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Pre-emptive and preventive NSAIDs for postoperative pain in adults undergoing all types of surgery (Review)

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[Intervention Review]

Pre-emptive and preventive NSAIDs for postoperative pain in adults undergoing all types of surgery

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ABSTRACT

Background

Postoperative pain is a common consequence of surgery and can have many negative perioperative effects. It has been suggested that the administration of analgesia before a painful stimulus may improve pain control. We defined pre-emptive nonsteroidal anti-inflammatories (NSAIDs) as those given before surgery but not continued afterwards and preventive NSAIDs as those given before surgery and continued afterwards. These were compared to a control group given the NSAIDs after surgery instead of before surgery.

Objectives

To assess the efficacy of preventive and pre-emptive NSAIDs for reducing postoperative pain in adults undergoing all types of surgery.

Search methods

We searched the following electronic databases: CENTRAL, MEDLINE, Embase, AMED and CINAHL (up to June 2020). In addition, we searched for unpublished studies in three clinical trial databases, conference proceedings, grey literature databases, and reference lists of retrieved articles. We did not apply any restrictions on language or date of publication.

Selection criteria

We included parallel-group randomized controlled trials (RCTs) only. We included adult participants undergoing any type of surgery. We defined pre-emptive NSAIDs as those given before surgery but not continued afterwards and preventive NSAIDs as those given before surgery and continued afterwards. These were compared to a control group given the NSAIDs after surgery instead of before surgery. We included studies that gave the medication by any route but not given on the skin.

Data collection and analysis

We used the standard methods expected by Cochrane, as well as a novel publication bias test developed by our research group. We used GRADE to assess the certainty of the evidence for each outcome. Outcomes included acute postoperative pain (minimal clinically important difference (MCID): 1.5 on a 0-10 scale), adverse events of NSAIDs, nausea and vomiting, 24-hour morphine consumption (MCID:

10 mg reduction), time to analgesic request (MCID: one hour), pruritus, sedation, patient satisfaction, chronic pain and time to first bowel movement (MCID: 12 hours).

Main results

We included 71 RCTs. Seven studies are awaiting classification. We included 45 studies that evaluated pre-emptive NSAIDs and 26 studies that evaluated preventive NSAIDs. We considered only four studies to be at low risk of bias for most domains. The operations and NSAIDs used varied, although most studies were conducted in abdominal, orthopaedic and dental surgery. Most studies were conducted in secondary care and in low-risk participants. Common exclusions were participants on analgesic medications prior to surgery and those with chronic pain.

Pre-emptive NSAIDs compared to post-incision NSAIDs

For pre-emptive NSAIDs, there is probably a decrease in early acute postoperative pain (MD -0.69, 95% CI -0.97 to -0.41; studies = 36; participants = 2032; I^2 = 96%; moderate-certainty evidence). None of the included studies that reported on acute postoperative pain reported adverse events as an outcome. There may be little or no difference between the groups in short-term (RR 1.00, 95% CI 0.34 to 2.94; studies = 2; participants = 100; I^2 = 0%; low-certainty evidence) or long-term nausea and vomiting (RR 0.85, 95% CI 0.52 to 1.38; studies = 5; participants = 228; I^2 = 29%; low-certainty evidence). There may be a reduction in late acute postoperative pain (MD -0.22, 95% CI -0.44 to 0.00; studies = 28; participants = 1645; I^2 = 97%; low-certainty evidence). There may be a reduction in 24-hour morphine consumption with pre-emptive NSAIDs (MD -5.62 mg, 95% CI -9.00 mg to -2.24 mg; studies = 16; participants = 854; I^2 = 99%; low-certainty evidence) and an increase in the time to analgesic request (MD 17.04 minutes, 95% CI 3.77 minutes to 30.31 minutes; studies = 18; participants = 975; I^2 = 95%; low-certainty evidence). There may be little or no difference in opioid adverse events such as pruritus (RR 0.40, 95% CI 0.09 to 1.76; studies = 4; participants = 254; I^2 = 0%; low-certainty evidence) or sedation (RR 0.51, 95% CI 0.16 to 1.68; studies = 4; participants = 281; I^2 = 0%; low-certainty evidence), although the number of included studies for these outcomes was small. No study reported patient satisfaction, chronic pain or time to first bowel movement for pre-emptive NSAIDs.

