day 4 if VAS on moving was less than 30 mm. <p>Both groups received naproxen 500 mg twice daily. Both groups had a general anaesthetic, the epidural group used the epidural intraoperatively.</p>
Outcomes	<ol style="list-style-type: none"> 1. Pain scores by VAS (0 to 100 mm) at rest, on coughing, and when moving on day 1 to 4 2. Mortality 3. Hospital stay 4. Quality of life (SF-36) at 3 and 6 weeks postoperatively
Notes	<p>1 participant in the IVPCA group was excluded as he did not undergo colonic resection.</p> <p>Supported by a grant from the Koller Foundation of the American Society of Regional Anesthesia and Pain Medicine and research funds from the Royal Victoria Hospital Research Institute. No reported declarations of interest</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No description of randomization method in text. Quote: "A total of 32 patients were randomized to the IVPCA group and 32 to the epidural group"
Allocation concealment (selection bias)	Unclear risk	No description of allocation concealment in text
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "The patients were not blinded, but both IVPCA and epidural groups were equally attractive to them"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Assessors unaware of the explicit hypothesis tested, however they were not blinded. Quote: "Daily assessments of VAS at rest, on coughing, and on moving were recorded by the research nurses, who were unaware of the results of the objective assessment and did not know the explicit hypothesis to be tested"
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 participant in the IVPCA group was excluded as he did not undergo colonic resection. Unlikely for this to be related to true outcome, unlikely to have a clinically relevant impact on the outcome
Selective reporting (reporting bias)	Unclear risk	No study protocol available
Other bias	Low risk	No indication of other bias

Chauvin 1993

Methods	Randomized controlled trial, parallel group
Participants	Participants N = 32, PCEA = 16, IVPCA = 16, 13 males, 19 females, mean age IVPCA group 46 (+/-11), PCEA group 49 (+/-15), ASA 1 to 2, undergoing general anaesthesia for major open abdominal surgery French study
Interventions	2 groups: IVPCA and PCEA group Both groups had their PCA started in recovery when participant complained of intense pain. Both PCAs had alfentanil with 250 µg boluses, maximum dose of 6 mg in 4 hours, PCA continued for 16 hours. The only difference was that the IVPCA group had a lockout of 5 minutes, whereas the PCEA group had a 10-minute lockout.
Outcomes	1. VAS at 10 min, 20 min, 1 h, 2 h, and 2 hourly for 16 hours 2. Sedation on a 4-point scale 3. Oxygen saturation
Notes	No funding sources declared. No conflicts of interest declared.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No description of randomization method in text. Quote: "The patients were selected randomly in two groups..."
Allocation concealment (selection bias)	Unclear risk	Method of concealment is not described in the paper.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "This study was not double blind..."
Blinding of outcome assessment (detection bias) All outcomes	High risk	Outcome assessors were not blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No apparent loss of data/missing data
Selective reporting (reporting bias)	Unclear risk	No study protocol available
Other bias	Low risk	No indication of other bias

Chen 2001

Methods	Randomized controlled trial, parallel group
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Chen 2001 (Continued)

Participants	Participants N = 40, 3 excluded, PCEA = 17, IVPCA = 20, 23 males, 14 females, adult patients, mean age IVPCA group 57 (+/-11), PCEA group 62 (+/-9), ASA 1 to 3, consented for an open elective total gastrectomy under general anaesthetic with epidural anaesthesia in all participants. Study from Hong Kong	
Interventions	2 groups, IVPCA and PCEA, both groups had an epidural intraoperatively, and was left in situ postoperatively (thoracic T8 to T9 or T9 to T10) and received pethidine through a PCA device, both groups had their PCA started in the recovery room following a loading dose of 25 mg of pethidine via assigned route. Both groups had the same PCA settings, 10 mg bolus (5 mg/mL), 10 minutes lockout, 4 hours maximum dose of 3 mg/kg. If analgesia was inadequate, another bolus dose of 25 mg was given in recovery through the assigned route.	
Outcomes	1. VAS (0 to 100 mm), at rest and on coughing, in median and range at 1 h, 4 h, 8 h, 24 h, and 48 h 2. Mortality 3. Failure 4. Hospital stay 5. Satisfaction (VAS 0 to 100 mm) 6. Pruritus 7. Nausea and vomiting 8. Sedation score	
Notes	3 participants in the epidural group were excluded: 1 participant's epidural catheter slipped out during transfer; 1 participant complained of unsatisfactory analgesia related to a technical problem with the PCEA pump; and 1 participant withdrew from the study after randomization without giving a reason. No reported funding sources and no declaration of conflict of interest	
Risk of bias		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization by coded shuffled envelopes. Quote: "Patients were then randomly allocated, using coded shuffled envelopes..."
Allocation concealment (selection bias)	Unclear risk	Randomization was completed after selection, consent, and induction of anaesthesia, using coded shuffled envelopes, however no description of the use of opaque and sealed tamper-proof envelopes.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Both participants and investigators were blinded. Quote: "In order to maintain blinding, the PCA device was connected to both the epidural filter and to a dedicated intravenous cannula via a concealed three-way stopcock that was opened to the route to which the patient had been randomized"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors were blinded. See above quote.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	3 participants in the PCEA group were excluded, 1 due to dislodgement of the epidural, 1 due to failure of PCEA pump, and 1 withdrew without giving a reason. The latter 2 are unlikely to be related to true outcome, however we are uncertain how these withdrawals will impact on the observed effect size.
Selective reporting (reporting bias)	Unclear risk	No study protocol available

Chen 2001 (Continued)

Other bias	Low risk	No indication of other bias
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Chen 2015a

Methods	Randomized controlled trial, parallel group
Participants	N = 53, PCEA = 26, IVPCA = 27, 33 males, 20 females, ASA 1 to 2, adult participants, mean age: PCEA group: 57.3 (+/-5.3), IVPCA group: 57.9 (+/-6.5), undergoing open hemicolectomies for colorectal cancer under general anaesthesia, study conducted from October 2011 to April 2012 Chinese study
Interventions	2 groups, PCEA and IVPCA 1. IVPCA group: morphine, bolus of 1 mg, lockout of 15 minutes, background infusion of 1 mg/h 2. PCEA group: 0.125% bupivacaine and 30 µg/mL morphine, bolus of 2 mL, lockout of 15 minutes, background of 2 mL/h The participants in both groups received the patient-controlled analgesia pump (epidural or intravenous) for 24 h.
Outcomes	1. Pain scores VAS (0 to 100 mm) at rest and on coughing at 24 hours (pain scores were also assessed at 48 hours and on day 5, however the IVPCA and the PCEA were removed at 24 hours, hence only pain scores from the first 24 hours were used in this review) 2. Mortality 3. Duration of hospital stay (days)
Notes	The research is sponsored by Program of Shanghai Subject Chief Scientist (2012 to 2014, 12XD1401900). The funders had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript. The authors have declared that no conflict of interest exists.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomized via a computer-generated number sequence to receive general anesthesia only (G group, n = 27) or general anesthesia combined with epidural anesthesia (E group, n = 26)"
Allocation concealment (selection bias)	Unclear risk	Method of concealment is not described in the paper.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No description of blinding of investigators or participants
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No description of blinding of outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data

Chen 2015a (Continued)

Selective reporting (reporting bias)	Unclear risk	No study protocol available
Other bias	Low risk	No indication of other bias

Donatelli 2006

Methods	Randomized controlled trial, parallel group
Participants	Participants N = 16, CEA = 8, IVPCA = 8, 9 males, 7 females, adults, mean age IVPCA group 59 (+/-16), CEA group 65 (+/-14), elective colon resection for benign and malignant lesions under general anaesthesia. From October 2004 to March 2005 Canadian study
Interventions	1. IVPCA group: morphine IVPCA started at the end of surgery, IVPCA programmed to obtain a VAS < 40 mm at rest 2. CEA group: epidural catheter was inserted between T9 and T11 before the induction of general anaesthesia. Neuraxial blockade was established with 15 mL bupivacaine, 0.5% to achieve a bilateral sensory block (to ice and pinprick) from T4 to S5 and maintained with intermittent boluses of 5 mL bupivacaine, 0.25% every hour. A continuous epidural infusion for postoperative analgesia was provided with a mixture of 0.1% bupivacaine and 2 µg/mL fentanyl at 8 to 15 mL/h supplemented with top-ups of 0.125% bupivacaine to maintain sensory block at T7 to L3, and VAS < 40 mm at rest.
Outcomes	1. Pain scores by VAS (0 to 100 mm) measured at 8 a.m. and 8 p.m. on days 1 and 2
Notes	Support was provided solely from institutional or departmental sources or both. Dr Donatelli is recipient of the McGill University Health Centre Foundation Fellowship.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The participants were assigned to 2 groups, A (IVPCA) and B (epidural) using a computer-generated randomization schedule.
Allocation concealment (selection bias)	Unclear risk	Method of concealment is not described in the paper.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No description of blinding of investigators or participants
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No description of blinding of outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data
Selective reporting (reporting bias)	Unclear risk	No study protocol

Donatelli 2006 (Continued)

Other bias	Low risk	No indication of other bias
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Elkaradawy 2011

Methods	Randomized controlled trial, parallel group
Participants	50 participants, CEA = 25, IVPCA = 25, 38 females, 12 males, ASA 2, with diabetes mellitus type 2 scheduled for open cholecystectomy. Age: CEA group: 44.08 +/- 5.94, IVPCA group: 44.12 +/- 6.06 Egyptian study
Interventions	<ol style="list-style-type: none"> 1. CEA group: epidural block (T7 to T8) with initial bolus of 15 mL of ropivacaine 0.2% with fentanyl 2 µg/mL then an infusion pump started to provide a continuous mixture of 5 to 8 mL/h of ropivacaine 0.1% and fentanyl 1 µg/mL epidural for 24 hours. Epidural commenced preoperatively. 2. IVPCA group: intraoperative analgesia with continuous IV fentanyl 100 µg/h. Postoperative analgesia was maintained by IV morphine patient-controlled analgesia at 1 mg/mL using 1 mL/h basal and 1 mL IVPCA with 6-minute lockout and 10 mL maximum dose/hour for the first 6 hours, then 1 mL IVPCA bolus dose without continuous basal rate infusion for the next 18 hours of the postoperative period.
Outcomes	<ol style="list-style-type: none"> 1. Pain score VAS (0 to 100 mm) in recovery, 4 hours postoperatively, 8 hours postoperatively, 12 hours postoperatively, 24 hours postoperatively 2. Postoperative mean blood pressure
Notes	No reported funding sources and no declaration of conflict of interest

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "A block-wise balanced randomisation procedure was used." Method of randomization into these blocks was not sufficiently described.
Allocation concealment (selection bias)	Low risk	Quote: "The allocation to general anaesthesia with either opioid analgesia or thoracic epidural analgesia was done on cards that were sealed into opaque and consecutively numbered envelopes. These envelopes were opened after taking decision for operation"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No description of blinding of investigators or participants
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "Data collection and analysis were conducted by a neutral researcher who was blinded with anaesthetic and analgesic techniques." Outcome assessors were blinded, however the pain intensity was evaluated by participants using VAS. Uncertain of the influence of blinding on the outcome measurement
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data
Selective reporting (reporting bias)	Unclear risk	No study protocol

Elkaradawy 2011 (Continued)

Other bias	Low risk	No indication of other bias
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Gupta 2006

Methods	Randomized controlled trial, parallel group
Participants	Participants N = 60, 4 participants excluded, adults, mean age IVPCA group 61.1 (+/-4.3), PCEA group 64.9 (+/-6.4), male, ASA 1 to 2, consented for a radical retropubic prostatectomy under combined epidural and general anaesthesia. Swedish study
Interventions	<p>All participants had an epidural inserted prior to randomization into 2 groups:</p> <ol style="list-style-type: none"> IVPCA group: 10 mL/h of placebo (normal saline) infusion in epidural and IVPCA morphine 1 mg/mL intravenously. Bolus of 1 mg, lockout 6 minutes, maximum dose of 10 mg/h. For 48 hours CEA group: 10 mL/h of 1 mg/mL ropivacaine, 2 µg/mL fentanyl, and 2 µg/mL adrenaline through the epidural for 48 hours. IVPCA placebo (normal saline) intravenously <p>Both groups were allowed to have rescue morphine 1 to 2 mg IV if NRS > 5. All participants received 1 g paracetamol every 6 hours throughout the hospital stay.</p>
Outcomes	<ol style="list-style-type: none"> Pain scores (NRS 0 to 10) at rest and while coughing Mortality Duration of hospital stay (days) Ambulation (hours) Quality of life (SF-36) Nausea and vomiting Sedation (4-point scale)
Notes	<p>4 participants were excluded: 1 due to subdural catheter position suspected due to high thoracic analgesia and confirmed on day 1 by computerized tomography with contrast injection (IVPCA group), 1 due to postoperative bleeding requiring reoperation (IVPCA group), 1 after a short period of asystole after anaesthetic induction (CEA group), and 1 due to postoperative bleeding that subsided with conservative management (CEA group).</p> <p>The pain scores were, according to the publication, given as median and interquartile range, however the graphs were difficult to interpret and the pain score results could not be used in this review. We were unable to contact the author for clarification.</p> <p>Supported in part by the Hospital Research Committee, Orebro County Council, Orebro, Sweden. No declaration of conflict of interest</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization by computer-generated randomized numbers. Quote: "The hospital pharmacy, which also prepared the drugs, randomized patients into two groups using computer-generated randomized numbers"
Allocation concealment (selection bias)	Low risk	Central allocation by pharmacy-controlled randomization. Participants were randomized and allocated after selection and epidural insertion. Quote: "After successful insertion of the epidural catheter, patients were randomized into two groups"

Gupta 2006 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinding of surgeons, anaesthetists, nurses, and participants. All participants had identical bags of drugs and placebo going both through the epidural and IVPCA; the content of the bag depended on the group to which the participant had been randomized.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors were blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	4 participants excluded after randomization, 2 in each group.
Selective reporting (reporting bias)	Unclear risk	No study protocol available
Other bias	Low risk	No indication of other bias

Heurich 2007

Methods	Randomized controlled trial, parallel group. There were 2 studies within the study: part 1 (comparing CEA and IVPCA) and part 2 (comparing CEA with local anaesthetic to CEA with opioids). Only part 1 was relevant to our review.	
Participants	<p>Participants N = 30, 11 participants excluded, CEA = 10, IVPCA = 9, 10 females, 9 males, adults, mean age IVPCA group 68.9 (+/-4.5), CEA group 64.6 (+/-3.1), ASA 1 to 3, scheduled for elective major abdominal surgery by midline incision under general anaesthesia</p> <p>German study</p>	
Interventions	<p>All participants received general anaesthesia, and postoperative analgesia was provided for 48 h either by CEA or IVPCA.</p> <ol style="list-style-type: none"> 1. CEA group: epidural catheter was placed at T11 to L1 level or L1 to L3 level before induction of general anaesthesia. A test dose of 3 mL lidocaine 1% was administered. 5 to 9 mL bupivacaine 0.5% was injected epidurally to achieve a bilateral T4 dermatomal level, verified by pin prick testing. Epidural analgesia was maintained via intraoperative bolus injections of bupivacaine 0.5% (3 to 4 mL/h). Post-operatively, analgesia was maintained by epidural administration of 0.0625% bupivacaine + 2 µg/mL fentanyl (for catheters inserted at L1 to L3 level), or by a combination of 0.125% bupivacaine and 4 µg/mL fentanyl (for catheters inserted at T11 to L1 level) delivered by an automated pump. The infusion rate was adjusted to a VAS at rest of 30 mm or less. 2. IVPCA group: intraoperative analgesia was provided by IV bolus injections of fentanyl as needed. Post-operative analgesia, an IVPCA pump was programmed to deliver an IV bolus of 2 mg piritramide with lockout of 10 minutes. Max dose within 4 hours was 30 mg. Supplementary analgesic medication (piritramide 2 to 5 mg IV) was available upon the participant's request. 	
Outcomes	<ol style="list-style-type: none"> 1. Pain score VAS (0 to 100 mm) was measured regularly for the first 48 hours 2. Failure rate 	
Notes	<p>11 exclusions: in 6 participants the analgesic regimen had to be stopped within 48 h because of dislocation of the epidural catheter (4 participants), relaparotomy (1 in the IVPCA group), or application of supplementary analgesic medication not included in the protocol (1 in the IVPCA group). 4 participants had to be excluded because of revoked consent (2 in each group), and 1 in the IVPCA group was excluded due to postoperative mechanical respiration for longer than 6 h.</p>	

Heurich 2007 (Continued)

This study was supported by the Deutsche Forschungsgemeinschaft (Bonn, Germany, Klinische Forschergruppe KFO 100/1). There were no conflicts of interest.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "A randomization list was generated by our department of statistics together with numbered envelopes"
Allocation concealment (selection bias)	Unclear risk	Method of concealment was not described in sufficient detail to permit judgement.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No clear description of blinding of participants, however the anaesthetist was informed of the allocation of the participant. Quote: "...the anesthesiologist assigned to the case was informed about the allocated treatment." It is unclear how this would influence the postoperative outcome measures.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The investigator assessing the histological outcomes was blinded to the treatment regimens, however there is no description of blinding of the investigators collecting pain scores and other data.
Incomplete outcome data (attrition bias) All outcomes	High risk	In part 1, 30 participants were selected, 11 participants were excluded from data analysis (in 6 of these participants the analgesic regimen had to be stopped within 48 h because of dislocation of the epidural catheter (4), relaparotomy (1 in the IVPCA group), or application of supplementary analgesic medication not included in the protocol (1 in the IVPCA group). 4 participants had to be excluded because of revoked consent (2 in each group), and 1 in the IVPCA group was excluded due to postoperative mechanical respiration for longer than 6 h. We judged this study as at high risk of attrition bias, as over 35% of participants were withdrawn from the study after randomization.
Selective reporting (reporting bias)	Unclear risk	No study protocol
Other bias	Low risk	No indication of other bias

Hübner 2015

Methods	Randomized controlled trial. Single-centre, parallel-group superiority study with balanced randomization (1:1). Outcomes analysed as per intention-to-treat principle.
Participants	Participants N = 128, 11 participants excluded postrandomization, final N = 122, PCEA = 65, IVPCA = 57, adults, mean age IVPCA group 61.2 ($\pm$ 17.8), CEA group 63.1 ($\pm$ 15.1), 71 males, 51 females, ASA 1 to 3, undergoing laparoscopic colorectal surgery under general anaesthesia within an enhanced recovery after surgery programme. Swiss study
Interventions	2 groups: 1. PCEA group: combined epidural and general anaesthesia. Thoracic epidural inserted at level T8 to T10 before induction of anaesthesia. 0.5% bupivacaine was used intraoperatively for analgesia. Postoperatively a PCEA with 0.1% bupivacaine, 2 μ g/mL fentanyl, and 2 μ g/mL adrenaline was started. PCEA programme: 3 mL bolus, 40 minutes lockout, 6 to 10 mL/h background infusion. Targeting a VAS score < 40 mm 2. IVPCA group: general anaesthesia with fentanyl IV as required intraoperatively. IVPCA program: 1 mg bolus of morphine, 5 minutes lockout, 1 mg/h background infusion

Hübner 2015 (Continued)

In addition paracetamol 4x 1 g/day and metamizole 4x 500 mg/day was routinely given in both groups unless contraindicated.

Outcomes	<ol style="list-style-type: none"> 1. Mortality 2. Pain scores VAS (0 to 100 mm), twice daily from evening on day of surgery to postop day 4 3. Duration of hospital stay (days) 4. Failure rate 5. Hypotension (% requiring vasopressor treatment during and after surgery)
Notes	No external funding required for this study. Authors declare no conflicts of interest.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization by a computerized online randomization program
Allocation concealment (selection bias)	Low risk	Central allocation using a computerized online randomization program, after enrolment had taken place. Quote: "Patients were randomly assigned by a dedicated study nurse using an online randomization program (Randomizer; Institute for Medical Informatics, Statistics, and Documentation, Medical University of Graz, Graz, Austria; URL http://www.randomizer.at)"
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding. Quote: "blinding was not performed because it seemed neither feasible nor realistic for this study"
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding of outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data
Selective reporting (reporting bias)	Low risk	Study protocol is available, and the outcomes of interest for the review were reported in the prespecified way.
Other bias	Low risk	No indication of other bias

Jayr 1998

Methods	Randomized controlled trial, parallel group
Participants	Participants N = 91 (total participant number is 130, however for the purpose of this review 1 group, combined CEA and IVPCA, was excluded as it did not meet our inclusion criteria), 7 participants excluded, CEA = 38, IVPCA = 46, adults, mean age PCEA group 63.1 ($\pm$ 15.1), IVPCA group 61.2 ($\pm$ 17.8), 39 females, 45 males, ASA 1 to 3, undergoing either cystectomy, radical abdominal hysterectomy, colonic resection, or rectum amputation under general anaesthesia. French study
Interventions	Interventions included in this review:

Jayr 1998 (Continued)

1. CEA group: epidural was inserted preoperatively, postoperatively a 20 mL dose of 0.2% ropivacaine (2 mg/mL) was given followed by a continuous infusion at 10 mL/h. Infusion rate was reduced if excessive block occurred.
 2. IVPCA group: 1 mg/mL of morphine, bolus of 1 mg, lockout of 5 minutes, no background infusion
- Both groups were allowed to have rescue morphine 1 to 2 mg IV.