Preventive NSAIDs compared to post-incision NSAIDs

For preventive NSAIDs, there may be little or no difference in early acute postoperative pain (MD -0.14, 95% CI -0.39 to 0.12; studies = 18; participants = 1140; I^2 = 75%; low-certainty evidence). One study reported adverse events from NSAIDs (reoperation for bleeding) although the events were low which did not allow any meaningful conclusions to be drawn (RR 1.95; 95% CI 0.18 to 20.68). There may be little or no difference in rates of short-term (RR 1.26, 95% CI 0.49 to 3.30; studies = 1; participants = 76; low-certainty evidence) or long-term (RR 0.85, 95% CI 0.52 to 1.38; studies = 5; participants = 456; I^2 = 29%; low-certainty evidence) nausea and vomiting. There may be a reduction in late acute postoperative pain (MD -0.33, 95% CI -0.59 to -0.07; studies = 21; participants = 1441; I^2 = 81%; low-certainty evidence). There is probably a reduction in 24-hour morphine consumption (MD -1.93 mg, 95% CI -3.55 mg to -0.32 mg; studies = 16; participants = 1323; I^2 = 49%; moderate-certainty evidence). It is uncertain if there is any difference in time to analgesic request (MD 8.51 minutes, 95% CI -31.24 minutes to 48.27 minutes; studies = 8; participants = 410; I^2 = 98%; very low-certainty evidence). As with pre-emptive NSAIDs, there may be little or no difference in other opioid adverse events such as pruritus (RR 0.56, 95% CI 0.09 to 3.35; studies = 3; participants = 211; I^2 = 0%; low-certainty evidence) and sedation (RR 0.84, 95% CI 0.44 to 1.63; studies = 5; participants = 497; I^2 = 0%; low-certainty evidence). There is probably little or no difference in patient satisfaction (MD -0.42; 95% CI -1.09 to 0.25; studies = 1; participants = 72; moderate-certainty evidence). No study reported on chronic pain. There is probably little or no difference in time to first bowel movement (MD 0.00; 95% CI -15.99 to 15.99; studies = 1; participants = 76; moderate-certainty evidence).

Authors' conclusions

There was some evidence that pre-emptive and preventive NSAIDs reduce both pain and morphine consumption, although this was not universal for all pain and morphine consumption outcomes. Any differences found were not clinically significant, although we cannot exclude this in more painful operations. Moreover, without any evidence of reductions in opioid adverse effects, the clinical significance of these results is questionable although few studies reported these outcomes. Only one study reported clinically significant adverse events from NSAIDs administered before surgery and, therefore, we have very few data to assess the safety of either pre-emptive or preventive NSAIDs. Therefore, future research should aim to adhere to the highest methodology and be adequately powered to assess serious adverse events of NSAIDs and reductions in opioid adverse events.

PLAIN LANGUAGE SUMMARY

Ibuprofen-like painkillers given before cutting the skin in surgery compared with given after cutting the skin in adults undergoing all types of surgery

We aimed to assess the effect of a single dose of a nonsteroidal anti-inflammatory drug (NSAID: for example, ibuprofen) given before making the first cut during surgery (pre-emptive NSAIDs) or given before the first cut and continued after surgery (preventive NSAIDs) on reducing pain in adults.

Review question

We reviewed the evidence for NSAID painkillers when given before surgery compared to the same painkiller given only after the surgeon has cut the skin in adults undergoing all types of surgery.

Background
Most people experience pain after surgery that requires strong opioid (similar to morphine) painkillers. These medications are associated with a number of side effects including reduced breathing, a slow heart rate, and low blood pressure, as well as vomiting, sleepiness, itching, and constipation. Reducing the amount of opioids needed after surgery can limit these side effects and improve the patient experience and outcomes. Compared to starting painkillers later, beginning painkillers before making the first cut for surgery may reduce pain sensitivity, and thus lessen the pain experienced. We wanted to find out whether giving NSAID painkillers before surgery was more effective than giving the same painkiller, at the same dose, after surgery.