Outcomes	<ol style="list-style-type: none"> 1. Pain scores VAS (0 to 100 mm) at rest and on coughing 2. Failures 3. Nausea and vomiting 4. Hypoxaemia $\text{SaO}_2 < 91\%$ 5. Hypotension needing treatment (no specific blood pressure defined as hypotension)
Notes	Study was funded by a grant from Astra Pain Control AB in Sweden. No declaration of conflicts of interest

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomized by coded envelopes. Quote: "Randomization envelopes were opened by the investigator immediately before preparing for anaesthesia"
Allocation concealment (selection bias)	Unclear risk	Method of concealment of the randomized coded envelopes was not described in sufficient detail to permit judgement.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No description of blinding of participants or personnel in the study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No description of blinding of outcome assessors in the study
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	7 participants were withdrawn, 5 in the CEA group and 2 in the IVPCA group. 2 of 5 in the CEA group were related to the epidural, 1 due to technical failure and the second due to a dural puncture. None of the withdrawals in the IVPCA group appeared to be related to the intervention. The risk of bias for this domain is unclear as it is uncertain if the withdrawals would change the final outcomes.
Selective reporting (reporting bias)	Unclear risk	No study protocol available
Other bias	Low risk	No indication of other bias

Kowalski 1992

Methods	Randomized controlled trial. Single-centre, double-blinded, parallel-group study
Participants	N = 18, CEA = 9, IVPCA = 9. Age, gender, and ASA scores were not described. All participants undergoing upper abdominal surgery under general anaesthesia with epidural analgesia. Canadian study
Interventions	All participants had an epidural inserted preoperatively. A block was established to T6 with 2% lidocaine with adrenaline. This was further supplemented with 0.25% bupivacaine intraoperatively as

Kowalski 1992 (Continued)

needed. IV fentanyl was used intraoperatively up to 5 µg/kg, as required. Postoperatively the participants were randomized into 2 groups, CEA fentanyl infusion and IVPCA morphine.

1. CEA group received a 1 µg/kg fentanyl loading dose with an initial infusion rate of 1 µg/kg/h. They could receive another loading dose of 0.5 µg/kg and the infusion further increased to 1.5 µg/kg/h if needed. This group had an IVPCA with placebo.
2. IVPCA group received morphine, 8 mg loading followed by the IVPCA. IVPCA programme: 1 mg bolus, 10 minutes lockout, background infusion of 1 mg/h. This could be changed to a lockout of 5 minutes if needed and an additional 4 mg of morphine administered as a second loading dose. This group was given a CEA with placebo.

Outcomes	1. Pain scores at rest VAS (0 to 100 mm) at 2, 4, 24, and 48 hours postoperatively 2. Respiratory complications
Notes	No reported funding sources and no declaration of conflicts of interest

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information regarding the randomization process to permit judgement
Allocation concealment (selection bias)	Unclear risk	Method of concealment is not described in the study.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Both participants and investigators were blinded. Quote: "Neither the patient nor the investigator knew which pump had active medication"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Investigators were blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Unclear risk	No study protocol available
Other bias	Low risk	No indication of other bias

Liu 1995

Methods	Randomized controlled trial, parallel group
Participants	Participants N = 16, IVPCA = 8, PCEA = 8, adults, mean age IVPCA group 59 ± 11, PCEA group 60 ± 8, male, ASA 1 to 3, undergoing radical retropubic prostatectomy under combined epidural and general anaesthesia. US study
Interventions	2 groups, IVPCA and PCEA hydromorphone. Both groups had the same settings of their PCA, with a 3-way stopcock determining if the PCA delivered the hydromorphone IV or epidurally. Both groups initially received a bolus of 1050 µg of hydromorphone.

Liu 1995 (Continued)

PCA settings: 2 mL bolus of 75 µg/mL hydromorphone solution and 15 minutes lockout. Inadequate analgesia was treated with a 300 µg bolus and a 50 µg increase in the PCA bolus, with a decrease in the lockout to 10 minutes. If analgesia remained inadequate, the bolus was increased by 50 µg every hour until analgesia was adequate. PCA was continued until discharge criteria were met.

Both groups received IM ketorolac 15 mg every 6 hours for 72 hours.

Outcomes	<ol style="list-style-type: none"> 1. Pain scores VAS (0 to 100 mm) 3 hours postop and in the morning for the next 72 hours 2. Duration of hospital stay (days) 3. Satisfaction score VAS (0 to 100 mm) mailed to participants postdischarge 4. Pruritus 5. Nausea and vomiting 6. Sedation
Notes	No reported funding sources and no declaration of conflict of interest

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomization method not specified. Quote: "Patients were randomized into one of two groups..."
Allocation concealment (selection bias)	Unclear risk	Randomization occurred in the recovery room postoperatively, however no description of the method of allocation is provided.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants and personnel were blinded. Quote: "the stopcock was adjusted by the recovery room nurse, who secured and concealed the stopcock. Neither the patients, surgeons, nor the investigators were aware of stopcock position"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors were blinded. See above quote
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data
Selective reporting (reporting bias)	Unclear risk	No study protocol available
Other bias	Low risk	No indication of other bias

Madej 1992

Methods	Randomized controlled trial, parallel group
Participants	Participants N = 30, CEA = 20, IVPCA = 10 (total participant number is 50, however for the purpose of this review 1 group (epidural bolus) was excluded as it did not meet our inclusion criteria), adults, mean age IVPCA group 40 (+/- 26 to 51), CEA group (44 +/- 31 to 70), all females, healthy, undergoing total abdominal hysterectomy under combined epidural and general anaesthesia. British study
Interventions	Interventions included in this review: <ol style="list-style-type: none"> 1. IVPCA group: 1 mg boluses of diamorphine with a lockout of 5 minutes

Madej 1992 (Continued)

2. CEA group: lumbar epidural infusion of 0.15% bupivacaine (1.5 mg/mL) and 0.01% diamorphine (100 µg/mL) at 4 to 6 mL/h

Both interventions were continued for 24 hours.

Outcomes	<ol style="list-style-type: none"> 1. Pain score VAS (0 to 100 mm) 4 hourly for 24 hours 2. DVT (method for detection not specified) 3. Pruritus 4. Nausea and vomiting 5. Sedation (method for assessment not specified) 6. hypoxaemia, SaO₂ < 94% mild, < 90% moderate, < 85% severe (with duration for more than 20 seconds or more than 20% of a 12-minute measurement period) measured with continuous saturation monitoring while participants breathing room air
Notes	No reported funding sources and no declaration of conflicts of interest

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization using table of random numbers. Quote: "The patients were allocated randomly, using a table of random numbers, to receive extradural or patient-controlled analgesia after the operation"
Allocation concealment (selection bias)	High risk	Allocation was based on an open random allocation schedule, i.e. a table of random numbers.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No description of blinding of participants or personnel in the study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No description of blinding of outcome assessor
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Unclear risk	No study protocol available
Other bias	Low risk	No indication of other bias

Mann 2000

Methods	Randomized controlled trial, parallel group
Participants	Participants N = 70, 6 participants excluded postrandomization, final N = 64, PCEA = 31, IVPCA = 33, age > 70, mean age IVPCA group 76.8 (+/-4.7), PCEA group 76.1 (+/-5.6), 32 females, 38 males, ASA 1 to 2, undergoing open abdominal surgery (colectomy, gastrectomy, and cephalic pancreatectomy) under general anaesthesia. French study
Interventions	2 groups:

Mann 2000 (Continued)

1. PCEA group: combined epidural and general anaesthesia. Thoracic epidural T7 to T11 depending on surgical site. Postoperatively a 0.125% bupivacaine and 0.5 µg/mL sufentanil PCEA was started. PCEA programme: 2 to 3 mL bolus, 12-minute lockout, 3 to 5 mL/h background infusion
2. IVPCA group: general anaesthesia with sufentanil IV as required intraoperatively. In the postoperative care unit a loading dose of morphine (up to 5 mg) was administered before the IVPCA was started. IVPCA programme: 1.5 mg bolus of morphine, 8-minute lockout, no background infusion

These programmes could be adjusted if required on the twice-daily ward round. In addition, IV paracetamol 2 g or IV ketoprofen 100 mg was administered when pain relief was inadequate (VAS > 30 mm).

Outcomes	<ol style="list-style-type: none"> 1. Pain scores VAS (0 to 100 mm) at rest and on coughing, assessed at 08:00, 12:00, and 20:00 during the first 5 postoperative days 2. Duration of hospital stay (days) 3. Time to ambulation (hours) 4. Satisfaction score (4-point scale, 0 to 3, not satisfied = 0; mildly satisfied = 1; good = 2; excellent = 3) 5. Pruritus 6. Nausea and vomiting 7. Sedation score (4-point scale 0 to 3, wide awake = 0; mildly sleepy, responsive to verbal command = 1; moderately sleepy, responsive to nociceptive stimulation = 2; extremely sleepy, not responsive to nociceptive stimulation = 3) 8. hypoxaemia (SaO₂ 90% to 95%, SaO₂ 85% to 90%) 9. Hypotension (systolic blood pressure < 90 mmHg)
Notes	<p>6 participants were withdrawn, 2 in the IVPCA group and 2 in the PCEA group due to absence of surgical resection, and 2 participants in the PCEA group due to refusal to use the PCEA device.</p> <p>Supported by grant ET7-204 from Fondation de l'Avenir, Paris, France. No reported declarations of interest</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization by a random number table
Allocation concealment (selection bias)	High risk	Allocation was based on an open random allocation schedule, i.e. a table of random numbers. Quote: "The day before surgery and after obtaining written informed consent, all subjects received written and verbal instructions for use of IVPCA or PCEA and were instructed to balance analgesia against sedation. Then, the patients were assigned to receive, as determined by a table of random numbers, either ... (IVPCA group) or ... (PCEA group)"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No description of blinding of participants or personnel in the study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No description of blinding of outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	<p>6 participants were withdrawn, 2 in the IVPCA group and 2 in the PCEA group due to absence of surgical resection, and 2 participants in the PCEA group due to refusal to use the PCEA device.</p> <p>Unclear if the refusal to use the PCEA device is related to the true outcome. Appears unlikely that the withdrawals would change the final outcome.</p>

Mann 2000 (Continued)

Selective reporting (reporting bias)	Unclear risk	No study protocol available
Other bias	Low risk	No indication of other bias

Motamed 1998

Methods	Randomized controlled trial, parallel group
Participants	Participants N = 60, 3 participants excluded postrandomization, final N = 57, CEA = 28, IVPCA = 29, adults, mean age IVPCA group 56 (+/-11), CEA group 60 (+/- 10), 37 females, 20 males, ASA 1 to 2, undergoing open abdominal surgery for cancer under general anaesthesia. French study
Interventions	<p>2 groups:</p> <ol style="list-style-type: none"> 1. IVPCA group: postoperatively loading doses of IV morphine were administered, 3 mg every 10 minutes until participants had adequate pain relief. IVPCA pump was attached. IVPCA programme: bolus of 1 mg morphine, lockout of 5 minutes, maximum dose of 20 mg in 4 hours, no background infusion 2. CEA group: thoracic epidural T9 to T11. Epidural was not used intraoperatively. Postoperatively a loading dose of 0.125% bupivacaine and 0.25 mg/mL morphine was administered to achieve a bilateral T6 sensory block. The CEA was started with the same mixture at 10 mL/h, the rate reduced if a motor block was achieved. <p>Both groups had a similar general anaesthetic with fentanyl analgesia. If supplementary analgesia was required postoperatively, the participant would be excluded from the study (no participants were excluded for this reason).</p>
Outcomes	<ol style="list-style-type: none"> 1. Pain score VAS (0 to 100 mm), measured at rest and on coughing at 2, 8, and 24 hours postoperatively 2. Satisfaction (4-point scale, poorly satisfied; mildly satisfied; satisfied; very satisfied) 3. Sedation (4-point scale, awake; sleepy, but easily wakeable; sleepy, but hardly wakeable; very sleepy) measured with pain scores 4. Hypoxaemia, SaO₂ was measured continuously, participants breathing room air, participants grouped into SaO₂ > 94%; SaO₂ 94% to 90%; SaO₂ 89% to 85%; SaO₂ 84% to 80%. If SaO₂ remained 84% or less for more than 2 minutes, supplementary oxygen was administered and the participant was excluded from the study.
Notes	<p>3 participants (2 in CEA group, 1 in IVPCA group) were excluded, all due to low SaO₂ needing supplementary oxygen.</p> <p>No reported funding sources and no declaration of conflict of interest</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No description of randomization method in the paper
Allocation concealment (selection bias)	Unclear risk	Method of concealment was not described in the paper.
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding. Quote: "This prospective randomized study was not double-blinded, and the results could have been confounded by observer bias"

Motamed 1998 (Continued)

Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding of outcome assessors, see above quote
Incomplete outcome data (attrition bias) All outcomes	Low risk	3 participants (2 in CEA group, 1 in IVPCA group) were excluded, all due to low SaO ₂ needing supplementary oxygen. Due to the relatively equal distribution of the excluded participants and the small numbers, the exclusions are unlikely to have a clinically relevant impact on the effect size.
Selective reporting (reporting bias)	Unclear risk	No study protocol available
Other bias	Low risk	No indication of other bias

Ngan 1997

Methods	Randomized controlled trial. Double-blinded, single-centre, cross-over study
Participants	Participants N = 80, 4 participants excluded postrandomization, final N = 76. All female, ASA 1 to 2, undergoing elective Caesarean section under epidural anaesthesia. Age (median and IQ range) pethidine IVPCA: 32 (29.5 to 34), pethidine PCEA: 31 (28 to 32), fentanyl IVPCA: 30 (28 to 33), fentanyl PCEA: 32.5 (30.5 to 35). Study from Hong Kong
Interventions	<p>4 intervention groups:</p> <ol style="list-style-type: none"> 2 pethidine groups divided into IVPCA and PCEA groups, which crossed over after 12 hours 2 fentanyl groups divided into IVPCA and PCEA groups, which crossed over after 12 hours <p>For the purpose of this review we used only the results from the first 12 hours.</p> <p>Intraoperatively all groups had the same management:</p> <ol style="list-style-type: none"> Epidural: 2% lidocaine with adrenaline 1:200,000 to establish block to T4 Pain: nitrous oxide via face mask, or ketamine 10 mg bolus as required <p>Both PCEA groups had epidurals at L2 to L4.</p> <p>Pethidine groups had the same PCA programmed to deliver pethidine 10 mg/mL. Loading 4 mL, then PCA 2 mL bolus and 15-minute lockout. 4 hours max 40 mL</p> <p>Fentanyl groups had the same PCA programmed to deliver fentanyl 20 µg/mL. Loading 4 mL, then PCA 2 mL bolus and 15-minute lockout. 4 hours max 40 mL</p>
Outcomes	<ol style="list-style-type: none"> Pain scores at rest, VAS (0 to 100 mm) measured 4 hourly for the first 24 hours, Due to cross-over design, only the first 12 hours are included in this review. Pruritus, VAS (0 to 100 mm) measured 4 hourly, reported as an aggregate Nausea, VAS (0 to 100 mm) measured 4 hourly, reported as an aggregate Sedation, 4-point scale, measured 4 hourly, reported as an aggregate
Notes	<p>4 participants were excluded postrandomization, with reasons for exclusion reported for only 2 of these. Both were in the fentanyl IVPCA group, 1 due to failure of the PCA device and 1 due to inadequate analgesia.</p> <p>Funding from a Small Projects Research Grant from the Chinese University of Hong Kong. No declaration of conflict of interest</p>

Risk of bias

Ngan 1997 (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "patients were randomized by drawing of shuffled coded envelopes"
Allocation concealment (selection bias)	Unclear risk	The envelopes used to randomize participants were not described in sufficient detail to permit judgement.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Both participants and investigators were blinded. Blinding might have been broken by some participants, however it is unlikely that this would influence the outcome.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Investigators were blinded. Quote: "PCA solution containing either pethidine 10 mg/mL or fentanyl 20 microg/mL was prepared by an anaesthetist not involved in patient assessment"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	2 missing participants in 1 group. No reasons for missing data provided.
Selective reporting (reporting bias)	Unclear risk	No study protocol available
Other bias	Unclear risk	Cross-over RCT with only the pre-cross-over data used for analysis

Paech 1994

Methods	Randomized controlled trial. Double-blinded, single-centre, cross-over study
Participants	Participants N = 50, 5 participants excluded postrandomization, final N = 45, PCEA = 24, IVPCA = 21. Female participants undergoing elective Caesarean section under epidural anaesthesia. Age (median and IQ range) IVPCA: 30 (24 to 35), PCEA: 33 (28 to 36). Australian study
Interventions	<p>2 intervention groups divided into IVPCA and PCEA groups, which crossed over after 12 hours</p> <p>For the purpose of this review we used only the results from the first 12 hours.</p> <p>Intraoperatively both groups had the same management: epidural at L1 to L3 to 0.5% bupivacaine + 5 µg/mL fentanyl max 20 mL for bilateral T4 block.</p> <p>Postoperatively both groups received pethidine 25 mg loading, then PCA with 20 mg bolus, 5-minute lockout, 200 mg/2 h maximum. The PCA was connected to both the IV and the epidural catheter by a concealed 3-way stopcock open to either the IV catheter or the epidural catheter as per a computer-derived randomization sequence.</p>
Outcomes	<ol style="list-style-type: none"> 1. Pain scores VAS (0 to 100 mm) at rest and while coughing, 4 hourly for 24 hours 2. Pruritus VAS (0 to 100 mm) at the end of each 12-hour period 3. Nausea VAS (0 to 100 mm) at the end of each 12-hour period 4. Respiratory complications, respiratory rate < 10 5. Satisfaction score VAS (0 to 100 mm) at the end of each 12-hour period
Notes	5 participants were excluded postrandomization, 1 participant from the PCEA group and 4 participants from the IVPCA group. 2 were excluded due to dislodgement of the epidural and 2 due to failure of the PCA pump. 1 participant withdrew from the IVPCA group due to dissatisfaction with the analgesia.

Paech 1994 (Continued)

Grant from the King Edward Memorial Hospital Research Foundation. No declarations of conflicts of interest

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "patients were randomized according to a computer-derived sequence..."
Allocation concealment (selection bias)	Unclear risk	Enrolment was done prior to surgery, and randomization was performed after surgery. Insufficient information on the computer-derived randomization sequence to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Both participants and investigators were blinded. Blinding might have been broken by some participants, however it is unlikely that this would influence the outcome. Quote: "The patient, research nurse and attending nursing staff were unaware of the route of administration"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The assessors and data collectors were unaware of the route of administration. Quote: "...the PCA pump was connected to both the intravenous cannula and the epidural filter via a concealed three-way stopcock, and the direction of administration was altered at 12 h by an anesthesiologist not involved in the study"
Incomplete outcome data (attrition bias) All outcomes	High risk	5 participants were excluded postrandomization, 1 participant from the PCEA group and 4 participants from the IVPCA group. 2 were excluded due to dislodgement of the epidural and 2 due to failure of the PCA pump. 1 participant withdrew from the IVPCA group due to dissatisfaction with the analgesia. As the withdrawals were unbalanced, with more than 15% of participants withdrawn in 1 group and only 4% in the other group, we judged this study as at high risk of attrition bias.
Selective reporting (reporting bias)	Unclear risk	No study protocol available
Other bias	Unclear risk	Cross-over RCT with only the pre-cross-over data used for analysis

Parker 1992

Methods	Randomized controlled trial, parallel group
Participants	Participants N = 117, 10 excluded before analysis, and 13 withdrawn during the study. IVPCA = 49, phase 1 PCEA = 17, phase 2 PCEA = 41, ASA 1 to 2, female participants undergoing elective Caesarean section under epidural anaesthesia. Age (mean $\pm$ SD) IVPCA: 28 ($\pm$ 5), phase 1 PCEA: 27 ($\pm$ 6), phase 2 PCEA: 28 ($\pm$ 6). US study
Interventions	<p>There were 3 groups: 1 IVPCA group (controls) and 2 PCEA groups divided into a phase 1 and a phase 2 group.</p> <p>Phase 1 PCEA group: hydromorphone epidural loading dose of 0.9 mg, followed by a PCEA with 0.15 mg boluses, 30-minute lockout.</p> <p>Phase 2 PCEA group: hydromorphone epidural loading dose of 0.225 mg, followed by a PCEA with 0.15 mg boluses, 30-minute lockout.</p> <p>IVPCA hydromorphone: bolus of 0.15 mg, 10-minute lockout</p>

Parker 1992 (Continued)

Outcomes	<ol style="list-style-type: none"> 1. Pain scores VAS (0 to 100 mm) assessed 8 hourly for 48 hours postoperatively 2. Failures 3. Duration of hospital stay (hours) 4. Time to ambulation (hours) 5. Pruritus 6. Nausea 7. Vomiting 8. Sedation score VAS (0 to 100 mm) assessed 8 hourly for 48 hours postoperatively 9. hypoxaemia (the lowest SpO₂ lasting more than 2 minutes (reported as a mean lowest SpO₂) and the number of participants within certain SpO₂ intervals)
Notes	<p>Due to a high incidence of pruritus and nausea in the initial 17 PCEA participants, the loading dose of the epidural hydromorphone was reduced and the initial 17 participants were named the phase 1 group, and the remaining 41 PCEA participants were named the phase 2 group.</p> <p>There were initially 117 participants randomized to the treatment groups, however at the start of the study there were only 107 participants. During the study 13 participants were withdrawn from analysis. This included 4 participants in the IVPCA group, 3 in the phase 1 PCEA group, and 6 in the phase 2 PCEA group. These are accounted for in the paper and were due to insufficient analgesia with requests for additional analgesia (3 participants), dislodgement of the epidural (5 participants), and side effect-related requests to discontinue the mode of analgesia. Data from these participants were included until the time of protocol violation. There are another 10 participants missing from the analysis.</p> <p>The study was supported in part by a grant from Knoll Pharmaceuticals, Whippany, New Jersey.</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgement. Quote: "117 adult women ... were randomly assigned to one of two PCA treatment protocols"
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement - no description of allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No description of attempts to blind participants or personnel
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No description of attempts to blind outcome assessors
Incomplete outcome data (attrition bias) All outcomes	High risk	There were initially 117 participants randomized to the treatment groups, however at the start of the study there were only 107 participants. During the study 13 participants were withdrawn from analysis. This included 4 participants in the IVPCA group, 3 in the phase 1 PCEA group, and 6 in the phase 2 PCEA group. These are accounted for in the paper and were due to insufficient analgesia with requests for additional analgesia (3 participants), dislodgement of the epidural (5 participants), and side effect-related requests to discontinue the mode of analgesia. Data from these participants were included until the time of protocol violation. There are another 10 participants missing from the analysis. These participants are not accounted, therefore we judged this study as at high risk of bias for this domain.

Parker 1992 (Continued)

Selective reporting (reporting bias)	Unclear risk	No study protocol available
Other bias	Low risk	No indication of other bias

Schricker 2000

Methods	Randomized controlled, parallel-group, single-centre trial
Participants	Participants N = 16, CEA = 8, IVPCA = 8, ASA 1 to 2, age: 57 ± 22 (mean ± SD) in IVPCA group, 53 ± 15 (mean ± SD) in epidural group, gender: 7 males, 9 females undergoing elective colorectal surgery under general anaesthesia. Canadian study
Interventions	2 groups, CEA and IVPCA: 1. CEA group a. Intraoperatively i. Epidural inserted at T10 to T12 - 0.5% bupivacaine bolus to establish bilateral block to T4, then 0.25% bupivacaine bolus for maintenance ii. Induction with thiopentone iii. Maintenance with isoflurane/oxygen/nitrous oxide b. Postoperatively i. CEA: 0.1% bupivacaine + 2 µg/mL fentanyl to maintain T8 to L3 blockade 2. IVPCA group a. Intraoperatively i. Induction with thiopentone ii. Maintenance with isoflurane/oxygen/nitrous oxide and fentanyl 3 µg/kg for analgesia b. Postoperatively i. IVPCA: morphine 1 to 2 mg bolus, 8-minute lockout
Outcomes	No outcomes included from this trial.
Notes	Funded in part by a grant from the Canadian Anaesthetic Society and by a Research Operating Grant from the Deutsche Forschungsgemeinschaft, Germany. No declarations of conflicts of interest

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The patients were allocated according to a computer-generated randomization schedule..."
Allocation concealment (selection bias)	Unclear risk	The method of concealment is not described in sufficient detail to permit judgement.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No description of attempts to blind participants or personnel
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No description of attempts to blind outcome assessors

Schricker 2000 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data
Selective reporting (reporting bias)	Unclear risk	No study protocol available
Other bias	Low risk	No indication of other bias

Schumann 2003

Methods	Randomized controlled trial, parallel group
Participants	Participants N = 114, IVPCA and LA = 39, CEA = 39, IVPCA = 36, adults, age (mean +/- SD): IVPCA and LA 40.2 (+/-12.4), CEA 40.0 (+/-10.5), IVPCA 40.6 (+/-9.8), 94 females, 20 males, obese BMI ≥ 30, undergoing gastric bypass surgery as treatment for obesity under general anaesthetic. US study
Interventions	<p>3 groups:</p> <ol style="list-style-type: none"> 1. IVPCA and local infiltration group: received pre- and postsurgical local anaesthetic field infiltration. 40 to 45 mL of 0.25% bupivacaine with 1:200,000 epinephrine infiltrated pre-incision and an equal amount after wound closure. Postoperatively the participant was loaded with morphine 2.5 mg IV every 5 minutes to maximum of 10 mg followed by starting an IVPCA. IVPCA programme: 2.5 mg bolus, 8-minute lockout, no background 2. IVPCA-only group: postoperatively the participant was loaded with morphine 2.5 mg IV every 5 minutes to maximum of 10 mg followed by starting an IVPCA. IVPCA programme: 2.5 mg bolus, 8-minute lockout, no background 3. CEA group: thoracic epidural placed preoperatively, this was used intraoperatively. Postoperatively an infusion was started with 0.1% bupivacaine and 1 mg/mL meperidine, titrated to a maximal rate of 14 mL/h. <p>All groups received ketorolac 30 mg 4 times per day until tolerating oral intake, then ibuprofen 600 mg 4 times per day was started instead.</p> <p>For the purpose of this review we considered both IVPCA groups as 1 group as described in our protocol.</p>
Outcomes	<ol style="list-style-type: none"> 1. Pain scores VAS (0 to 100 mm) every 6 hours at rest 2. Epidural failure rate 3. Pruritus 4. Nausea and vomiting
Notes	<p>High numbers of missing data, only 51% of VAS scores at 48 hours (see 'Risk of bias' table below)</p> <p>Funding from the Saltonstall Fund for Pain Research, educational grant from Abbott Laboratories. No reported declarations of interest</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization was done by shuffling envelopes with allocation codes. Quote: "Successive envelopes containing allocation codes were opened by one investigator"

Schumann 2003 (Continued)

Allocation concealment (selection bias)	Unclear risk	Randomization was done after consent and enrolment, however the method of concealment is not described in sufficient detail to allow judgement.
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding. Quote: "This was a randomized, comparative, open-label, single site study"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The outcome assessors were ward nursing staff. It is unclear if they were aware if the patient was part of the study or not.
Incomplete outcome data (attrition bias) All outcomes	High risk	<p>High numbers of missing data, only 51% of VAS scores at 48 hours. Quote: "Decreases in the number of patients contributing data points across time were not because of additional dropouts, but instead reflected incomplete capture or documentation of VAS scores by ward nursing staff (80% of subjects at time 0 versus 51% at 48 h)"</p> <p>High number of missing data in the CEA group due to failure of the epidural (failure rate of 27.8%), 3 preoperatively and 7 postoperatively (data not collected once epidural failed).</p> <p>5 participants in the CEA group were excluded after randomization, but before data collection, of which 3 were due to failure of placing the epidural, as mentioned above, and 2 were due to intraoperative events.</p> <p>6 participants in the IVPCA groups were excluded due to intraoperative events.</p>
Selective reporting (reporting bias)	Unclear risk	No study protocol available
Other bias	Low risk	No indication of other bias

Steinberg 2002

Methods	Randomized controlled trial. Multicentre, parallel group
Participants	Participants N = 48, 7 participants did not complete the protocol, final N = 41, PCEA = 20, IVPCA = 21, ASA 1 to 3, age (mean $\pm$ SD): IVPCA: 62 ($\pm$ 10), PCEA: 61 ($\pm$ 15), 25 males and 16 females undergoing elective partial colon resection under general anaesthesia. US study
Interventions	<p>2 groups:</p> <ol style="list-style-type: none"> 1. PCEA group <ol style="list-style-type: none"> a. Intraoperative management <ol style="list-style-type: none"> i. General anaesthesia with isoflurane/oxygen/nitrous oxide ii. Epidural at T7 to T10 - 6 to 10 mL of 0.75% ropivacaine loading, then 0.2% ropivacaine + 2 μg/mL fentanyl infusion at 8 to 10 mL/h, 5 mL bolus as required every 15 minutes for hypertension b. Postoperative PCEA <ol style="list-style-type: none"> i. 0.2% ropivacaine + 2 μg/mL fentanyl 4 mL/h background, bolus 2 mL, 15-minute lockout 2. IVPCA group <ol style="list-style-type: none"> a. Intraoperative management <ol style="list-style-type: none"> i. General anaesthesia with isoflurane/oxygen/nitrous oxide ii. Morphine 0.1 mg/kg after intubation before incision b. Postoperative IVPCA <ol style="list-style-type: none"> i. Morphine 2 to 3 mg bolus in PACU until pain score < 50, then IVPCA with 1 mg bolus, 8-minute lockout

Steinberg 2002 (Continued)

Both groups: ketorolac 15 mg IM or IV every 6 hours for 3 days, then ibuprofen 400 mg every 6 hours until discharge or day 6

Outcomes	<ol style="list-style-type: none"> 1. Pain scores VAS (0 to 100 mm) at rest and with coughing and during ambulation. Measured twice daily 2. Duration of hospital stay (days) 3. Time to ambulation (hours) 4. Pruritus 5. Nausea 6. Vomiting 7. Hypotension requiring treatment
Notes	Supported by a grant from AstraZeneca R&D in Sweden. No declarations of conflict of interest

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information regarding the random sequence generation to permit judgement. Quote: "After providing their informed, written consent to participate in the study, patients were randomized to receive...". No further information provided regarding randomization method.
Allocation concealment (selection bias)	Unclear risk	The paper does not describe a method of concealment.
Blinding of participants and personnel (performance bias) All outcomes	High risk	This was an open trial.
Blinding of outcome assessment (detection bias) All outcomes	High risk	This was an open trial. No blinding of outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Missing outcome data are evenly balanced across the groups, however no reasons are provided for missing data.
Selective reporting (reporting bias)	Unclear risk	No study protocol available
Other bias	Low risk	No indication of other bias

Taqi 2007

Methods	Randomized controlled trial, parallel group
Participants	Participants N = 50, CEA = 25, IVPCA = 25, adults, age (mean $\pm$ SD): IVPCA: 61.24 ($\pm$ 14.91), CEA: 65 ($\pm$ 16.18), 27 males, 23 females, ASA 1 to 3, undergoing laparoscopic colorectal surgery under general anaesthesia. Italian study
Interventions	<p>2 groups:</p> <ol style="list-style-type: none"> 1. CEA group: thoracic epidural inserted preoperatively at T8/9 or T9/10 interspace. The epidural was used intraoperatively. Postoperatively the CEA was started with 0.1% bupivacaine and 3 μg/mL fen-

Taqi 2007 (Continued)

tanyl at a rate of 5 to 15 mL/h. This was continued for up to 3 postoperative days. The infusion was adjusted to keep a sensory block between T7 and L3.

2. IVPCA group: IVPCA started postoperatively. IVPCA programme: 1 to 2 mg bolus of morphine, 5-minute lockout, no background infusion. This was continued for up to 3 days postoperatively. The bolus was increased if VAS > 50 mm at rest.

Both groups received naproxen 500 mg twice a day and paracetamol 1 g 4 times per day for 4 days.

Outcomes	<ol style="list-style-type: none"> 1. Pain scores VAS (0 to 100 mm) measured daily, at rest, on coughing, and with ambulation 2. Epidural failures 3. Duration of hospital stay 4. Time to ambulation 5. Nausea 6. Vomiting
Notes	<p>Funding sources: McGill University Health Centre (MUHC) Foundation, University of Milan and the Societa' Italiana di Anestesia, Rianimazione e Terapia Intensiva (SIARTI) and the MUHC Research Institute.</p> <p>No reported declarations of interest</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No description of randomization method in text. Quote: "The patients were randomized into two groups: PCA (n = 25) and epidural (n = 25)"
Allocation concealment (selection bias)	Unclear risk	No description of allocation concealment in the paper
Blinding of participants and personnel (performance bias) All outcomes	High risk	This was an open trial, however it is difficult to judge how this would influence the outcome measures, as the participants were unaware of the study hypothesis. Quote: "Although the patients were not blinded, they were not aware of the study hypothesis"
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding of outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data
Selective reporting (reporting bias)	Unclear risk	No study protocol available
Other bias	Low risk	No indication of other bias

Tsui 1997

Methods	Randomized controlled trial, parallel group
Participants	N = 120, 9 participants excluded postrandomization, final N = 111, CEA = 57, IVPCA = 54, adults, age (mean +/- SD): IVPCA: 48 (+/-11), CEA: 51 (+/-16), all females, ASA 1 to 2, undergoing gynaecological open lower abdominal surgery through a vertical incision. Study from Hong Kong
Interventions	2 groups:

Epidural analgesia versus patient-controlled intravenous analgesia for pain following intra-abdominal surgery in adults (Review)

Tsui 1997 (Continued)

1. CEA group: lumbar epidural in L2/L3 or L3/L4 interspace. Epidural infusion of 0.0625% bupivacaine and 3.3 µg/mL fentanyl was started intraoperatively. In the recovery room the participants were administered 0.25% bupivacaine in 5 mL boluses every 15 minutes until VRS was equal to or less than 3. An infusion of 0.0625% bupivacaine and 3.3 µg/mL fentanyl was continued on the ward, and the rate adjusted as needed between 0 to 15 mL/h targeting a VRS of 3 or less.
2. IVPCA group: participants received boluses of IV morphine 1 mg every 5 minutes in the recovery room to achieve a VRS of 3 or less. An IVPCA morphine was then connected. IVPCA programme: 1 mg bolus, lockout 5 minutes, no background infusion, 1-hour maximum dose of 0.1 mg/kg

Both were continued for 48 hours.

Outcomes	<ol style="list-style-type: none"> 1. Pain scores (VRS) during rest and on coughing, measured every 4 hours from the end of surgery 2. Failure rate 3. Satisfaction score, on a 3-point scale: good, fair, and unsatisfactory 4. Pruritus 5. Nausea and vomiting 6. Respiratory depression (respiratory rate less than 10/min, measured hourly) 7. hypoxaemia (SaO₂ of less than 90% for longer than 1 minute, measured hourly) 8. Hypotension (systolic blood pressure of less than 30% of preoperative value, measured hourly)
Notes	<p>9 participants dropped out: 5 in the IVPCA group due to IV cannula failure, 2 in the CEA group due to epidural dislodgement during the study period, and 2 due to failure to receive a vertical incision, 1 in each group. Final numbers were: CEA group N = 57, IVPCA group N = 54.</p> <p>No funding sources declared. No conflicts of interest declared.</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No description of randomization method in text
Allocation concealment (selection bias)	Unclear risk	No description of allocation concealment in text
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding. Quote: "A limitation to our study was the lack of a double-blind design"
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding of outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	9 participants dropped out: 5 in the IVPCA group due to IV cannula failure, 2 in the CEA group due to epidural dislodgement during the study period, and 2 due to failure to receive a vertical incision, 1 in each group. Final numbers were: CEA group N = 57, IVPCA group N = 54. The reasons for missing data were unlikely to be related to the true outcome, however as there is 10% dropout in the IVPCA arm, we judged the study as at unclear risk for this domain.
Selective reporting (reporting bias)	Unclear risk	No study protocol available
Other bias	Low risk	No indication of other bias

Wang 2004

Methods	Randomized controlled trial, parallel group
Participants	30 participants undergoing hysterectomy were randomized to 3 groups: Group E (continuous epidural anaesthesia, n = 10), Group G +E (epidural anaesthesia combined with general anaesthesia, n = 10), and Group G (general anaesthesia, n = 10). Ages were from 31 to 57. ASA 1 to 3. Chinese study
Interventions	1. PCEA group: epidural anaesthesia at L1 to L2. Block aim for T6 to L3, followed by general anaesthesia 2. IVPCA group: general anaesthesia only
Outcomes	No outcomes included from this trial.
Notes	No funding sources declared. No conflicts of interest declared.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Stated that participants were randomly selected and randomly allocated, however no referral to method
Allocation concealment (selection bias)	Unclear risk	Method of concealment was not described in sufficient detail to permit judgement.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No description of attempts to blind participants or personnel
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No description of attempts to blind outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data
Selective reporting (reporting bias)	Unclear risk	No study protocol
Other bias	Low risk	No indication of other bias

Welchew 1991

Methods	Randomized controlled trial, stratified randomization by gender
Participants	Participants N = 20, PCEA = 10, IVPCA = 10, 10 males, 10 females, adults, age (mean +/- SD): PCEA: 47.9 (+/-14.99), IVPCA: 42.9 (+/-8.10), ASA 1 to 2, undergoing open upper abdominal surgery under general anaesthesia. UK study
Interventions	2 groups: 1. PCEA group: thoracic epidural inserted after induction at T7 to T8 interspace. The epidural was not used during the procedure, postoperatively the PCEA machine was connected to the participant and the participant received a loading dose of 10 mL of 10 µg/mL fentanyl through the epidural. The PCEA

Welchew 1991 (Continued)

was then started. PCEA programme: bolus 5 µg, lockout 2 minutes, 20 µg/h background. PCEA was continued for 24 hours.

2. IVPCA group: postoperatively the IVPCA machine was connected to the participant. The participant received a 10 mL loading dose of 10 µg/mL IV postoperatively. The IVPCA was started. IVPCA programme: bolus of 20 µg, lockout 2 minutes, 20 µg/h background infusion. IVPCA was continued for 24 hours.