Study characteristics
We searched the medical literature for randomized controlled trials (a type of study in which participants are assigned to a treatment group using a random method). The evidence is current to June 2020. Patients were randomly allocated to one of two groups. One group was treated with NSAIDs before the surgeon cut the skin, whilst the other group was given the same medication after the surgeon cut the skin. We found 71 trials with patients aged 18 years or over who were undergoing many different operations. Nearly all patients were fit and healthy undergoing procedures in hospitals around the world.

Key results
In 36 trials (2032 patients), use of pre-emptive NSAIDs resulted in a small reduction in the pain experienced in the first six hours after surgery. No studies included serious side effects from NSAIDs as an outcome (bleeding, heart attacks or kidney failure). There was no difference in nausea and vomiting after surgery. In 28 studies (1645 patients), there was no difference in pain at 24 to 48 hours after surgery. In 16 studies (854 patients) there was a reduction in the amount of strong painkillers used after surgery and an increase in the time until patients needed these strong painkillers. Despite this, we found no reduction in the side effects from these strong painkillers (itching or sleepiness). No studies reported patient satisfaction, long-term pain after surgery or the time until patients opened their bowels.

For preventive NSAIDs, in 18 studies (1140 patients), there was no difference in the pain experienced in the first six hours after surgery. One study reported bleeding after surgery requiring another operation and found no difference, although there were not enough events to be certain of this result. There was no difference in nausea and vomiting. In 21 studies (1441 patients), there was a reduction in pain at 24 to 48 hours after surgery and in 16 studies (1323 patients) a reduction in the amount of strong painkillers used after surgery. There was no difference in the time to requesting strong painkillers. There was no difference in itching, sleepiness or patient satisfaction. No study reported long-term pain. There was no difference in time to first bowel movement.

Certainty of the evidence
Although we found some differences in pain and painkiller usage, the certainty of the evidence ranged from very low to moderate. Also, any differences found were not large enough for patients to consider important. This was due to deficiencies in how the studies were conducted, the small numbers of patients recruited for some outcomes and differences in the results between studies, which means we are uncertain any differences we found are real and, therefore, future research is required.

SUMMARY OF FINDINGS

Summary of findings 1. Summary of findings

Pre-emptive NSAIDs compared with post-incision NSAIDs for postoperative pain

Patient or population: adults undergoing surgery

Settings: secondary care and dental clinics

Intervention: pre-emptive NSAIDs

Comparison: post-incision NSAIDs

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Post-incision NSAIDs	Pre-emptive NSAIDs				
Early acute postoperative pain (within 6 hours postoperatively using a validated pain scale: 0, no pain to 10, maximum pain)	The mean pain ranged across post-incision groups from 0.32 to 6.37	**Overall** MD -0.69 (95% CI -0.97 to -0.41) **Mild pain** MD -0.24 (95% CI -0.51 to 0.03) **Moderate pain** MD -1.19 (95% CI -1.52 to -0.86) **Severe pain** MD -1.44 (95% CI -2.28 to -0.59)		2032 (36)	⊕⊕⊕⊖ **moderate**[1]	Results not clinically significant
Adverse events	N/A	N/A	N/A	N/A	N/A	No study reported this outcome
Nausea and vomiting (1-6 hours postoperatively)	120 per 1000	120 per 1000 (41 to 353)	**RR 1.00** (0.34 to 2.94)	100 (2)	⊕⊕⊖⊖ **low**[2]	