Outcomes	1. Pain scores (VAS) at rest, measured every hour from the end of surgery for 24 hours 2. Nausea and vomiting (VAS), measured every hour from the end of surgery for 24 hours 3. Sedation score (VAS), measured every hour from the end of surgery for 24 hours
Notes	Loan of equipment from Janssen Pharmaceutical Limited. No funding sources declared. No conflicts of interest declared.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No description of randomization method in text. Quote: "Patients of each sex were randomly allocated to either the epidural or intravenous group after induction of anaesthesia, so that there would be an equal number of each sex in each group"
Allocation concealment (selection bias)	Unclear risk	Randomization occurred after selection of participants, however there is no description of the method used to conceal allocation.
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding of participants, who made continuous observations on an electronic linear visual analogue system
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "The observations were analysed blind in a standard manner in pairs to give the hourly pain, sedation and nausea scores, which had been corrected for periods of sleep"
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data
Selective reporting (reporting bias)	Unclear risk	No study protocol available
Other bias	Low risk	No indication of other bias

Yosunkaya 2003

Methods	Randomized controlled, parallel-group, single-centre trial
Participants	N = 40, PCEA = 20, IVPCA = 20, ASA 1 to 2, age (mean ± SD): IVPCA: 38 (±12.9), PCEA: 41.7 (±11.8), 17 males and 23 females scheduled for elective upper abdominal surgery under general anaesthesia. Turkish study
Interventions	2 groups:

Yosunkaya 2003 (Continued)

1. PCEA group
 - a. Intraoperatively
 - i. Epidural T6 to T8 - 1.5% lidocaine with 1:200,000 adrenaline, 8 to 11 mL
 - ii. Induction: propofol/fentanyl
 - iii. Maintenance: isoflurane/oxygen/nitrous oxide/fentanyl/tenoxicam
 - b. Postoperatively
 - i. PCEA: morphine 2 mg loading, then 0.2 mg/h background, 0.5 mg bolus with 30-minute lockout. 4-hour max 3 mg
2. IVPCA
 - a. Intraoperatively
 - i. Induction: propofol/fentanyl
 - ii. Maintenance: isoflurane/oxygen/nitrous oxide/fentanyl/tenoxicam
 - b. Postoperatively
 - i. IVPCA: morphine 2 mg loading, then 0.3 mg/h background, 1 mg bolus, 15-minute lockout

Outcomes	<ol style="list-style-type: none"> 1. Pruritus 2. Nausea and vomiting 3. Respiratory complications, respiratory rate < 10
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Notes	No reported funding sources and no declarations of conflicts of interest
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Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information about the sequence generation process to permit judgement. Quote: "A non-blinded randomized study was designed to compare intravenous and thoracic epidural with morphine". No further information regarding the randomization process is provided.
Allocation concealment (selection bias)	Unclear risk	The method of concealment is not described.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No description of attempts to blind participants or personnel
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No description of attempts to blind outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing data
Selective reporting (reporting bias)	Unclear risk	No study protocol available
Other bias	Low risk	No indication of other bias

Zeng 2003

Methods	Randomized controlled, single-centre, parallel-group study with 5 groups
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Zeng 2003 (Continued)

Participants	Participants N = 42, PCEA ropivacaine fentanyl (RF) group = 8, PCEA bupivacaine fentanyl (BF) group = 8, PCEA bupivacaine morphine (BM) group = 9, IVPCA morphine group - with intraoperative epidural = 9, IVPCA morphine-only group (no intraoperative epidural) = 8. Age 37 to 70, ASA 1 to 2, undergoing elective abdominal surgery under general anaesthesia. Gender not specified. Chinese study
Interventions	<p>5 groups, 3 PCEA and 2 IVPCA groups</p> <p>All participants received general anaesthetic with propofol, fentanyl, vecuronium, and isoflurane/nitrous oxide. All groups except the IVPCA morphine-only group received an epidural, which was started before the general anaesthetic.</p> <ol style="list-style-type: none"> 1. PCEA ropivacaine fentanyl (RF) group: postop PCEA with ropivacaine and fentanyl 1.2 g/L ropivacaine and 2 mg/L fentanyl. 4 mL/h background with 2 mL boluses and a 20-minute lockout 2. PCEA bupivacaine fentanyl (BF) group: postop PCEA with bupivacaine and fentanyl, 1.2 g/L bupivacaine and 2 mg/L fentanyl. 4 mL/h background with 2 mL boluses and a 20-minute lockout 3. PCEA bupivacaine morphine (BM) group: postop PCEA with bupivacaine and morphine, 1.2 g/L bupivacaine and 80 mg/L morphine. 4 mL/h background with 2 mL boluses and a 20-minute lockout 4. IVPCA morphine group - with intraoperative epidural. Epidural catheter was removed at the end of surgery. IVPCA started postop: morphine 0.5 g/L, 2 mL (1 mg) bolus, 6-minute lockout, 1 mL/h background infusion 5. IVPCA morphine-only group. No intraoperative epidural. IVPCA started postop: morphine 0.5 g/L, 2 mL (1 mg) bolus, 6-minute lockout, 1 mL/h background infusion
Outcomes	<ol style="list-style-type: none"> 1. Pain scores (VAS 0 to 100 mm) measured at 24 hours 2. Pruritus 3. Nausea 4. Respiratory depression (respiratory rate less than 10/min)
Notes	No reported funding sources and no declarations of conflicts of interest

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "They were allocated into five groups using a randomization table"
Allocation concealment (selection bias)	Unclear risk	The table used to randomize participants is not described in sufficient detail to permit judgement.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No description of blinding of participants and personnel
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No description of blinding of outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "42 patients ... were allocated into five groups using randomization table." No missing outcome data
Selective reporting (reporting bias)	Unclear risk	No study protocol available
Other bias	Low risk	No indication of other bias

Zutshi 2005

Methods	Randomized controlled trial, parallel group
Participants	Participants N = 59, PCEA = 31, IVPCA = 28, adults, age (median): IVPCA: 47.4, PCEA: 44.5, the gender distribution is not clear, ASA 1 to 4, undergoing open colectomy under general anaesthetic. US study
Interventions	<p>2 groups:</p> <ol style="list-style-type: none"> 1. PCEA group: thoracic epidural inserted at T8 to 9 or T9 to 10 interspace before surgery. Epidural was started before incision. Postoperatively the PCEA with bupivacaine and fentanyl (concentrations not stated) was started. PCEA programme: bolus of 2 to 4 mL, lockout 15 minutes, including background (background rate not stated) 2. IVPCA group: morphine (1 participant had fentanyl) IVPCA started postoperatively. No further description of IVPCA programme <p>Both groups had their analgesia changed to oral oxycodone after 48 hours.</p>
Outcomes	<ol style="list-style-type: none"> 1. VAS (0 to 100 mm), at rest and on coughing, in median and range at 1, 4, 8, 24, and 48 hours 2. DVT rate at 30 days 3. Epidural failure rate 4. Duration of hospital stay (days) 5. Hospital satisfaction score (as per SF-36), measured on discharge, on day 10 and day 30 6. Quality of life score (as per SF-36), measured on discharge, on day 10 and day 30
Notes	No funding sources declared. No conflicts of interest declared.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was performed using sealed envelopes"
Allocation concealment (selection bias)	Unclear risk	Method of concealment is not described in sufficient detail to permit judgement. Unclear if the sealed envelopes were sequentially numbered and opaque
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No description of blinding of investigators or participants in text
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No description of blinding of outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No missing data for analysis of all outcomes, except quality of life and satisfaction score (SF-36). The loss to follow-up at 30 days of SF-36 was 11 (35%) participants in the PCEA group and 14 (50%) participants in the IVPCA group. All endpoints were analysed using the intention-to-treat principle. Quote: "Protocol violations were noted, and analyses were performed by intention-to-treat principles"
Selective reporting (reporting bias)	Unclear risk	No study protocol available

Zutshi 2005 (Continued)

Other bias	Low risk	No indication of other bias
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Acronyms and abbreviations used

ASA: American Society of Anesthesiologists physical status classification system score; BMI: body mass index; CEA: continuous epidural analgesia; DVT: venous thromboembolism; GA: general anaesthesia; IM: intramuscular; IQ: interquartile; IV: intravenous; IVPCA: intravenous patient-controlled analgesia; N: number of participants; NRS: numerical rating scale; PACU: postanesthesia care unit; PCA: patient-controlled analgesia; PCEA: patient-controlled epidural analgesia; SD: standard deviation; SF-36: 36-item Short Form Health Survey; TPN: total parenteral nutrition; VAS: visual analogue scale; VRS: verbal rating scale; LA: Local anaesthetic infiltration;

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Aono 1998	Study of intraoperative stress hormone levels, no continuation of study into the postoperative period. Analgesic regimen unclear
Aygun 2004	29 of 80 participants in the study did not have an intra-abdominal procedure.
Basse 2002	Epidural in both trial arms
Beilin 2003	Contacted author. Pseudorandomized trial: 1st patient went to group A, 2nd patient to group B, 3rd patient to group C, etc.
Bowdle 1997	Not randomized. Epidural analgesia was based on patient preference.
Brandt 1976	Study of intraoperative plasma hormone levels, no continuation of study into postoperative period. Analgesic regimen unclear
Brodner 2001	Opioid not delivered by IVPCA
Buckley 1982	IM diamorphine boluses in control group; no IVPCA
Buggy 2002	3 participants in epidural group had a retroperitoneal procedure.
Cade 1993	Morphine bolus injection instead of CEA
Ceriati 2003	The epidural morphine was given by bolus only, not by PCEA or CEA.
Dill-Russell 2001	Not a randomized controlled trial
Dyer 1992	IV and IM morphine boluses postop; no IVPCA
El Sayed Moawad 2014	Includes pancreatic resection, which is retroperitoneal
Engquist 1980	Article not a randomized controlled trial
Estok 1987	Lower extremity surgical procedures included.
Fayed 2014	IV pethidine was given to nearly all participants in both arms for breakthrough pain.
Feo 2009	No IVPCA for morphine
Frings 1982	IM opioids in control group; no IVPCA
Geller 1993	10 of 45 participants in the study had a retroperitoneal procedure (nephrectomy).

Study	Reason for exclusion
Gelman 1980	Analgesia given as boluses in both EA and control group; no CEA or IVPCA.
George 1994	3 of 21 participants had a retroperitoneal procedure (all 3 in IVPCA group).
Gherghina 2012	This article was retracted from publication.
Glass 1992	Further information requested from author, but no reply to request via email. Article includes lower limb surgery.
Gottschalk 1998	Epidural analgesia in both arms of the study
Han 2007	Group A did not receive an IVPCA.
Harrison 1988	Morphine boluses in epidural group; no CEA/PCEA
Harukuni 1995	No IVPCA. The choice of postoperative analgesia was based on the individual clinician's decision and included either pentazocine, 30 mg IM, or morphine, 2 mg epidurally.
Haythornthwaite 1998	Epidural in all arms of the study postoperatively
Hendolin 1986	Nurse administered IM or IV oxycodone boluses as required in the control group; no IVPCA.
Hendolin 1987	Same participants as Hendolin 1986 . Nurse administered IM or IV oxycodone boluses as required in the control group; no IVPCA.
Hjortso 1984	The morphine group did not receive PCA, and the epidural group did not receive PCEA or CEA.
Hjortso 1985	The systemic morphine group received morphine via intramuscular injection route.
Hord 1988	Article not a randomized controlled trial
Hosoda 1993	Postoperative analgesia not administered as IVPCA, CEA, or PCEA. Retroperitoneal procedures included in the study.
Kilbride 1992	The epidural group received morphine via bolus and then bolus only postop, not via PCEA or CEA.
King 2006	Epidural in both arms of the study postoperatively
Kouraklis 2000	Nurse administered IV or IM opioid boluses; no IVPCA.
Lattermann 2003	Study only extended 2 hours into postoperative period. Continuous IV morphine infusion in the control group; no IVPCA
Levy 2011	Use of oral tramadol was part of the study protocol for regular analgesia when diclofenac was contraindicated, which is an exclusion criterion of this review.
Li 2008	Pethidine 50 mg IM 4 to 8 hourly in control group; no IVPCA
Licker 1994	Opioid infusion in control group; no IVPCA
Lomessy 1984	Opioid intermittent boluses, no IVPCA, included thoracic surgical procedures
Loper 1989	Morphine intermittent injection, no CEA. Article was not a randomized controlled trial
Mellbring 1982	Opioid boluses in EA group; no PCEA or CEA

Study	Reason for exclusion
Menigaux 2001	5 of 20 participants had a retroperitoneal procedure (nephrectomy).
Neudecker 1999	All arms of the study received analgesia by IVPCA.
Noreng 1987	No discussion of mode of postoperative analgesia in the control group. Only data on hormone levels postop, hence no data of interest to this review
Page 2008	Not a randomized controlled trial
Paulsen 2001	Included patients who had a retroperitoneal procedure (nephrectomy), and these could not be separately identified
Rapp-Zingraff 1997	Morphine intermittent injection, no CEA
Rigg 2002	The study did not specify the type of IV morphine delivery device during the trial, included both IV infusion and IVPCA (from email correspondence with the author).
Rockermann 1996	In this study Group 1 and 2 received EA + PCA, and Group 3 received PCA only, hence this study did not compare EA to PCA.
Seeling 1991	Includes infra renal aortic aneurysm repairs
Senagore 2003	All arms of the study received opioids by a different route for breakthrough pain if required.
Shapiro 2003	Not a randomized controlled trial
Smith 1991	Morphine intermittent injection, no CEA
Stehr-Zirngibl 1997	The study included thoracic surgery.
Stevens 1998	Epidural group given morphine boluses - did not receive PCEA or CEA.
Stoddart 1993	Diamorphine intermittent injection, no CEA
Susa 2004	The control group received an opioid infusion for the first 24 hours postoperatively, before being changed to an IVPCA. In addition, the 2 groups were very different: the epidural group had a smaller incision, and was part of a fast-track surgical programme, while the control group had a normal incision and was treated with standard care.
Suttner 2005	This article was retracted from publication.
Tilleul 2012	Not a randomized controlled trial
Voloshin 2011	This was not a randomized controlled trial, and there was no IVPCA.
Wheatley 1990	EA group received nurse/clinician-administered opioid boluses; no PCEA or CEA.
Wiedemann 1991	Study compares subcutaneous piritramide versus thoracic epidural.
Xue 2000	No reply to request for information to quantify numbers of participants having thoracic surgery and abdominal surgery
Yardeni 2007	Contacted author. Pseudorandomized trial: 1st patient went to group A, 2nd patient to group B, 3rd patient to group C, etc.

Study	Reason for exclusion
Yeager 1987	Included intrathoracic surgical procedures
Zgaia 2017	No IVPCA; IV group received a morphine infusion
Zhao 2015	No discussion of the type of postoperative analgesia in the control group. Only data on hormone levels postop, hence no data of interest to this review
Zingg 2009	IVPCA was only given to a minority in the control group.

Acronyms and abbreviations used

CEA: continuous epidural analgesia; EA: epidural analgesia; IM: intramuscular; IV: intravenous; IVPCA: intravenous patient-controlled analgesia; PCA: patient-controlled analgesia; PCEA: patient-controlled epidural analgesia

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

[Ahn 2015](#)

Methods	Randomized controlled trial
Participants	N = 97, PCEA = 46, conventional group = 51, participants with gastric cancer undergoing laparoscopic gastric surgery between October 2012 and August 2014. South Korean study
Interventions	PCEA group: PCEA Conventional group: unknown
Outcomes	1. Pain score visual analogue scale 2. Hospital stay 3. Ambulation 4. Quality of life
Notes	Only published at a conference, unable to obtain a formal publication. There is uncertainty regarding the mode of analgesia in the conventional group.

[Aloia 2017](#)

Methods	Not yet assessed
Participants	
Interventions	
Outcomes	
Notes	

[Chen 2015b](#)

Methods	Not yet assessed
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Chen 2015b *(Continued)*

Participants

Interventions

Outcomes

Notes

Cho 2017

Methods

Not yet assessed

Participants

Interventions

Outcomes

Notes

Golubovic 2012

Methods

Awaiting further information

Participants

Interventions

Outcomes

Notes

Mohamad 2017

Methods

Not yet assessed

Participants

Interventions

Outcomes

Notes

Siekman 2017

Methods

Not yet assessed

Siekman 2017 *(Continued)*

Participants

Interventions

Outcomes

Notes

Wang 2015

Methods	Not yet assessed
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Participants

Interventions

Outcomes

Notes

Zhang 2015

Methods	Not yet assessed
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Participants

Interventions

Outcomes

Notes

Zheng 2016

Methods	Not yet assessed
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Participants

Interventions

Outcomes

Notes

Acronyms and abbreviations used

N: number of participants; PCEA: patient-controlled epidural analgesia

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

Klotz 2016

Trial name or title	Intravenous versus epidural analgesia to reduce the incidence of gastrointestinal complications after elective pancreatoduodenectomy (the PAKMAN trial, DRKS 00007784)
Methods	An adaptive, pragmatic, randomized, controlled, multicentre, open-label, superiority trial with 2 parallel study groups
Participants	370 adult patients, male and female, scheduled for elective pancreatoduodenectomy will be randomized after giving written informed consent; 278 patients are needed for analysis.
Interventions	Group A intervention includes intraoperative general anaesthesia and postoperative intravenous patient-controlled analgesia. Group B intervention comprises combined intraoperative general anaesthesia and epidural analgesia with postoperative epidural analgesia.
Outcomes	Primary outcomes 1. Delayed gastric emptying 2. Pancreatic fistula 3. Biliary leak 4. Gastrointestinal bleeding 5. Postoperative ileus Secondary outcomes 1. Pneumonia 2. Mortality 3. Hospital stay 4. Fluid therapy 5. Vasopressor therapy 6. Weight change 7. Reoperation 8. Postoperative pain
Starting date	23 March 2015
Contact information	
Notes	

DATA AND ANALYSES

Comparison 1. Epidural analgesia versus intravenous patient-controlled analgesia

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain score early phase - at rest	7	384	Mean Difference (IV, Random, 95% CI)	-5.70 [-9.48, -1.92]
1.1 PCEA	5	336	Mean Difference (IV, Random, 95% CI)	-6.59 [-11.21, -1.97]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.2 CEA	2	48	Mean Difference (IV, Random, 95% CI)	-2.46 [-12.17, 7.25]
2 Pain score mid-phase - at rest	11	558	Mean Difference (IV, Random, 95% CI)	-9.02 [-13.41, -4.63]
2.1 PCEA	7	431	Mean Difference (IV, Random, 95% CI)	-7.07 [-12.34, -1.80]
2.2 CEA	4	127	Mean Difference (IV, Random, 95% CI)	-15.42 [-22.85, -6.00]
3 Pain score late phase - at rest	7	393	Mean Difference (IV, Random, 95% CI)	-5.14 [-9.38, -0.90]
3.1 PCEA	4	296	Mean Difference (IV, Random, 95% CI)	-4.66 [-9.76, 0.44]
3.2 CEA	3	97	Mean Difference (IV, Random, 95% CI)	-6.21 [-13.84, 1.42]
4 Mortality rate at 30 days	9	560	Risk Ratio (M-H, Random, 95% CI)	3.37 [0.72, 15.88]
4.1 PCEA	4	254	Risk Ratio (M-H, Random, 95% CI)	3.99 [0.46, 34.49]
4.2 CEA	5	306	Risk Ratio (M-H, Random, 95% CI)	2.82 [0.30, 26.14]
5 Best-case scenario for EA - mortality	9	609	Risk Ratio (M-H, Random, 95% CI)	0.27 [0.11, 0.69]
5.1 PCEA	4	280	Risk Ratio (M-H, Random, 95% CI)	0.25 [0.06, 1.00]
5.2 CEA	5	329	Risk Ratio (M-H, Random, 95% CI)	0.30 [0.08, 1.16]
6 Worst-case scenario for EA - mortality	9	609	Risk Ratio (M-H, Random, 95% CI)	9.05 [2.76, 29.64]
6.1 CEA	5	329	Risk Ratio (M-H, Random, 95% CI)	6.95 [1.59, 30.33]
6.2 PCEA	4	280	Risk Ratio (M-H, Random, 95% CI)	14.72 [1.99, 108.81]
7 Pain score early phase - on coughing	2	80	Mean Difference (IV, Random, 95% CI)	-16.44 [-45.83, 12.95]
7.1 PCEA	2	80	Mean Difference (IV, Random, 95% CI)	-16.44 [-45.83, 12.95]
8 Pain score mid-phase - on coughing	5		Mean Difference (IV, Random, 95% CI)	Subtotals only
8.1 PCEA	3	133	Mean Difference (IV, Random, 95% CI)	-11.30 [-16.72, -5.88]
8.2 CEA	2	79	Mean Difference (IV, Random, 95% CI)	-32.21 [-44.06, -20.35]
9 Pain score late phase - on coughing	4		Mean Difference (IV, Random, 95% CI)	Subtotals only
9.1 PCEA	2	80	Mean Difference (IV, Random, 95% CI)	-2.67 [-11.50, 6.16]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9.2 CEA	2	79	Mean Difference (IV, Random, 95% CI)	-20.97 [-33.03, -8.92]
10 Failure of analgesic technique	10	678	Risk Ratio (M-H, Random, 95% CI)	2.48 [1.13, 5.45]
10.1 PCEA	3	268	Risk Ratio (M-H, Random, 95% CI)	2.71 [1.06, 6.89]
10.2 CEA	7	410	Risk Ratio (M-H, Random, 95% CI)	2.64 [0.69, 10.12]
11 Best-case scenario analysis - failure of analgesic technique	10	709	Risk Ratio (M-H, Random, 95% CI)	1.28 [0.65, 2.53]
11.1 PCEA	3	285	Risk Ratio (M-H, Random, 95% CI)	1.55 [0.72, 3.33]
11.2 CEA	7	424	Risk Ratio (M-H, Random, 95% CI)	1.23 [0.41, 3.70]
12 Worst-case scenario analysis - failure of analgesic technique	10	709	Risk Ratio (M-H, Random, 95% CI)	3.39 [1.54, 7.47]
12.1 PCEA	3	285	Risk Ratio (M-H, Random, 95% CI)	4.25 [1.76, 10.28]
12.2 CEA	7	424	Risk Ratio (M-H, Random, 95% CI)	3.32 [0.86, 12.88]
13 Length of hospital stay	3	186	Mean Difference (IV, Random, 95% CI)	-0.34 [-0.64, -0.05]
13.1 PCEA	2	147	Mean Difference (IV, Random, 95% CI)	-0.32 [-0.62, -0.03]
13.2 CEA	1	39	Mean Difference (IV, Random, 95% CI)	-1.0 [-2.79, 0.79]
14 Venous thromboembolism rate	2	101	Risk Ratio (M-H, Random, 95% CI)	0.32 [0.03, 2.95]
14.1 PCEA	1	59	Risk Ratio (M-H, Random, 95% CI)	0.30 [0.01, 7.13]
14.2 CEA	1	42	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.01, 7.74]
15 Pruritus	8	492	Risk Ratio (M-H, Random, 95% CI)	2.36 [1.67, 3.35]
15.1 PCEA	4	244	Risk Ratio (M-H, Random, 95% CI)	2.28 [1.54, 3.38]
15.2 CEA	4	248	Risk Ratio (M-H, Random, 95% CI)	2.69 [1.26, 5.77]
16 Best-case scenario for EA - pruritus	8	519	Risk Ratio (M-H, Random, 95% CI)	1.67 [1.23, 2.27]
16.1 PCEA	4	261	Risk Ratio (M-H, Random, 95% CI)	1.74 [1.04, 2.90]
16.2 CEA	4	258	Risk Ratio (M-H, Random, 95% CI)	1.58 [0.88, 2.85]
17 Worst-case scenario for EA - pruritus	8	519	Risk Ratio (M-H, Random, 95% CI)	2.68 [1.91, 3.76]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
17.1 PCEA	4	261	Risk Ratio (M-H, Random, 95% CI)	2.56 [1.75, 3.74]
17.2 CEA	4	258	Risk Ratio (M-H, Random, 95% CI)	3.00 [1.24, 7.24]
18 Nausea and vomiting rate	10	618	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.69, 1.27]
18.1 PCEA	4	244	Risk Ratio (M-H, Random, 95% CI)	1.23 [0.73, 2.08]
18.2 CEA	6	374	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.56, 1.21]
19 Best-case scenario for EA - nausea and vomiting	10	645	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.65, 1.11]
19.1 PCEA	4	263	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.59, 1.51]
19.2 CEA	6	382	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.56, 1.15]
20 Worst-case scenario for EA - nausea and vomiting	10	645	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.75, 1.57]
20.1 PCEA	4	263	Risk Ratio (M-H, Random, 95% CI)	1.77 [0.87, 3.61]
20.2 CEA	6	382	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.56, 1.28]
21 Sedation	4	223	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.40, 1.87]
21.1 PCEA	2	136	Risk Ratio (M-H, Random, 95% CI)	0.38 [0.08, 1.85]
21.2 CEA	2	87	Risk Ratio (M-H, Random, 95% CI)	1.32 [0.28, 6.14]
22 Best-case scenario for EA - sedation	4	237	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.33, 1.83]
22.1 PCEA	2	147	Risk Ratio (M-H, Random, 95% CI)	0.28 [0.06, 1.33]
22.2 CEA	2	90	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.58, 1.60]
23 Worst-case scenario for EA - sedation	4	237	Risk Ratio (M-H, Random, 95% CI)	1.66 [0.62, 4.46]
23.1 PCEA	2	147	Risk Ratio (M-H, Random, 95% CI)	1.80 [0.69, 4.74]
23.2 CEA	2	90	Risk Ratio (M-H, Random, 95% CI)	2.15 [0.15, 31.39]
24 Respiratory complications - hypoxaemia	5	328	Risk Ratio (M-H, Random, 95% CI)	1.29 [0.71, 2.37]
24.1 PCEA	1	64	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.07, 16.29]
24.2 CEA	4	264	Risk Ratio (M-H, Random, 95% CI)	1.50 [0.50, 4.50]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
25 Hypotension - requiring treatment	6	479	Risk Ratio (M-H, Random, 95% CI)	7.13 [2.87, 17.75]
25.1 PCEA	3	245	Risk Ratio (M-H, Random, 95% CI)	8.44 [2.64, 26.97]
25.2 CEA	3	234	Risk Ratio (M-H, Random, 95% CI)	5.45 [1.25, 23.71]

Analysis 1.1. Comparison 1 Epidural analgesia versus intravenous patient-controlled analgesia, Outcome 1 Pain score early phase - at rest.

Analysis 1.2. Comparison 1 Epidural analgesia versus intravenous patient-controlled analgesia, Outcome 2 Pain score mid-phase - at rest.

Analysis 1.3. Comparison 1 Epidural analgesia versus intravenous patient-controlled analgesia, Outcome 3 Pain score late phase - at rest.

Analysis 1.4. Comparison 1 Epidural analgesia versus intravenous patient-controlled analgesia, Outcome 4 Mortality rate at 30 days.

Analysis 1.5. Comparison 1 Epidural analgesia versus intravenous patient-controlled analgesia, Outcome 5 Best-case scenario for EA - mortality.

Analysis 1.6. Comparison 1 Epidural analgesia versus intravenous patient-controlled analgesia, Outcome 6 Worst-case scenario for EA - mortality.

Analysis 1.7. Comparison 1 Epidural analgesia versus intravenous patient-controlled analgesia, Outcome 7 Pain score early phase - on coughing.

Analysis 1.8. Comparison 1 Epidural analgesia versus intravenous patient-controlled analgesia, Outcome 8 Pain score mid-phase - on coughing.

Analysis 1.9. Comparison 1 Epidural analgesia versus intravenous patient-controlled analgesia, Outcome 9 Pain score late phase - on coughing.

Analysis 1.10. Comparison 1 Epidural analgesia versus intravenous patient-controlled analgesia, Outcome 10 Failure of analgesic technique.

Analysis 1.11. Comparison 1 Epidural analgesia versus intravenous patient-controlled analgesia, Outcome 11 Best-case scenario analysis - failure of analgesic technique.

Analysis 1.12. Comparison 1 Epidural analgesia versus intravenous patient-controlled analgesia, Outcome 12 Worst-case scenario analysis - failure of analgesic technique.

Analysis 1.13. Comparison 1 Epidural analgesia versus intravenous patient-controlled analgesia, Outcome 13 Length of hospital stay.

Analysis 1.14. Comparison 1 Epidural analgesia versus intravenous patient-controlled analgesia, Outcome 14 Venous thromboembolism rate.

Analysis 1.15. Comparison 1 Epidural analgesia versus intravenous patient-controlled analgesia, Outcome 15 Pruritus.

Analysis 1.16. Comparison 1 Epidural analgesia versus intravenous patient-controlled analgesia, Outcome 16 Best-case scenario for EA - pruritus.

Analysis 1.17. Comparison 1 Epidural analgesia versus intravenous patient-controlled analgesia, Outcome 17 Worst-case scenario for EA - pruritus.

Analysis 1.18. Comparison 1 Epidural analgesia versus intravenous patient-controlled analgesia, Outcome 18 Nausea and vomiting rate.

Analysis 1.19. Comparison 1 Epidural analgesia versus intravenous patient-controlled analgesia, Outcome 19 Best-case scenario for EA - nausea and vomiting.

Analysis 1.20. Comparison 1 Epidural analgesia versus intravenous patient-controlled analgesia, Outcome 20 Worst-case scenario for EA - nausea and vomiting.

Analysis 1.21. Comparison 1 Epidural analgesia versus intravenous patient-controlled analgesia, Outcome 21 Sedation.

Analysis 1.22. Comparison 1 Epidural analgesia versus intravenous patient-controlled analgesia, Outcome 22 Best-case scenario for EA - sedation.

Analysis 1.23. Comparison 1 Epidural analgesia versus intravenous patient-controlled analgesia, Outcome 23 Worst-case scenario for EA - sedation.

Study or subgroup	EA n/N	IVPCA n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Test for overall effect: $Z=1(P=0.32)$					
Test for subgroup differences: $\text{Chi}^2=0.01, \text{df}=1 (P=0.9), I^2=0\%$					
Favours EA 0.01 0.1 1 10 100 Favours IVPCA					

Analysis 1.24. Comparison 1 Epidural analgesia versus intravenous patient-controlled analgesia, Outcome 24 Respiratory complications - hypoxaemia.

Study or subgroup	EA n/N	IVPCA n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.24.1 PCEA					
Mann 2000	1/31	1/33		4.94%	1.06[0.07,16.29]
Subtotal (95% CI)	31	33		4.94%	1.06[0.07,16.29]
Total events: 1 (EA), 1 (IVPCA)					
Heterogeneity: Not applicable					
Test for overall effect: $Z=0.04(P=0.96)$					
1.24.2 CEA					
Aceto 2002	0/20	0/19			Not estimable
Jayr 1998	13/38	13/46		90.38%	1.21[0.64,2.29]
Madej 1992	5/20	0/10		4.68%	5.76[0.35,94.91]
Tsui 1997	0/57	0/54			Not estimable
Subtotal (95% CI)	135	129		95.06%	1.5[0.5,4.5]
Total events: 18 (EA), 13 (IVPCA)					
Heterogeneity: $\text{Tau}^2=0.26; \text{Chi}^2=1.24, \text{df}=1(P=0.27); I^2=19.43\%$					
Test for overall effect: $Z=0.72(P=0.47)$					
Total (95% CI)	166	162		100%	1.29[0.71,2.37]
Total events: 19 (EA), 14 (IVPCA)					
Heterogeneity: $\text{Tau}^2=0; \text{Chi}^2=1.25, \text{df}=2(P=0.54); I^2=0\%$					
Test for overall effect: $Z=0.83(P=0.4)$					
Test for subgroup differences: $\text{Chi}^2=0.05, \text{df}=1 (P=0.82), I^2=0\%$					
EA 0.01 0.1 1 10 100 IVPCA					

Analysis 1.25. Comparison 1 Epidural analgesia versus intravenous patient-controlled analgesia, Outcome 25 Hypotension - requiring treatment.

Study or subgroup	EA n/N	IVPCA n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.25.1 PCEA					
Hübner 2015	19/65	2/57		41.63%	8.33[2.03,34.22]
Mann 2000	5/31	0/33		10.2%	11.69[0.67,202.97]
Zutshi 2005	3/31	0/28		9.75%	6.34[0.34,117.65]
Subtotal (95% CI)	127	118		61.58%	8.44[2.64,26.97]
Total events: 27 (EA), 2 (IVPCA)					
Heterogeneity: $\text{Tau}^2=0; \text{Chi}^2=0.09, \text{df}=2(P=0.96); I^2=0\%$					
Test for overall effect: $Z=3.6(P=0)$					
EA 0.01 0.1 1 10 100 IVPCA

ADDITIONAL TABLES

Table 1. Summary of results for trials reporting median VAS scores at rest in the early phase after operation (0 to 6 hours)

Trial	PCEA/CEA participants	PCEA group (median VAS and range)	CEA group (median VAS and range)	IVPCA participants	IVPCA group (median VAS and range)	Favours
Barratt 2002	25	N/A	0 (0 to 100)	22	63 (0 to 100)	CEA
Chen 2001	17	35 (0 to 70)	N/A	20	41 (0 to 70)	Neither
Heurich 2007	10	N/A	8 (6 to 11 IQR)	9	14 (12 to 17 IQR)	CEA
Jayr 1998	38	N/A	8 (0 to 20 IQR)	46	26 (10 to 43 IQR)	CEA
Motamed 1998	28	N/A	20 (1 to 39)	29	34 (11 to 64)	CEA
Ngan 1997	20 fentanyl 20 pethidine	17 (10 to 40) fentanyl 10 (0 to 23) pethidine	N/A	18 fentanyl 18 pethidine	23 (5 to 40) fentanyl 28 (17 to 43) pethidine	PCEA
Paech 1994	24	7 (0 to 20)	N/A	21	22 (15 to 45)	PCEA
Schumann 2003	27	N/A	0 (0 to 70)	29	60 (0 to 100)	CEA
Steinberg 2002	20	0 (0 to 15)	N/A	21	50 (40 to 70)	PCEA
Tsui 1997	57	N/A	25 (15 to 35 IQR)	54	50 (40 to 60 IQR)	CEA

Acronyms and abbreviations used in this table

CEA: continuous epidural analgesia

IQR: interquartile range

IVPCA: intravenous patient-controlled analgesia

N/A: not applicable in this trial

PCEA: patient-controlled epidural analgesia

VAS: visual analogue scale (0 = no pain; 100 = worst pain imaginable)

Table 2. Summary of results for trials reporting median VAS scores at rest in the mid-phase after operation (> 6 to 24 hours)

Trial	PCEA/CEA participants	PCEA group (median VAS and range)	CEA group (median VAS and range)	IVPCA participants	IVPCA group (median VAS and range)	Favours
Barratt 2002	25	N/A	10 (0 to 100)	22	50 (0 to 80)	CEA
Chen 2001	17	32 (0 to 50)	N/A	20	24 (0 to 79)	Neither
Heurich 2007	10	N/A	9 (8 to 11 IQR)	9	8 (6 to 9 IQR)	IVPCA
Jayr 1998	38	N/A	14 (4 to 27.5 IQR)	46	17.5 (7 to 36 IQR)	CEA
Motamed 1998	28	N/A	15 (1 to 31)	29	38 (11 to 53)	CEA
Ngan 1997	20 fentanyl 20 pethidine	10 (5 to 27) fentanyl 10 (0 to 20) pethidine	N/A	17 fentanyl 18 pethidine	23 (10 to 45) fentanyl 20 (10 to 44) pethidine	PCEA
Paech 1994	24	5 (0 to 20 IQR)	N/A	21	18 (8 to 36 IQR)	PCEA
Schumann 2003	25	N/A	10 (0 to 40)	24	30 (0 to 60)	CEA
Steinberg 2002	20	2 (0 to 13)	N/A	21	32 (15 to 54)	PCEA
Taqi 2007	25	N/A	10 (8 to 20.9)	25	40 (27.4 to 50.2)	CEA
Tsui 1997	57	N/A	15 (0 to 30 IQR)	54	20 (0 to 40 IQR)	CEA
Zutshi 2005	31	25.4 (0 to 40)	N/A	28	31.3 (0 to 50)	PCEA

Acronyms and abbreviations used in this table

CEA: continuous epidural analgesia

IQR: interquartile range

IVPCA: intravenous patient-controlled analgesia

N/A: not applicable in this trial

PCEA: patient-controlled epidural analgesia

VAS: visual analogue scale (0 = no pain; 100 = worst pain imaginable)

Table 3. Summary of results for trials reporting median VAS on movement in the mid-phase after operation (> 6 to 24 hours)

Trial	PCEA/CEA participants	PCEA group (median VAS and range)	CEA group (median VAS and range)	IVPCA participants	IVPCA group (median VAS and range)	Favours
Carli 2001	21	N/A	10 (95% CI 5 to 33)	21	40 (95% CI 29 to 79)	CEA
Steinberg 2002	20	8 (0 to 20 IQR)	N/A	21	48 (31 to 60 IQR)	PCEA
Taqi 2007	25	N/A	20 (95% CI 13.7 to 33.7)	25	50 (95% CI 42.2 to 67.4)	CEA

Acronyms and abbreviations used in this table

CEA: continuous epidural analgesia

CI: confidence interval

IQR: interquartile range

IVPCA: intravenous patient-controlled analgesia

N/A: not applicable in this trial

PCEA: patient-controlled epidural analgesia

VAS: visual analogue scale (0 = no pain; 100 = worst pain imaginable)

Table 4. Summary of results for trials reporting median VAS scores at rest in the late phase (> 24 hours) after operation

Trial	PCEA/CEA participants	PCEA group (median VAS and range)	CEA group (median VAS and range)	IVPCA participants	IVPCA group (median VAS and range)	Favours
Barratt 2002	25	N/A	30 (5 to 80)	22	60 (0 to 100)	CEA
Chen 2001	17	24 (0 to 40)	N/A	20	22 (0 to 50)	Neither
Heurich 2007	10	N/A	30 (20 to 40) (IQR)	9	17 (15 to 19) (IQR)	CEA
Motamed 1998	28	N/A	15 (3 to 37)	29	34 (11 to 54)	CEA
Schumann 2003	15	N/A	35 (20 to 50)	15	30 (0 to 70)	Neither
Steinberg 2002	20	5 (0 to 10) (IQR)	N/A	21	11 (4 to 28) (IQR)	PCEA
Taqi 2007	25	N/A	10 (95% CI 11.8 to 30.4)	25	30 (95% CI 16.7 to 36.9)	CEA
Tsui 1997	57	N/A	10 (0 to 20) (IQR)	54	10 (0 to 30) (IQR)	Neither
Zutshi 2005	31	24.6 (0 to 50) (IQR)	N/A	28	33.3 (20 to 50) (IQR)	PCEA

Acronyms and abbreviations used in this table

CEA: continuous epidural analgesia

CI: confidence interval

IQR: interquartile range

IVPCA: intravenous patient-controlled analgesia

N/A: not applicable in this trial

PCEA: patient-controlled epidural analgesia

VAS: visual analogue scale (0 = no pain; 100 = worst pain imaginable)

Table 5. Summary of results for trial reporting median VAS scores in the late phase after operation (> 24 hours)

Trial	PCEA/CEA participants	PCEA group (median VAS and range)	CEA group (median VAS and range)	IVPCA participants	IVPCA group (median VAS and range)	Favours
Carli 2001	21	N/A	7 (95% CI 6 to 31)	21	20 (95% CI 16 to 68)	CEA
Steinberg 2002	20	10 (4 to 20) (IQR)	N/A	21	26 (9 to 44) (IQR)	PCEA
Taqi 2007	25	N/A	30 (95% CI 20.5 to 41)	25	40 (95% CI 29.53 to 49.7)	CEA

Acronyms and abbreviations used in this table

CEA: continuous epidural analgesia

CI: confidence interval

IQR: interquartile range

IVPCA: intravenous patient-controlled analgesia

N/A: not applicable in this trial

PCEA: patient-controlled epidural analgesia

VAS: visual analogue scale (0 = no pain; 100 = worst pain imaginable)

Table 6. Summary of results for trials reporting median VAS scores in the early phase with coughing after operation (0 to 6 hours)

Trial	PCEA/CEA participants	PCEA group (median VAS and range)	CEA group (median VAS and range)	IVPCA participants	IVPCA group (median VAS and range)	Favours
Barratt 2002	25	N/A	20 (0 to 100)	22	80 (40 to 100)	CEA
Chen 2001	17	51 (15 to 80)	N/A	20	66 (25 to 100)	PCEA
Heurich 2007	10	N/A	28 (25 to 32) (IQR)	9	35 (31 to 39) (IQR)	CEA
Jayr 1998	38	N/A	27 (0 to 46) (IQR)	46	49 (30 to 74) (IQR)	CEA
Motamed 1998	28	N/A	29 (13 to 48)	29	53 (31 to 75)	CEA
Paech 1994	24	23 (9 to 46) (IQR)	N/A	21	52 (33 to 69) (IQR)	PCEA
Steinberg 2002	20	0 (0 to 30) (IQR)	N/A	21	59 (49 to 87) (IQR)	PCEA
Tsui 1997	57	N/A	40 (30 to 50) (IQR)	54	60 (50 to 70) (IQR)	CEA

Acronyms and abbreviations used in this table

CEA: continuous epidural analgesia

IQR: interquartile range

IVPCA: intravenous patient-controlled analgesia

N/A: not applicable in this trial

PCEA: patient-controlled epidural analgesia

VAS: visual analogue scale (0 = no pain; 100 = worst pain imaginable)

Table 7. Summary of results for trials reporting median VAS scores in the mid-phase with coughing after operation (> 6 to 24 hours)

Trial	PCEA/CEA participants	PCEA group (median VAS and range)	CEA group (median VAS and range)	IVPCA participants	IVPCA group (median VAS and range)	Favours
Barratt 2002	25	N/A	25 (5 to 100)	22	65 (40 to 100)	CEA
Chen 2001	17	50 (22 to 70)	N/A	20	63 (22 to 90)	PCEA
Heurich 2007	10	N/A	28 (25 to 32) (IQR)	9	36 (33 to 39) (IQR)	CEA
Jayr 1998	38	N/A	36 (19 to 66) (IQR)	46	50 (27 to 66) (IQR)	CEA
Motamed 1998	28	N/A	32 (14 to 79)	29	52 (31 to 72)	CEA
Paech 1994	24	25 (16 to 40) (IQR)	N/A	21	49 (38 to 67) (IQR)	PCEA
Steinberg 2002	20	12 (4 to 35) (IQR)	N/A	21	60 (32 to 78) (IQR)	PCEA
Taqi 2007	25	N/A	30 (95% CI 23.3 to 42.3)	25	70 (95% CI 51.8 to 74.6)	CEA
Tsui 1997	57	N/A	35 (15 to 55) (IQR)	54	40 (20 to 60) (IQR)	CEA

Acronyms and abbreviations used in this table

CEA: continuous epidural analgesia

CI: confidence interval

IQR: interquartile range

IVPCA: intravenous patient-controlled analgesia

N/A: not applicable in this trial

PCEA: patient-controlled epidural analgesia

VAS: visual analogue scale (0 = no pain; 100 = worst pain imaginable)

Table 8. Summary of results for trials reporting median VAS scores in the late phase with coughing after operation (> 24 hours)

Trial	PCEA/CEA participants	PCEA group (median VAS and range)	CEA group (median VAS and range)	IVPCA participants	IVPCA group (median VAS and range)	Favours
Barratt 2002	25	N/A	30 (5 to 80)	22	60 (0 to 100)	CEA
Chen 2001	17	47 (15 to 90)	N/A	20	53 (11 to 82)	Neither
Heurich 2007	10	N/A	22 (20 to 25) (IQR)	9	39 (36 to 42) (IQR)	CEA
Motamed 1998	28	N/A	30 (20 to 55)	29	51 (31 to 71)	CEA

Table 8. Summary of results for trials reporting median VAS scores in the late phase with coughing after operation (> 24 hours) (Continued)

Steinberg 2002	20	16 (9 to 33) (IQR)	N/A	21	30 (12 to 62) (IQR)	PCEA
Taqi 2007	25	N/A	40 (95% CI 32 to 50.2)	25	50 (95% CI 38.5 to 62.3)	Neither
Tsui 1997	57	N/A	30 (20 to 40) (IQR)	54	40 (30 to 50) (IQR)	CEA

Acronyms and abbreviations used in this table

CEA: continuous epidural analgesia

CI: confidence interval

IQR: interquartile range

IVPCA: intravenous patient-controlled analgesia

N/A: not applicable in this trial

PCEA: patient-controlled epidural analgesia

VAS: visual analogue scale (0 = no pain; 100 = worst pain imaginable)

Table 9. Summary of results of trials reporting median length of stay (days)

Trial	PCEA/CEA participants	PCEA group (median LOS and range)	CEA group (median LOS and range)	IVPCA participants	IVPCA group (median LOS and range)	Favours
Barratt 2002	12 (CEA) 13 (CEA+ IVN)	N/A	21 days (15 to 28) (IQR (CEA)) 19 days (14 to 21) (IQR (CEA + IVN))	10 (IVPCA) 12 (IVPCA + IVN)	20 days (14 to 22) (IQR (IVPCA)) 17 days (13 to 22) (IQR (IVPCA + IVN))	Neither
Carli 2001	21	N/A	8.2 days (95% CI 3 to 12.2)	21	7.1 days (95% CI 4.6 to 11)	Neither
Carli 2002	32	N/A	7 (95% CI 3 to 11)#	31	8 (95% CI 3 to 13)#	Neither
Chen 2001	9	8 days (6 to 29)	N/A	11	10 days (5 to 31)	Neither
Gupta 2006	28	N/A	4 days (3 to 12)	28	5 days (3 to 6)	Neither
Hübner 2015	65	7 days (4.5 to 12) (IQR)	N/A	57	5 days (4 to 8) (IQR)	Neither
Mann 2000	31	10.5 days (8.5 to 15) (IQR)	N/A	33	11.5 days (8 to 16) (IQR)	Neither
Steinberg 2002	20	5 days (2 to 18.7)	N/A	21	4.8 days (3.8 to 30)	Neither
Taqi 2007	25	N/A	5 days (95% CI 4.65 to 6.16)	25	5 days (95% CI 4.23 to 9.53)	Neither
Zutshi 2005	28	5 days (4 to 7) (IQR)	N/A	31	5 days (4 to 8.5) (IQR)	Neither

#Carli 2002 reports the 95% confidence interval with a single digit, as follows: CEA 7 days (95% CI = 4), IVPCA 8 days (95% CI = 5), which we have interpreted as in the table above.