Nausea and vomiting (6-48 hours postoperatively)	336 per 1000	278 per 1000 (175 to 464)	**RR 0.85** (0.52 to 1.38)	228 (5)	⊕⊕⊖⊖ **low[2]**	
Late acute postoperative pain (24-48 hours postoperatively using a validated pain scale: 0, no pain to 10, maximum pain)	The mean pain ranged across post-incision groups from 0.25 to 3.49	**Overall** MD -0.22 (95% CI -0.44 to 0.00) **Mild pain** MD -0.14 (95% CI -0.37 to 0.10) **Moderate pain** MD -0.77 (95% CI -1.08 to 0.47)		1645 (28)	⊕⊕⊖⊖ **low[3]**	Results not clinically significant
24-hour morphine consumption (mg)	The mean morphine consumption ranged across post-incision groups from 1.97 mg to 122.75 mg	**Overall** MD -5.62 mg (95% CI -9.00 mg to -2.24 mg) **Low consumption** MD -2.66 mg (95% CI -4.54 mg to -0.79 mg) **Medium consumption** MD -5.46 mg (95% CI -10.73 mg to -0.19 mg) **High consumption** MD -15.22 mg (95% CI -29.67 mg to -0.77 mg)		854 (16)	⊕⊕⊖⊖ **low[3]**	Results not clinically significant
Time to first analgesic request (mean time in minutes)	The mean time ranged across post-incision groups from 29.6 minutes to 1146 minutes	MD 17.04 minutes (95% CI 3.77 minutes to 30.31 minutes)		975 (18)	⊕⊕⊖⊖ **low[3]**	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

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

Very low certainty: We are very uncertain about the estimate.

[1]Downgraded owing to concerns over risk of bias (one level)
[2]Downgraded owing to concerns over risk of bias (one level) and imprecision (one level)
[3]Downgraded owing to concerns over risk of bias (one level) and unexplained heterogeneity (one level)

Abbreviations:
CI: confidence intervals
MD: mean difference
mg: milligrams
N/A: not applicable
No: number
NSAIDs: nonsteroidal anti-inflammatory drugs
RR: risk ratio

Summary of findings 2. Summary of findings

Preventive NSAIDs compared with post-incision NSAIDs for postoperative pain

Patient or population: adults undergoing surgery

Settings: secondary care and dental clinics

Intervention: preventive NSAIDs

Comparison: post-incision NSAIDs

Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of Participants (studies)**	**Certainty** of the evidence (GRADE)	**Comments**
	Assumed risk	**Corresponding risk**				
	Post-incision NSAIDs	**Preventive NSAIDs**				
Early acute postoperative pain (within 6 hours postoperatively using a validated pain scale: 0, no pain to 10, maximum pain)	The mean pain ranged across post-incision groups from 0.18 to 6.42	**Overall** MD -0.14 (95% CI -0.39 to 0.12) **Mild pain** MD -0.04 (95% CI -0.31 to 0.24) **Moderate pain** MD -0.24 (95% CI -0.92 to 0.45) **Severe pain**		1140 (18)	⊕⊕⊖⊖ **low[1]**	

		MD -0.80 (95% CI -1.23 to -0.37)				
Adverse events (Re-operation for bleeding (reoperation for major bleeding within 30 days (yes/no)))	25 per 1000	49 per 1000 (5 to 517)	**RR 1.95** (0.18 to 20.68)	81 (1)	⊕⊕⊖⊖ **very low[2]**	Study performed in tonsillectomy so unclear for other operations. Other adverse events not reported
Nausea and vomiting (1-6 hours postoperatively)	162 per 1000	205 per 1000 (79 to 535)	**RR 1.26** (0.49 to 3.30)	76 (1)	⊕⊕⊕⊖ **low[3]**	
Nausea and vomiting (6-48 hours postoperatively)	245 per 1000	282 per 1000 (159 to 299)	**RR 0.89** (0.65 to 1.22)	456 (8)	⊕⊕⊖⊖ **low[4]**	
Late acute postoperative pain (24-48 hours postoperatively using a validated pain scale: 0, no pain to 10, maximum pain)	The mean pain ranged across post-incision groups from 0.42 to 4.6	**Overall** MD -0.33 (95% CI -0.59 to -0.07) **Mild pain** MD -0.33 (95% CI -0.62 to -0.05) **Moderate pain** MD -0.23 (95% CI -0.65 to 0.19)		1441 (21)	⊕⊕⊖⊖ **low[1]**	Results not clinically significant
24-hour morphine consumption (mg)	The mean morphine consumption ranged across post-incision groups from 1.08 mg to 42.31 mg	**Overall** MD -1.93 mg (95% CI -3.55 mg to -0.32 mg) **Low consumption** MD -0.32 mg (95% CI -0.40 mg to -0.24 mg) **Medium consumption** MD -3.77 mg (95% CI -7.27 mg to -0.26 mg)		1323 (16)	⊕⊕⊕⊖ **moderate[5]**	Results not clinically significant
Time to first analgesic request (mean time in minutes)	The mean time ranged across post-incision	MD 8.51 minutes (95% CI -31.24 minutes to 48.27 minutes)		410 (8)	⊕⊖⊖⊖ **very low[6]**	