Acronyms and abbreviations used in this table

CEA: continuous epidural analgesia
 CI: confidence interval
 LOS: length of stay
 IQR: interquartile range
 IVPCA: intravenous patient-controlled analgesia
 IVN: intravenous nutrition
 N/A: not applicable in this trial
 PCEA: patient-controlled epidural analgesia
 VAS: visual analogue scale (0 = no pain; 100 = worst pain imaginable)

Table 10. Summary of results for time to ambulation

Trial	PCEA/CEA participants	PCEA group (median time to ambulation and range)	CEA group (median time to ambulation and range)	IVPCA participants	IVPCA group (median time to ambulation and range)	Favours
Gupta 2006	28	N/A	20 hours (15.25 to 27.5)	28	21 hours (15 to 48)	Neither
Mann 2000	31	98 hours (72 to 120) (IQR)	N/A	33	98 hours (84 to 144) (IQR)	Neither
Steinberg 2002	20	24 hours (14.4 to 48)	N/A	21	26 hours (3.8 to 30)	Neither

Acronyms and abbreviations used in this table

CEA: continuous epidural analgesia
 IQR: interquartile range
 IVPCA: intravenous patient-controlled analgesia
 N/A: not applicable in this trial
 PCEA: patient-controlled epidural analgesia

Table 11. Summary of results for trials reporting patient satisfaction scores

Trial	Reporting/ measurement type	PCEA/CEA participants	PCEA group	CEA group	IVPCA partic- ipants	IVPCA group	Favours
Chen 2001	Median VAS and range	17	75/100 (53 to 100/100)	N/A	20	83/100 (41 to 99/100)	Neither
Paech 1994	Median VAS and IQR	24	90/100 (70 to 100/100)	N/A	21	61/100 (33 to 81/100)	PCEA
Zutshi 2005	Median and IQR Overall hospital satisfaction	31	N/A	9/10 (7 to 10/10)	28	9/10 (8 to 10/10)	Neither
Aceto 2002	4-point scale: very satisfied (VS)/ satisfied (S)/ mildly satis- fied (MS)/ poorly satisfied (PS)	18	N/A	VS:4 S:14 MS:0 PS:0	19	VS:13 S:4 MS:2 PS:0	Unable to comment
Mann 2000	4-point scale: excellent (E)/ good (G)/ mild (M)/ nil (N)	31	E:21 G:9 M:1 N:0	N/A	33	E:11 G:19 M:3 N:0	Unable to comment
Motamed 1998	4-point scale: very satisfied (VS)/ satisfied (S)/ mildly satis- fied (MS)/ poorly satisfied (PS)	28	N/A	VS:8 S:8 MS:9 PS:3	29	VS:8 S:12 MS:1 PS:8	Unable to comment
Tsui 1997	3-point scale: good (G)/ fair (F)/ unsatisfactory (U)	53	N/A	G:48 F:5 U:0	48	G:39 F:9 U:0	Unable to comment

Acronyms and abbreviations used in this table

CEA: continuous epidural analgesia

IQR: interquartile range
IVPCA: intravenous patient-controlled analgesia
N/A: not applicable in this trial
PCEA: patient-controlled epidural analgesia
VAS: visual analogue scale (0 = no pain; 100 = worst pain imaginable)

APPENDICES

Appendix 1. Search strategy for CENTRAL, the Cochrane Library

- #1 PCA or PCEA
- #2 (patient* near control*) and (analg* or pain*)
- #3 MeSH descriptor Analgesia, Patient-Controlled explode all trees
- #4 (#1 OR #2 OR #3)
- #5 MeSH descriptor Analgesia, Epidural explode all trees
- #6 (epidural or peridural) near analg*
- #7 (#5 OR #6)
- #8 (abdom* or laparotom* or gastr* or intestin* or bowel or hepat* or biliary)
- #9 (#4 AND #7 AND #8)

Appendix 2. Search strategy for MEDLINE (OvidSP)

- 1. ((PCA or PCEA or ((patient* adj3 control*) and (analg* or pain*))).mp. or exp Analgesia, Patient-Controlled/) and (exp Analgesia, Epidural/ or ((epidural or peridural) adj3 analg*).mp.)
- 2. ((abdom* or laparotom* or gastr* or intestin* or bowel or hepat* or biliary) adj3 (surg* or operat*))).mp.
- 3. ((randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or placebo.ab. or clinical trials as topic.sh. or randomly.ab. or trial.ti.) not (animals not (humans and animals)).sh.
- 4. 1 and 2 and 3

Appendix 3. Search strategy for Embase (OvidSP)

- 1. ((PCA or PCEA or ((patient* adj3 control*) and (analg* or pain*))).mp. or exp patient-controlled-analgesia/) and (exp epidural-anesthesia/ or ((epidural or peridural) adj3 analg*).mp.)
- 2. ((abdom* or laparotom* or gastr* or intestin* or bowel or hepat* or biliary) adj5 (surg* or operat*))).ti.ab.
- 3. (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.
- 4. 1 and 2 and 3

Appendix 4. Data extraction form

CARG

Data collection form

Review title or ID

Study ID (surname of first author and year first full report of study was published e.g. Smith 2001)

Report IDs of other reports of this study (e.g. duplicate publications, follow-up studies)

(Continued)

Notes:

1. General Information

Date form completed (dd/mm/yyyy)

Name/ID of person extracting data

Report title

(title of paper/ abstract/ report that data are extracted from)

Report ID

(ID for this paper/ abstract/ report)

Reference details

Report author contact details

Publication type

(e.g. full report, abstract, letter)

Study funding sources

(including role of funders)

Possible conflicts of interest

(for study authors)

Notes:

2. Study Eligibility

Study Character-istics	Eligibility criteria <i>(Insert eligibility criteria for each characteristic as defined in the Protocol)</i>	Yes	No	Unclear	Location in text <i>(pg & ¶/fig/table)</i>
Type of study	Randomized Controlled Trial				
Partici-pants	Adult patients aged 16 years and above undergoing in-tra-abdominal surgery.				
Types of interven-tion	IVPCA with opioid compared with epidural analgesia using CEA or PCEA. Medication for epidural might be any opioid, local anaes-thetic agent or combination of these two.				
Types of outcome measures	Primary outcome measures <ol style="list-style-type: none"> Pain score by visual analogue scale (VAS) or similar, during the initial six hour period (early phase), six to twenty four hour period (mid phase), and twenty four hour to seventy two hour period (late phase.) All cause mortality rate at 30 days Secondary outcomes <ol style="list-style-type: none"> Demonstrated venous thromboembolism rate The number of failures (defined as a clinical decision to use a second analgesic technique - and could be due to multiple reasons such as failure of insertion of epidural, inadequate analgesia, epidural catheter withdrawal or dislodgment, infection, neurological deficit etc Length of hospital stay Time to ambulation Patient satisfaction-as by a scale Quality of life Adverse effects <ol style="list-style-type: none"> Prurits Nausea and vomiting Epidural haematoma Sedation 				

(Continued)

5. Respiratory complications such as respiratory depression (respiratory rate less than 10 per minute or requirement for opioid antagonist), Hypoxemia (defined as $\text{SpO}_2 < 90\%$ by pulse oximetry)
6. Hypotension requiring treatment

INCLUDE	EXCLUDE
---------	---------

Reason for
exclusion

Notes:

DO NOT PROCEED IF STUDY EXCLUDED FROM REVIEW

3. Population and setting

	Description	Location in text
	<i>Include comparative information for each group (i.e. intervention and controls) if available</i>	<i>(pg & ¶/fig/table)</i>
Population description		
<i>(from which study participants are drawn)</i>		
Setting		
<i>(including location and social context)</i>		
Inclusion criteria		
Exclusion criteria		
Method/s of recruitment of participants		
Informed consent obtained		
	Yes No Unclear	

Notes:

(Continued)

4. Methods

	Descriptions as stated in report/paper	Location in text (pg & ¶/fig/table)
Aim of study		
Design (e.g. parallel, crossover, cluster)		
Unit of allocation (by individuals, cluster/ groups or body parts)		
Start date		
End date		
Total study duration		
Ethical approval needed/ obtained for study	Yes No Unclear	
Notes:		

5. Risk of Bias assessment

See Chapter 8 of the Cochrane Handbook

Domain	Risk of bias	Support for judgement	Location in text
--------	--------------	-----------------------	------------------

Epidural analgesia versus patient-controlled intravenous analgesia for pain following intra-abdominal surgery in adults (Review)

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(Continued)

(pg & ¶/fig/ta-
ble)

Low risk	High risk	Unclear
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Random sequence generation

(selection bias)

Allocation concealment

(selection bias)

Blinding of participants and personnel

(performance bias)

Outcome group:
All/

(if required)

Outcome group:

Blinding of outcome assessment

(detection bias)

Outcome group:
All/

(if required)

Outcome group:

Incomplete outcome data

(attrition bias)

Selective outcome reporting?

(reporting bias)

Other bias

Notes:

6. Participants

Provide overall data and, if available, comparative data for each intervention or comparison group.

	Description as stated in report/paper	Location in text (pg & ¶/fig/table)
Total no. randomized <i>(or total pop. at start of study for NRCTs)</i>		
Clusters <i>(if applicable, no., type, no. people per cluster)</i>		
Baseline imbalances		
Withdrawals and exclusions <i>(if not provided below by outcome)</i>		
Age		
Sex		
Race/Ethnicity		
Severity of illness		
Co-morbidities		
Other treatment received <i>(additional to study intervention)</i>		
Other relevant sociodemographics		
Subgroups measured		
Subgroups reported		
Notes:		

7. Intervention groups

Copy and paste table for each intervention and comparison group

Intervention Group 1

	Description as stated in report/paper	Location in text (pg & ¶/fig/table)
Group name		
No. randomized to group (specify whether no. people or clusters)		
Theoretical basis (include key references)		
Description (include sufficient detail for replication, e.g. content, dose, components)		
Duration of treatment period		
Timing (e.g. frequency, duration of each episode)		
Delivery (e.g. mechanism, medium, intensity, fidelity)		
Providers (e.g. no., profession, training, ethnicity etc. if relevant)		
Co-interventions		
Economic variables (i.e. intervention cost, changes in other costs as result of intervention)		
Resource requirements to replicate intervention (e.g. staff numbers, cold chain, equipment)		
Notes:		

8. Outcomes

Copy and paste table for each outcome.

Outcome 1

Description as stated in report/paper	Location in text
---------------------------------------	------------------

(Continued)

(pg & ¶/fig/table)

Outcome name
Time points measured
Time points reported
Outcome definition (with diagnostic criteria if relevant)

Person measuring/reporting
Unit of measurement

(if relevant)

Scales: upper and lower limits (indicate whether high or low score is good)

Is outcome/tool validated?

Yes No Unclear

Imputation of missing data

(e.g. assumptions made for ITT analysis)

Assumed risk estimate

(e.g. baseline or population risk noted in Background)

Power
Notes:

9. Results

Copy and paste the appropriate table for each outcome, including additional tables for each time point and subgroup as required.

Dichotomous outcome

Description as stated in report/paper

Location in
text

(Continued)

(pg & ¶/fig/
table)

Comparison

Outcome

Subgroup

Timepoint
(specify whether from start or end of intervention)

Results
Intervention
Comparison

No. events

No. participants

No. events

No. participants

No. missing participants and reasons

No. participants moved from other group and reasons

Any other results reported

Unit of analysis *(by individuals, cluster/groups or body parts)*

Statistical methods used and appropriateness of these methods *(e.g. adjustment for correlation)*

Reanalysis required? *(specify)*

Yes No Unclear

Reanalysis possible?

Yes No Unclear

Reanalysed results

Notes:

Continuous outcome

Description as stated in report/paper				Location in text (pg & ¶/fig/table)		
Comparison						
Outcome						
Subgroup						
Timepoint (specify whether from start or end of intervention)						
Post-intervention or change from baseline?						
Results	Intervention			Comparison		
	Mean	SD (or other variance)	No. participants	Mean	SD (or other variance)	No. participants
No. missing participants and reasons						
No. participants moved from other group and reasons						
Any other results reported						
Unit of analysis (individuals, cluster/ groups or body parts)						
Statistical methods used and appropriateness of these methods (e.g. adjustment for correlation)						
Reanalysis required? (specify)						
Yes No Unclear						

(Continued)

Reanalysis possible?

Yes No Unclear

Reanalysed results

Notes:

Other outcome

Description as stated in report/paper					Location in text (pg & ¶/fig/table)
Comparison					
Outcome					
Subgroup					
Timepoint (specify whether from start or end of intervention)					
Results	Intervention result	SD (or other variance)	Control result	SD (or other variance)	
	Overall results		SE (or other variance)		
No. participants	Intervention		Control		
No. missing participants and reasons					
No. participants moved from other group and reasons					
Any other results reported					
Unit of analysis (by individuals, cluster/groups or body parts)					
Statistical methods used and appropriateness of these methods					
Reanalysis required? (specify)					
	Yes	No	Unclear		
Reanalysis possible?					
	Yes	No	Unclear		
Reanalysed results					
Notes:					

(Continued)

10. Applicability

Have important populations been excluded from the study? (*consider disadvantaged populations, and possible differences in the intervention effect*)

Yes No Unclear

Is the intervention likely to be aimed at disadvantaged groups? (*e.g. lower socioeconomic groups*)

Yes No Unclear

Does the study directly address the review question?

(*any issues of partial or indirect applicability*)

Yes No Unclear

Notes:

11. Other information

**Description as stated
in report/paper**

Location in text
(*pg & ¶/fig/table*)

Key conclusions of study authors

References to other relevant studies

Correspondence required for further study information (*from whom, what and when*)

Notes:

(Continued)

Appendix 5. Participant characteristics

Study ID	Data
Aceto 2002	<p>Age 28 to 70, ASA 1 to 3, undergoing general anaesthesia for colorectal surgery.</p> <p>Exclusion criteria: history of severe heart disease (New York Heart Association class > II), hepatic or renal insufficiency (as determined by preoperative blood test), contraindications either to NSAIDs (such as bleeding problems, anticoagulant medications, history of peptic ulcer) or to opioids (known narcotic use or alcohol abuse), psychiatric disease, endocrine disease, including diabetes mellitus, inability to comprehend pain scoring. Participants with coagulopathy, known allergy to local anaesthetics or with another contraindication to epidural techniques were also excluded.</p>
Aydogan 2015	<p>Age 18 to 65, ASA 1 to 2 undergoing partial hepatectomy as donor for liver transplantation. Age 29.8 ± 9.1 (SD) for IVPCA and 27.4 ± 8.6 (SD) for PCEA. Exclusion criteria were not specified.</p>
Barratt 2002	<p>Age 21 to 80. Participants were excluded if they required intravenous nutrition because of severe malnutrition, or if postoperative complications such as sepsis or haemorrhage developed. Surgery involving the diaphragm or thorax was excluded. Participants were excluded if they had significant cardiac disease (severe angina, congestive cardiac failure, recent acute myocardial infarction), respiratory disease (preoperative $\text{PaO}_2 < 50$ mmHg (room air), $\text{Pa CO}_2 > 50$ mmHg (room air)), renal disease (plasma creatinine > 0.2 mmol/L), musculoskeletal or neurological disease; haematological disease; drug dependency disorder; or psychiatric disease.</p>
Carli 2001	<p>Participants were ASA 1 to 3. Age 64 ± 11 (SD) for IVPCA, and 68 ± 8 (SD) for epidural. Exclusion criteria included malnutrition, severe cardiopulmonary diseases, sepsis, inflammatory bowel disease, chemotherapy or radiotherapy 6 months before surgery, and inability to communicate and understand the aim of the project.</p>
Carli 2002	<p>Participants were ASA 1 to 3. Age 62 ± 12 (SD) for IVPCA, and 59 ± 12 (SD) for epidural. The target population was adults undergoing elective colorectal surgery for non-metastatic conditions. People with malnutrition (serum albumin < 35 g/L, severe cardiopulmonary disease (American Society of Anesthesiologists physical status IV), sepsis (febrile on antibiotics), inflammatory bowel disease, chemotherapy or radiotherapy within the 6 months preceding surgery, and inability to communicate or understand the aim of the project (questionnaire and consent form would need to be translated) were excluded.</p>
Chauvin 1993	<p>Participants were ASA 1 to 2. Exclusion criteria were cardiac or respiratory failure, a history of drug abuse, a neurotic personality, or an inability to understand the study protocol. Age 46 ± 11 (SD) for IVPCA and 49 ± 15 for epidural</p>
Chen 2001	<p>Participants were ASA 1 to 3, between the ages of 18 and 70 scheduled for elective total gastrectomy. People who had a history of opioid abuse, allergy to pethidine, severe renal or respiratory impairment, and those with any contraindication to epidural analgesia were excluded. Age 57 ± 11 (SD) for IVPCA, and 62 ± 9 (SD) for epidural</p>
Chen 2015a	<p>Participants were ASA 1 to 2, between the ages of 18 and 75 with BMI 18.5 to 30 scheduled for open colorectal surgery for colorectal cancer. Exclusion criteria included a history of abdominal surgery, endocrine or immune system dysfunction (such as diabetes, thyroid disease, multiple sclerosis, and rheumatoid arthritis), recent blood transfusions, preoperative treatment with opioids, hormone, non-steroid anti-inflammatory, or other immunomodulatory substances, and contraindi-</p>

(Continued)

	cation to epidural anaesthesia. Age 57.9 ± 6.5 (mean $\pm$ SD) for IVPCA, and 57.3 ± 5.3 (mean $\pm$ SD) for epidural
Donatelli 2006	Participants were scheduled for elective colon resection for benign and malignant lesions. Exclusion criteria were as follows: more than 20% loss of body weight in the past 6 months, evidence of metastatic disease, severe cardiac and respiratory diseases, diabetes and albumin below 35 g/L, and anaemia (haemoglobin less than 100 g/L). Participants were ASA 1 to 3. Age 59 ± 16 (mean $\pm$ SD) for IVPCA, 65 ± 14 (mean $\pm$ SD) for epidural
Elkaradawy 2011	<p>Participants were ASA 2 undergoing open cholecystectomy. They all had diabetes mellitus type 2, glycosylated haemoglobin $< 8.5\%$, negative stress exercise test to exclude preoperative ischaemic coronary artery disease. All participants had at least 2 risk factors for developing coronary artery disease in addition to diabetes mellitus and abdominal surgery. These risk factors included age > 60 years, sedentary lifestyle, total cholesterol > 240 mg/dL, LDL > 160 mg/dL or HDL < 35 mg/dL, current smoking, family history of premature coronary artery disease.</p> <p>Exclusion criteria included any person with history of coronary artery disease, heart failure, hypertension, respiratory, renal, or hepatic insufficiency, having any contraindications for epidural anaesthesia.</p>
Gupta 2006	Participants were ASA 1 to 2 undergoing radical retropubic prostatectomy for prostatic cancer. Exclusion criteria were chronic pain, use of preoperative opioid analgesic, known contraindications for epidural analgesia, intolerance to morphine or local anaesthetics, and age older than 70. Age 61.1 ± 4.3 (mean and SD) IVPCA, 64.5 ± 4.9 (mean and SD) epidural.
Heurich 2007	Participants were older than 18 years. ASA 1 to 3, scheduled for elective major abdominal surgery via midline incision (prostatectomy, cystectomy, hysterectomy, hemicolectomy). None of the participants were obese, taking opioids or medication likely to alter the local inflammatory process (corticosteroids, NSAIDs), or had a history of cytostatic therapy. Further exclusion criteria were contraindications to epidural anaesthesia (e.g. preoperative coagulopathy, localized infection) or to study drugs, mechanical ventilation for longer than 6 h postoperatively, and termination of the analgesic regimen within 48 h postoperatively. Age 68.9 ± 4.5 (mean and SEM) IVPCA, 64.6 ± 3.1 (mean and SEM) epidural
Hübner 2015	Participants were 18 years and older, undergoing elective laparoscopic colorectal surgery. Exclusion criteria included inability to provide informed consent, medical contraindications to epidural analgesia. ASA 1 to 3. Age 61.2 ± 17.8 (mean and SD) IVPCA, 63.1 ± 15.1 (mean and SD) epidural
Jayr 1998	Inclusion criteria were: individuals undergoing cystectomy, radical abdominal hysterectomy with pelvic lymphadenectomy, colon resection, or rectum amputation, aged 18 to 75 years, ASA 1 to 3, and weight 50 to 110 kg. Individuals were excluded if they had contraindications to epidural analgesia or concomitant disease that would influence postoperative assessments. Age 56 ± 13 (mean and SD) IVPCA, 57 ± 12 (mean and SD) epidural
Kowalski 1992	Participants underwent upper abdominal surgery. There was no further information about participant characteristics.
Liu 1995	Participants were ASA 1 to 3, aged 18 to 80 who underwent radical retropubic prostatectomy with or without pelvic lymph node dissection. Exclusion criteria included history of chronic pain or narcotic dependence, presence of contraindications to epidural catheter placement (coagulation defects, infection at puncture site, patient's refusal to undergo epidural anaesthesia), presence of contraindications to patient-controlled analgesia (inability to understand IVPCA, history of drug abuse), contraindication to ketorolac use (serum creatinine < 2 mg/dL, history of haemorrhagic peptic ulcer disease, history of hypersensitivity to aspirin). Age 59 ± 11 (mean and SD) IVPCA, 60 ± 8 (mean and SD) epidural
Madej 1992	Participants underwent total abdominal hysterectomy. No other demographic data were provided.
Mann 2000	Inclusion criteria were age older than 70, ASA 1 to 2, normal preoperative mental status defined by a modified Abbreviated Mental Test score of at least 8, elective major abdominal surgery for can-

(Continued)

	cer via a midline or bisubcostal incision, absence of contraindications to epidural anaesthesia (e.g. preoperative coagulopathy, localized infection), and absence of extreme malnutrition or cerebral vascular insufficiency. Age 76.8 ± 4.7 (mean $\pm$ SD) IVPCA, 76.1 ± 5.6 (mean $\pm$ SD) epidural
Motamed 1998	Participants were ASA 1 to 2, age 18 to 70, undergoing major abdominal surgery for cancer (midline or bisubcostal incision). Exclusion criteria were: obesity, pulmonary disease, heavy smoking (> 20 pack years), and contraindications to extradural analgesia. Age 56 ± 11 (mean $\pm$ SD) IVPCA, 60 ± 10 (mean $\pm$ SD) epidural
Ngan 1997	Participants were ASA 1 to 2, undergoing elective Caesarean section. Age 32 (29.5 to 34) median and IQ range pethidine IVPCA; 31 (28 to 32) median and IQ range pethidine epidural. Age 30 (28 to 33) median and IQ range fentanyl IVPCA; 32.5 (30.5 to 35) median and IQ range fentanyl epidural
Paech 1994	Participants were undergoing elective Caesarean section. Age 30 (24 to 35) median and IQ range IVPCA; 33 (28 to 36) median and IQ range epidural
Parker 1992	Participants were ASA 1 to 2, undergoing elective Caesarean section. Individuals with evidence of bacteraemia or coagulopathy, as well as those reluctant to have an epidural catheter remain in place after their operation were excluded. Age 28 ± 5 (mean $\pm$ SD) IVPCA, 27 ± 6 (mean $\pm$ SD) epidural phase I, 28 ± 6 (mean $\pm$ SD) epidural phase II
Schricker 2000	Participants were ASA 1 to 2, with localized non-metastatic adenocarcinoma of the rectosigmoid colon who were scheduled for elective colorectal surgery. None of the participants suffered from cardiac, hepatic, renal, or metabolic disease. No participant had a history of recent weight loss or had a plasma albumin concentration < 35 g/L. Age 57 ± 22 (mean $\pm$ SD) IVPCA, 53 ± 15 (mean $\pm$ SD) epidural
Schumann 2003	Participants were 18 to 80 years, scheduled for gastric bypass surgery as a treatment for obesity. Obesity was defined as a BMI greater than or equal to 30. Patients with significant cardiovascular, hepatic, pulmonary, renal, haematological, neurologic, or psychiatric disease were excluded from participation in the study. Other exclusion criteria were: known hypersensitivity to any of the study drugs, a history of drug or alcohol abuse within the previous year, pre-existing chronic or acute pain, or with previous abdominal surgery or any surgery in the previous 3 months. Age Group A 40.2 ± 12.4 (mean $\pm$ SD), Group B 40.0 ± 10.5 (mean $\pm$ SD), Group C 40.6 ± 9.8 (mean $\pm$ SD)
Steinberg 2002	Participants were ASA 1 to 3, age 18 to 80 and weighing 50 to 110 kg undergoing elective partial colon resection. Exclusion criteria included contraindications to placement of an epidural catheter and use of NSAIDs, history of allergy to local anaesthetics or opioids, presence of complete bowel obstruction or inflammatory bowel disease, planned total colectomy or colostomy, previous history of abdominal radiation, recent use of corticosteroids, alcohol or drug abuse, pregnancy, and patient refusal. Age 62 ± 10 (mean $\pm$ SD) IVPCA, 61 ± 15 (mean $\pm$ SD) epidural
Taqi 2007	Participants were undergoing elective laparoscopic colorectal surgery for benign and malignant colorectal lesions. Exclusion criteria included open colorectal resection, a history of chemoradiation within the 6 months preceding surgery, a contraindication to the epidural technique, and inability to communicate or understand the purpose of the study. Participants were ASA 1 to 3, age 61.24 ± 14.91 (mean $\pm$ SD) IVPCA, 65 ± 16.18 (mean $\pm$ SD) epidural.
Tsui 1997	Participants were ASA 1 to 2, scheduled for gynaecological lower abdominal operations through a vertical midline incision. Exclusion criteria included: age > 65 , mental defect, contraindications to regional block, significant cardiopulmonary dysfunction, or abdominal incision other than vertical midline. Age 51 ± 16 (mean $\pm$ SD) IVPCA, 48 ± 11 (mean $\pm$ SD) epidural
Wang 2004	Participants were ASA 1 to 3, undergoing elective hysterectomy, aged 31 to 57. Participants did not have the following comorbidities: hypertension, coronary artery disease, diabetes mellitus, surgical history, renal or hepatic dysfunction. Exclusion criteria included patients with anaemia, coagulopathy, current anticoagulation or antifibrinolytic medication, NSAIDs and hormone history.

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Welchew 1991	Participants were ASA 1 to 2, scheduled for non-cancer upper abdominal surgery, receiving no regular medications and having no known allergies. Age 42.9 ± 8.10 (mean $\pm$ SD) IVPCA, 47.9 ± 14.99 (mean $\pm$ SD) epidural
Yosunkaya 2003	Participants were ASA 1 to 2, aged 20 to 60 years scheduled for elective upper abdominal surgery such as pyloroplasty, open cholecystectomy, gastroenterostomy, hepatic resection, or hydatid cyst surgery. Exclusion criteria included patients under chronic treatment with analgesics or corticosteroids, with contraindications for epidural, allergy to opioids, and any significant medical history or concomitant disease that would influence postoperative assessments. Age 38 ± 12.9 (mean $\pm$ SD) IVPCA, 41.7 ± 11.8 (mean $\pm$ SD) epidural
Zeng 2003	Participants were ASA 1 to 2, aged 37 to 70, who underwent elective abdominal surgery. Exclusion criteria included preop immunological/endocrinological diseases and duration of surgery > 4 hours. There were no significant differences in gender, age, height, weight, duration of surgery, surgery type amongst the 5 groups.
Zutshi 2005	Participants were scheduled for elective segmental intestinal resection by laparotomy. Reoperative cases and patients with comorbidities were excluded. Patients were considered to be undergoing their first operation if they had not undergone prior intestinal resection. Participants were ASA 1 to 4. Age 47.4 (32.8, 56.9) median (IQ range) IVPCA, 44.5 (30.5, 53.7) median (IQ range) epidural

Acronyms and abbreviations used in this appendix

ASA: American Society of Anesthesiologists physical status classification system; BMI: body mass index; HDL: high-density lipoprotein cholesterol; IQ: interquartile; IVPCA: intravenous patient-controlled analgesia; LDL: low-density lipoprotein cholesterol; NSAIDs: non-steroidal anti-inflammatory drugs; PCEA: patient-controlled epidural analgesia; SD: standard deviation; SEM: standard error of the mean

Appendix 6. Types of interventions

Study ID	Group Name	Allocation	N	Surgical anaesthesia	Anaesthesia agents	Postoperative analgesia	Analgnesia drugs	Duration (postoperative)
Aceto 2002	Group B	Intervention	20	GA + epidural	Sevoflurane/oxygen epidural - 5 mL 0.2% ropivacaine + sufentanil 10 µg	Thoracic epidural T6 to T9 via CEA	0.2% ropivacaine + sufentanil 0.75 µg/mL	3 days
Aceto 2002	Group A	Control	19	GA	Sevoflurane/oxygen/fentanyl	Multimodal IVPCA	Continuous infusion tramadol 6.25 mg/mL + ketorolac 1.875 mg/mL at 2 mL/h. IVPCA morphine 0.6 mg bolus, 7-minute lockout	Tramadol/ketorolac infusion for 48 hours. IVPCA morphine for 3 days
Aydogan 2015	Group E	Intervention	20	GA	Isoflurane/oxygen/remifentanyl infusion	Epidural - level not stated via PCEA	15 minutes from end of operation epidural morphine 2 mg bolus, then PCEA 0.5 mg bolus, 30-minute lockout, 4-hour maximum 10 mg	24 hours
Aydogan 2015	Group C	Control	20	GA	Isoflurane/oxygen/remifentanyl infusion	IVPCA	15 min from end of operation IV morphine 5 mg bolus, then IVPCA with 1 mg bolus, 15-minute lockout, 4-hour maximum 20 mg	24 hours
Barratt 2002	MMA + IVN MMA	Intervention	25	GA + epidural	Isoflurane/oxygen/nitrous oxide Epidural - 0.5% bupivacaine	Thoracic epidural T7 to T10 via CEA	0.25% bupivacaine + fentanyl 2.5 µg/mL at 5 to 10 mL/h + ketorolac 10 to 5 mg IMI every 6 hours	Ketorolac for 48 hours Epidural for 3.2 ± 0.6 days
Barratt 2002	IVPCA + IVN IVPCA	Control	22	GA	Isoflurane/oxygen/nitrous oxide	IVPCA	Morphine 1 to 2 mg bolus, 5-minute lockout OR fentanyl 10 to 20 µg bolus, 5-minute lockout	IVPCA 4.1 ± 0.8 days

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Carli 2001	Epidural	Intervention	21	GA + epidural	Isoflurane/oxygen/nitrous oxide/fentanyl Epidural - 0.5% bupivacaine 5 mL/h bolus	Thoracic epidural T8 to T9 via CEA + NSAID	0.1% bupivacaine + 2 µg/mL fentanyl at 8 to 12 mL/h. 0.25% bupivacaine bolus for rescue naproxen 500 mg (oral or per rectum)	4 days
Carli 2001	IVPCA	Control	21	GA	Isoflurane/oxygen/nitrous oxide/fentanyl	IVPCA + NSAID	Morphine 1 to 2 mg bolus, 5- to 10-minute lockout naproxen 500 mg twice daily (oral or per rectum)	4 days
Carli 2002	Epidural	Intervention	32	GA + epidural	Isoflurane/oxygen/nitrous oxide/fentanyl Epidural - 0.5% bupivacaine 15 to 20 mL + 5 mL/h bolus	Thoracic epidural T8 to T9 via CEA + NSAID	Bupivacaine 0.1% + 2 µg/mL fentanyl at 4 to 15 mL/h naproxen 500 mg twice daily (oral or per rectum)	4 days
Carli 2002	IVPCA	Control	31	GA	Isoflurane/oxygen/nitrous oxide/fentanyl	IVPCA + NSAID	Morphine 1 to 2 mg bolus, 5-minute lockout naproxen 500 mg twice daily (oral or per rectum)	3 to 4 days
Chauvin 1993	Epidural	Intervention	16	GA	Halothane/oxygen/nitrous oxide/fentanyl	Thoracic epidural at T9 to T11 via PCEA	Alfentanil 250 µg bolus, 10-minute lockout	16 hours
Chauvin 1993	IV	Control	16	GA	Halothane/oxygen/nitrous oxide/fentanyl	IVPCA	Alfentanil 250 µg bolus, 5-minute lockout	16 hours
Chen 2001	Epidural	Intervention	17	GA + epidural	Isoflurane/oxygen/nitrous oxide Epidural - 2% lidocaine	Thoracic epidural at T8 to T10 via PCEA	Pethidine 25 mg loading, then 10 mg bolus with 10-minute lockout, 4-hour maximum 3 mg/kg	48 hours
Chen 2001	Intravenous	Control	20	GA	Isoflurane/oxygen/nitrous oxide	IVPCA	Pethidine 25 mg loading, then 10 mg bolus with 10-minute lockout, 4-hour maximum 3 mg/kg	48 hours

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Chen 2015a	Group E	Intervention	26	GA + epidural	Sevoflurane/fentanyl/propofol Epidural - 3 mL 2% lidocaine test, then 8 mL 0.375% bupivacaine, then 4 mL bolus every 50 minutes	Thoracic epidural at T10 to T11 via PCEA	0.125% bupivacaine + 30 µg/mL morphine at 2 mL/h background + 2 mL bolus with 15-minute lockout	24 hours
Chen 2015a	Group G	Control	27	GA	Sevoflurane/fentanyl/propofol	IVPCA	Morphine 1 mg/h background + 1 mg bolus with 15-minute lockout	24 hours
Donatelli 2006	Group B	Intervention	8	GA + epidural	Desflurane/oxygen/nitrous oxide/fentanyl Epidural - 0.5% 15 mL bupivacaine, then 5 mL bolus hourly of 0.25% bupivacaine	Thoracic epidural to T9 to T11 via CEA	0.1% bupivacaine + 2 µg/mL fentanyl at 8 to 15 mL/h	2 days
Donatelli 2006	Group A	Control	8	GA	Desflurane/oxygen/nitrous oxide/fentanyl	IVPCA	Morphine	2 days
Elkaradawy 2011	Group G/Ep	Intervention	25	GA + epidural	Isoflurane/air/oxygen Epidural - 15 mL 0.2% ropivacaine + 2 µg/mL fentanyl, then epidural infusion of 5 to 8 mL/h 0.1% ropivacaine + 1 µg/mL fentanyl	Thoracic epidural at T7 to T8 via CEA	5 to 8 mL/h 0.1% ropivacaine + 1 µg/mL fentanyl	24 hours
Elkaradawy 2011	Group G/O	Control	25	GA	Isoflurane/air/oxygen/fentanyl infusion at 100 µg/h	IVPCA	Morphine 1 mg/h background + 1 mg bolus, 6-minute lockout for first 6 hours, then no background	24 hours
Gupta 2006	Group E	Intervention	28	GA + epidural	Sevoflurane/oxygen/nitrous oxide Epidural - 2% mepivacaine with adrenaline at 2 to 5 mL/h	Epidural at T10 to T12 via CEA + regular paracetamol	0.1% ropivacaine + 2 µg/mL fentanyl + 2 µg/mL adrenaline at 10 mL/h	48 hours

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Gupta 2006	Group P	Control	28	GA + epidural	Sevoflurane/oxygen/nitrous oxide Epidural - 2% mepivacaine with adrenaline at 2 to 5 mL/h	IVPCA + regular paracetamol	Morphine 1 mg bolus, 6-minute lockout	48 hours
Heurich 2007	EDA	Intervention	10	GA + epidural	Isoflurane/oxygen/nitrous oxide Epidural - test dose of 3 mL 1% lidocaine, then 5 to 9 mL of 0.5% bupivacaine. Bolus 3 to 4 mL/h of 0.5% bupivacaine	Epidural at T11 to L1 or epidural at L1 to L3, via CEA	T11 to L1 - 0.125% bupivacaine + 4 µg/mL fentanyl by CEA. L1 to L3 - 0.0625% bupivacaine + 2 µg/mL fentanyl by CEA	48 hours
Heurich 2007	PCIA	Control	9	GA	Isoflurane/oxygen/nitrous oxide	IVPCA	Piritramide 2 mg bolus, 10-minute lockout	48 hours
Hübner 2015	EDA	Intervention	65	GA + epidural	Sevoflurane/oxygen/air Epidural - 5 mL 0.5% bupivacaine bolus, then 0.5% bupivacaine infusion at 5 mL/h	Epidural at T8 to T10 by PCEA + regular paracetamol and metamizole	0.1% bupivacaine + 2 µg/mL fentanyl + 2 µg/mL adrenaline at 6 to 10 mL/h, with 3 mL bolus and 40-minute lockout. 1 g paracetamol 4 times daily (oral) and metamizole 500 mg 4 times daily (oral)	POD 2 72% POD 3 18% POD 4 4.6% POD 5 1.5% POD 6 1.5% POD 7 1.5%
Hübner 2015	IVPCA	Control	57	GA	Sevoflurane/oxygen/air/fentanyl	IVPCA	Morphine 1 mg bolus, 5-minute lockout. 40 mg 4 hours maximum	POD 2 6%
Jayr 1998	Ropi	Intervention	38	GA	Isoflurane/oxygen/nitrous oxide/fentanyl	Epidural - level not stated, via CEA	0.2% ropivacaine 20 mL bolus, then infusion at 10 mL/h	24 hours
Jayr 1998	IVPCA	Control	46	GA	Isoflurane/oxygen/nitrous oxide/fentanyl	IVPCA	Morphine 1 mg bolus, 5-minute lockout	24 hours
Kowalski 1992	Group F	Intervention	9	GA + epidural	Isoflurane/oxygen/nitrous oxide	Epidural - level not stated	Fentanyl 1 µg/kg bolus, then 1 µg/kg/h infusion, could be increased to 1.5 µg/kg/h with ad-	48 hours

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					Epidural - 2% lidocaine with adrenaline to establish, then 0.25% bupivacaine top-up.		ditional bolus 0.5 µg/kg if required	
					IV fentanyl up to 5 µg/kg			
Kowalski 1992	Group M	Control	9	GA + epidural	Isoflurane/oxygen/nitrous oxide Epidural - 2% lidocaine with adrenaline to establish, then 0.25% bupivacaine top-up. IV fentanyl up to 5 µg/kg	IVPCA	Morphine 8 mg IV load, then 1 mg/h background, and 1 mg bolus with 10-minute lockout	48 hours
Liu 1995	Epidural	Intervention	8	GA + epidural	Isoflurane/oxygen/nitrous oxide Epidural - 10 mL bolus of 1.5% lidocaine with adrenaline, then 3 mL every 45 minutes	Epidural at T10 to L1 via PCEA + NSAID	Hydromorphone 1.05 mg load, then PCEA 150 µg bolus, 15-minute lockout. If analgesia was inadequate, a further 300 µg load was given, and lockout decreased to 10 minutes. If still inadequate, then the bolus was increased by 50 µg each hour, until analgesia was satisfactory.	72 hours
Liu 1995	IV	Control	8	GA + epidural	Isoflurane/oxygen/nitrous oxide Epidural - 10 mL bolus of 1.5% lidocaine with adrenaline, then 3 mL every 45 minutes	IVPCA + NSAID	Hydromorphone 1.05 mg load, then PCA 150 µg bolus, 15-minute lockout. If analgesia was inadequate, a further 300 µg load was given, and lockout decreased to 10 minutes. If still inadequate, then the bolus was increased by 50 µg each hour, until analgesia was satisfactory.	72 hours
Madej 1992	Group EI	Intervention	20	GA + epidural	Enflurane/oxygen/nitrous oxide	Epidural at lumbar level via CEA	0.15% bupivacaine + 0.01% diamorphine at 4 to 6 mL/h	24 hours
Madej 1992	Group PCA5	Control	10	GA + epidural	Enflurane/oxygen/nitrous oxide	IVPCA	Diamorphine 1 mg bolus, 5-minute lockout	24 hours

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Mann 2000	PCEA Group	Intervention	31	GA + epidural	Isoflurane/oxygen/nitrous oxide Epidural - 2% lidocaine with adrenaline to commence, then 0.25% bupivacaine + 1 µg/mL sufentanil infusion to maintain	Epidural at T7 to T11 via PCEA	0.125% bupivacaine + 0.5 µg/mL sufentanil via PCEA with background infusion of 3 to 5 mL/h, and 2 to 3 mL bolus, 12-minute lockout	79 ± 22 hours
Mann 2000	IVPCA Group	Control	33	GA	Isoflurane/oxygen/nitrous oxide/sufentanil 0.5 µg/kg bolus, then 0.2 to 0.4 µg/kg bolus as required	IVPCA	Morphine 1.5 mg bolus, 8-minute lockout	70 ± 20 hours
Motamed 1998	EXI Group	Intervention	28	GA	Isoflurane/oxygen/nitrous oxide/fentanyl 1 µg/kg	Epidural at T9 to T11 via CEA	0.125% bupivacaine + morphine 0.25 mg/mL loading to achieve bilateral T6 block, then infusion at 10 mL/h	48 hours
Motamed 1998	IVPCA Group	Control	29	GA	Isoflurane/oxygen/nitrous oxide/fentanyl 1 µg/kg	IVPCA	Morphine 3 mg loading boluses in recovery until pain score of nil-moderate, then IVPCA morphine with 1 mg bolus, 5-minute lockout, 20 mg 4 hours maximum	48 hours
Ngan 1997	Group Peth-E/I	Intervention	20	Epidural	Epidural - 2% lidocaine with adrenaline 1:200,000 to establish block to T4. Pain - nitrous oxide via face mask, or ketamine 10 mg bolus as required	Epidural at L2 to L4 via PCEA	Pethidine 10 mg/mL. Loading 4 mL, then PCA 2 mL bolus and 15-minute lockout. 4-hour maximum 40 mL	12 hours
Ngan 1997	Group Peth-I/E	Control	18	Epidural	Epidural - 2% lidocaine with adrenaline 1:200,000 to establish block to T4. Pain - nitrous oxide via face mask, or ketamine 10 mg bolus as required	IVPCA	Pethidine 10 mg/mL. Loading 4 mL, then IVPCA 2 mL bolus and 15-minute lockout. 4-hour maximum 40 mL	12 hours
Ngan 1997	Group Fent-E/I	Intervention	20	Epidural	Epidural - 2% lidocaine with adrenaline 1:200,000 to establish block to T4.	Epidural at L2 to L4 via PCEA	Fentanyl 20 µg/mL. Loading 4 mL, then PCA 2 mL bolus and	12 hours

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					Pain - nitrous oxide via face mask, or ketamine 10 mg bolus as required		15-minute lockout. 4-hour maximum 40 mL	
Ngan 1997	Group Fent-I/E	Control	17	Epidural	Epidural - 2% lidocaine with adrenaline 1:200,000 to establish block to T4. Pain - nitrous oxide via face mask, or ketamine 10 mg bolus as required	IVPCA	Fentanyl 20 µg/mL. Loading 4 mL, then IVPCA 2 mL bolus and 15-minute lockout. 4-hour maximum 40 mL	12 hours
Paech 1994	Group 1	Intervention	24	Epidural	Epidural - 0.5% bupivacaine + 5 µg/mL fentanyl max 20 mL for bilateral T4 block	Epidural at L1 to L3 via PCEA	Pethidine 25 mg loading, then PCEA with 20 mg bolus, 5-minute lockout. 200 mg/2-hour maximum	12 hours
Paech 1994	Group 2	Control	21	Epidural	Epidural - 0.5% bupivacaine + 5 µg/mL fentanyl max 20 mL for bilateral T4 block	IVPCA	Pethidine 25 mg loading, then IVPCA with 20 mg bolus, 5-minute lockout. 200 mg/2-hour maximum	12 hours
Parker 1992	EPI-PCA Phase 1	Intervention	17	Epidural	Epidural - 0.5% bupivacaine (5 participants - unclear which groups required fentanyl 50 µg immediately after delivery)	Lumbar Epidural via PCEA	Loading dose of 900 µg hydromorphone, then PCEA hydromorphone 150 µg bolus, 30-minute lockout	24 hours
Parker 1992	EPI-PCA Phase 2	Intervention	41	Epidural	Epidural - 0.5% bupivacaine (5 participants - unclear which groups required fentanyl 50 µg immediately after delivery)	Lumbar Epidural via PCEA	Loading dose of 225 µg hydromorphone, then PCEA hydromorphone 150 µg bolus, 30-minute lockout	24 hours
Parker 1992	IV-PCA	Control	49	Epidural	Epidural - 0.5% bupivacaine (5 participants - unclear which groups required fentanyl 50 µg immediately after delivery)	IVPCA	Hydromorphone 150 µg bolus, 10-minute lockout	24 hours
Schricker 2000	Epidural	Intervention	8	GA + epidural	Isoflurane/oxygen/nitrous oxide Epidural - 0.5% bupivacaine bolus to establish	Epidural at T10 to T12 via CEA	0.1% bupivacaine + 2 µg/mL fentanyl via CEA to maintain T8 to L3 blockade	24 hours

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					bilateral block to T4, then 0.25% bupivacaine bolus for maintenance			
Schricker 2000	Control	Control	8	GA	Isoflurane/oxygen/nitrous oxide fentanyl 3 µg/kg	IVPCA	Morphine 1 to 2 mg bolus, 8- minute lockout	24 hours
Schumann 2003	Group B	Intervention	36	GA + epidur- al	Isoflurane/oxygen/nitrous oxide Epidural - drugs not listed	Thoracic epidural via CEA + NSAID	0.1% bupivacaine + 1 mg/mL pethidine up to 14 mL/h NSAID - ketorolac 30 mg 4 times daily until able to take orally, then ibuprofen 600 mg 4 times daily orally until day 5 postop	48 hours
Schumann 2003	Group C	Control	32	GA	Isoflurane/oxygen/nitrous oxide	IVPCA + NSAID	Morphine loading 2.5 mg every 5 minutes up to 10 mg un- til pain controlled, then IVP- CA morphine 2.5 mg bolus, 8- minute lockout. NSAID - ketorolac 30 mg 4 times daily until able to take orally, then ibuprofen 600 mg 4 times daily until day 5 postop	48 hours
Schumann 2003	Group A	Control + In- filtration	37	GA + LA infil- tration	Isoflurane/oxygen/nitrous oxide LA - infiltration 40 to 45 mL 0.25% bupivacaine + adrenaline 1:200,000 pre-incision, and then the same amount before extu- bation	IVPCA + NSAID	Morphine loading 2.5 mg every 5 minutes up to 10 mg un- til pain controlled, then IVP- CA morphine 2.5 mg bolus, 8- minute lockout. NSAID - ketorolac 30 mg 4 times daily until able to take orally, then ibuprofen 600 mg 4 times daily until day 5 postop	48 hours
Steinberg 2002	PCEA	Intervention	20	GA + epidur- al	Isoflurane/oxygen/nitrous oxide Epidural - 6 to 10 mL of 0.75% ropivacaine + 0.2% ropivacaine + 2 µg/mL fentanyl infusion at 8 to	Epidural at T7 to T10 via PCEA + NSAID	0.2% ropivacaine + 2 µg/mL fentanyl 4 mL/h background, bolus 2 mL, 15-minute lockout	72 hours

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					10 mL/h, 5 mL bolus as required every 15 minute for hypertension			
Steinberg 2002	IVPCA	Control	21	GA	Isoflurane/oxygen/nitrous oxide morphine 0.1 mg/kg after intubation before incision	IVPCA + NSAID	Morphine 2 to 3 mg bolus in PACU until pain score < 50 mm, then IVPCA 1 mg bolus, 8-minute lockout. Ketorolac 15 mg intramuscular or IV 4 times daily for 3 days, then ibuprofen 400 mg 4 times daily until discharge or day 6	72 hours
Taqi 2007	Epidural	Intervention	25	GA + epidural	Desflurane/oxygen Epidural - 0.5% bupivacaine max 20 mL to establish block from T4 to L4, + hourly boluses 0.25% bupivacaine 5 to 10 mL	Epidural at T8 to T9 via CEA + NSAID + paracetamol	0.1% bupivacaine + 3 µg/mL fentanyl at 5 to 15 mL/h. 500 mg naproxen twice daily (orally or per rectum) for 4 days. Paracetamol 1 g 4 times daily (orally) for 4 days	2.8 days ± 0.6 days
Taqi 2007	IVPCA	Control	25	GA	Desflurane/oxygen/250 µg fentanyl	IVPCA + NSAID + paracetamol	Morphine 1 to 2 mg bolus, 5-minute lockout. 500 mg naproxen twice daily (oral or per rectum) for 4 days. Paracetamol 1 g 4 times daily (orally) for 4 days	3.1 days ± 0.5 days
Tsui 1997	Group EPI	Intervention	57	GA + epidural	Isoflurane/oxygen/nitrous oxide/fentanyl Epidural - 3 mL 0.5% bupivacaine (test dose), then 0.25% bupivacaine up to 0.2 mL/kg	Epidural at L2 to L4 via CEA	0.0625% bupivacaine + 3.3 µg/mL fentanyl at 0 to 15 mL/h	48 hours
Tsui 1997	Group IVPCA	Control	54	GA + epidural	Isoflurane/oxygen/nitrous oxide/fentanyl Epidural - 3 mL 0.5% bupivacaine (test dose), then	IVPCA	Morphine 1 mg bolus, 5-minute lockout. Max 0.1 mg/kg/h	48 hours

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					0.25% bupivacaine up to 0.2 mL/kg			
Wang 2004	Group E	Intervention	10	Epidural	Epidural - 2% lidocaine 4 to 5 mL, then 0.75% bupivacaine 8 to 10 mL. 0.75% bupivacaine 8 to 10 mL was repeated every 50 to 60 minutes through operation.	Epidural at L1 to L2 via PCEA	Bupivacaine 0.125% + fentanyl 2 µg/mL: background 2 to 3 mL/h, bolus 3 mL 15-minute lockout. Max 15 mL/h	3 days
Wang 2004	Group G + E	Intervention	10	GA + epidural	Isoflurane/oxygen/fentanyl 2 to 3 µg/kg Epidural - 2% lidocaine 4 to 5 mL, then 0.75% bupivacaine 8 to 10 mL. 0.75% bupivacaine 8 to 10 mL was repeated every 50 to 60 minutes through operation.	Epidural at L1 to L2 via PCEA	Bupivacaine 0.125% + fentanyl 2 µg/mL: background 2 to 3 mL/h, bolus 3 mL 15-minute lockout. Max 15 mL/h	3 days
Wang 2004	Group G	Control	10	GA	Isoflurane/oxygen/fentanyl 2 to 3 µg/kg	IVPCA	Fentanyl 3 µg/h background, bolus 15 µg, 10-minute lockout. 60 to 70 µg/h max	3 days
Welchew 1991	Epidural	Intervention	10	GA	Halothane/oxygen/nitrous oxide	Epidural at T7 to T8 via PCEA	Fentanyl 100 µg loading, then 5 µg bolus, 2-minute lockout	24 hours
Welchew 1991	Intravenous	Control	10	GA	Halothane/oxygen/nitrous oxide	IVPCA	Fentanyl 100 µg loading, then 20 µg bolus, 2-minute lockout	24 hours
Yosunkaya 2003	Group PCEM	Intervention	20	GA + epidural	Isoflurane/oxygen/nitrous oxide/fentanyl/tenoxicam Epidural - 1.5% lidocaine with 1:200,000 adrenaline 8 to 11 mL	Epidural at T6 to T8 via PCEA	Morphine 2 mg loading, then 0.2 mg/h background, 0.5 mg bolus with 30-minute lockout. 4 hours maximum 3 mg	48 hours
Yosunkaya 2003	Group PCIM	Control	20	GA	Isoflurane/oxygen/nitrous oxide/fentanyl/tenoxicam	IVPCA	Morphine 2 mg loading, then 0.3 mg/h background, 1 mg bolus, 15-minute lockout	48 hours

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Zeng 2003	M Group	Control	8	GA	Isoflurane/oxygen/nitrous oxide/fentanyl	IVPCA	Morphine 1 mg bolus, 6-minute lockout, 0.5 mg/h background infusion	24 hours
Zeng 2003	EM Group	Control	8	GA + epidural	Isoflurane/oxygen/nitrous oxide/fentanyl Epidural - bolus of 4 mL of 2% lidocaine then maintenance of 4 to 6 mL of 2% lidocaine and 0.33% tetracaine mix	IVPCA	Morphine 1 mg bolus, 6-minute lockout, 0.5 mg/h background infusion	24 hours
Zeng 2003	RF Group	Intervention	8	GA + epidural	Isoflurane/oxygen/nitrous oxide/fentanyl Epidural - bolus of 4 mL of 2% lidocaine then maintenance of 4 to 6 mL of 2% lidocaine and 0.33% tetracaine mix	PCEA	0.12% ropivacaine + 2 µg/mL fentanyl: 4 mL/h background infusion, 2 mL bolus, 20-minute lockout	24 hours
Zeng 2003	BF Group	Intervention	9	GA + epidural	Isoflurane/oxygen/nitrous oxide/fentanyl Epidural - bolus of 4 mL of 2% lidocaine then maintenance of 4 to 6 mL of 2% lidocaine and 0.33% tetracaine mix	PCEA	0.12% bupivacaine + 2 µg/mL fentanyl: 4 mL/h background infusion, 2 mL bolus, 20-minute lockout	24 hours
Zeng 2003	BM Group	Intervention	9	GA + epidural	Isoflurane/oxygen/nitrous oxide/fentanyl Epidural - bolus of 4 mL of 2% lidocaine then maintenance of 4 to 6 mL of 2% lidocaine and 0.33% tetracaine mix	PCEA	0.12% bupivacaine + 8 µg/mL morphine: 4 mL/h background infusion, 2 mL bolus, 20-minute lockout	24 hours
Zutshi 2005	Epidural	Intervention	31	GA + ? epidural	Drugs not specified.	Epidural at T8 to T10 via PCEA	Bupivacaine + fentanyl with background, and bolus 2 to 4 mL, 15-minute lockout. Concentration not specified.	48 hours

(Continued)

Zutshi 2005	IVPCA	Control	28	GA	Drugs not specified.	IVPCA	Morphine - IVPCA protocol not given	48 hours
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Acronyms and abbreviations used in this appendix

CEA: continuous epidural analgesia; GA: general anaesthesia; IMI: intramuscular injection; IV: intravenous; IVN: intravenous narcotic; IVPCA: intravenous patient-controlled analgesia; LA: local anaesthesia; MMA: multimodal analgesia; NSAID: non-steroidal anti-inflammatory drug; PACU: postanaesthesia care unit; PCA: patient-controlled analgesia; PCEA: patient-controlled epidural analgesia; POD: postoperative day; T: thoracic vertebra

WHAT'S NEW

Date	Event	Description
4 October 2018	Amended	Acknowledgement section amended to include Co-ordinating Editor

CONTRIBUTIONS OF AUTHORS

Jon H Salicath and Emily CY Yeoh contributed equally to this review.

Jon H Salicath: data collection, authorship of the Background, Results, and Discussion sections, 'Risk of bias' analysis, data analysis, and proofreading.

Emily CY Yeoh: data collection, planning and authorship of the Methods, Results, and Discussion sections, data analysis, and proofreading.

Michael H Bennett: meta-analytic expert advice, proofreading, and assistance with statistical plan.

DECLARATIONS OF INTEREST

Jon H Salicath: I declare I have not received any payments for research activity, consultancy, honoraria, travel expenses or similar with any relevance to this review. I declare I am a consultant specialist anaesthetist in Australia, however I am currently working as a paediatric anaesthetic consultant at the Great North Children's Hospital/Royal Victoria Infirmary in Newcastle upon Tyne, United Kingdom. I further declare I have no other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what we have written in this review.

Emily CY Yeoh: I declare I have not received any payments for research activity, consultancy, honoraria, travel expenses or similar with any relevance to this review. I declare I am a consultant specialist anaesthetist at Prince of Wales Hospital in Sydney, Australia and Auburn Hospital in Sydney, Australia. I declare I am a consultant pain specialist at Sydney Children's Hospital in Sydney, Australia. I further declare I have no other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what we have written in this review.

Michael H Bennett: I declare I have not received any payments for research activity, consultancy, honoraria, travel expenses or similar with any relevance to this review. I declare I am a consultant specialist anaesthetist at Prince of Wales Hospital in Sydney, Australia. I further declare I have no other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what we have written in this review.

SOURCES OF SUPPORT

Internal sources

- The authors have no source of internal support to declare, Australia.

External sources

- The authors have no source of external support to declare, Australia.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We made the following changes to the published protocol ([Yeoh 2013](#)).

- Title:** we added the word 'adult' to the title to make the population of interest clear. We have changed the order of interventions such that it now states "Epidural analgesia versus patient-controlled analgesia". This brings all sections of the review into alignment and helps remove confusion within the review.

2. **Objectives:** we have clarified the comparators for this review compared to the review it replaces as follows: "The objective of this review is to update and expand a previously published Cochrane Review on IVPCA versus CEA for pain after intra-abdominal surgery with the addition of the comparator PCEA. We have compared IVPCA to both epidural techniques combined (CEA and PCEA), but considered subgroup analysis by epidural technique where appropriate."
3. We added the VAS used as the 0-to-100 scale in the **Types of outcome measures** section.
4. We moved 'pain on coughing' to the secondary outcomes, and kept 'pain at rest and on movement' as primary outcomes to comply with formatting criteria for Cochrane Reviews.
5. We removed the intention to perform a dichotomous analysis for pain score.
6. We clarified the meaning of the **secondary outcome** 'failure of analgesic technique'; it now reads: "The number of failures to establish the allocated technique (defined as a clinical decision to use a second analgesic technique, which could be due to multiple reasons such as failure of insertion of epidural, inadequate analgesia, epidural catheter withdrawal or dislodgement, infection, neurological deficit, etc.)". We have modified the Main results section of the Abstract and the Effects of interventions section of the review accordingly.
7. We amended the electronic searches section on the advice of the Information Specialist (Janne Vendt).
8. **Data extraction and management:** at the request of a peer reviewer, we added the following: "We contacted the authors of individual studies where we could not extract data that were likely to exist."
9. **Data extraction and management:** at the request of a peer reviewer, we added the following: "We only included data from cross-over RCTs prior to cross-over due to concerns with potential carry-over effects."
10. **Assessment of risk of bias in included studies:** at the request of a peer reviewer, we added the following: "We considered cross-over RCTs as at unclear risk of bias for the 'other potential sources of bias' criterion, as we could only use pre-cross-over data for analysis in the review."
11. Added a new section 'Presentation of results' to the Methods at the request of a peer reviewer: "We have adjusted all VAS numbers to a zero (no pain) to 100 (maximum possible pain) scale. We analysed pain at three time points. When there was more than one estimate in a time period, we chose the latest pain score relevant to each phase. We have presented all differences between interventions as positive values to make the direction of benefit clear and to avoid the presentation of a 'negative benefit'."
12. Added to 'Presentation of results': "To assess the clinical significance of differences in pain scores we used as a guide the article 'Measuring acute postoperative pain using the visual analogue scale: the minimal clinically important difference and patient acceptable symptom state' (Myles 2017). The minimal clinically important difference (MCID) is 9.9 mm on the VAS scale. Any analgesic interventions with a change of 10 mm or more out of 100 mm on the VAS scale signify a clinically significant difference."
13. **'Summary of findings' and GRADE:** at the request of a peer reviewer, we added the following: "Problems identified in any of these five domains resulted in downgrading the quality of the evidence one level for each problem."

NOTES

March 2014

This review updates and replaces a previously published Cochrane Review comparing the efficacy of intravenous patient-controlled analgesia (IVPCA) versus continuous epidural analgesia (CEA), most recently updated in 2008 (Werawatganon 2013). That review concluded that CEA was superior to IVPCA in relieving postoperative pain for up to 72 hours in individuals undergoing intra-abdominal surgery. There was an increased rate of pruritus in the CEA group, but insufficient evidence to draw conclusions for other clinical advantages and disadvantages. This revised review includes patient-controlled epidural analgesia in addition to CEA in order to further identify the best strategy.

INDEX TERMS

Medical Subject Headings (MeSH)

*Analgesia, Epidural [adverse effects] [mortality]; *Analgesia, Patient-Controlled [adverse effects] [mortality]; Analgesics, Opioid [therapeutic use]; Pain Measurement; Pain, Postoperative [*drug therapy]; Randomized Controlled Trials as Topic

MeSH check words

Adult; Humans