			groups from 3.15 minutes to 523.1 minutes		

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

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

[1]Downgraded owing to concerns over risk of bias (one level) and unexplained heterogeneity (one level)
[2]Downgraded owing to concerns over imprecision (two levels) and indirectness of evidence (one level)
[3]Downgraded owing to concerns over imprecision (one level) and indirectness of evidence (one level)
[4]Downgraded owing to concerns over risk of bias (one level) and imprecision (one level)
[5]Downgraded owing to concerns over risk of bias (one level)
[6]Downgradedowing to concerns over imprecision (one level), risk of bias (one level) and unexplained heterogeneity (one level)

Abbreviations:
CI: confidence intervals
MD: mean difference
mg: milligrams
N/A: not applicable
No: number
NSAIDs: nonsteroidal anti-inflammatory drugs
RR: risk ratio

BACKGROUND

This review contains text from a previous Cochrane protocol and review on pre-emptive and preventive opioids (Doleman 2017a; Doleman 2018b). Throughout the review, we have used nonsteroidal anti-inflammatory drugs (NSAIDs) as an umbrella term which consists of non-selective NSAIDs (no specific enzyme activity) and cyclooxygenase-2 (COX-2) inhibitors (specific for COX-2 enzyme).

Description of the condition

Postoperative pain is a common consequence of surgery that affects around 80% of patients. The severity of postoperative pain is variable, with 18% to 25% of patients suffering extreme pain (Apfelbaum 2003; Gerbershagen 2014). Pain can have deleterious effects during the postoperative period, including patient dissatisfaction (Myles 2000), interference with daily activities (Strassels 2002), pulmonary complications (Desai 1999), increases in the stress response to surgery (Desborough 2000), and an increased risk of chronic postsurgical pain (Kehlet 2006). Risk factors for severe postoperative pain include gender (Gerbershagen 2014), age (Gerbershagen 2014), the presence of preoperative pain (Gerbershagen 2014), preoperative anxiety and the type of surgery (Ip 2009). Intravenous opioids are commonly used to treat pain in the postoperative period (Benhamou 2008), however, their use is associated with many side effects such as vomiting, pruritus (itching), sedation (sleepiness) and patient concerns over addiction (Apfelbaum 2003). Therefore, alternative strategies to manage both postoperative pain and reduce postoperative opioid consumption may have important benefits for patients undergoing surgery (Frauenknecht 2019; Zhao 2004).

Description of the intervention

Nonsteroidal anti-inflammatory drugs (NSAIDs) are a commonly used analgesic during the peri-operative period and include as examples: ibuprofen, naproxen, diclofenac and ketorolac. The mechanism of action of NSAIDs involves inhibition of cyclooxygenase (COX) enzymes, which are involved in the formation of hyperalgesic compounds called prostaglandins (Burian 2005). NSAIDs are effective in reducing postoperative pain, even when added to standard regimens including paracetamol (Ong 2010; Thybo 2019). Adverse events around the peri-operative period include possible increases in bleeding (Warltier 2003), acute kidney injury and gastrointestinal ulceration (Gilron 2003). However, newer COX-2-specific agents that do not target gastrointestinal COX-1 may offer lower occurrence of gastrointestinal ulceration compared with traditional NSAIDs (Jüni 2002), although studies have suggested an increased risk of cardiac events in high-risk patients (Nussmeier 2005). Examples of these agents include celecoxib, parecoxib and rofecoxib.

Pre-emptive analgesia involves the initiation of an analgesic agent (painkiller) prior to surgical incision (before the surgeon cuts the skin). It is thought that by initiating analgesic interventions before surgical injury, the analgesic can provide reductions in intra-operative nociception to the central nervous system and, therefore, provide superior pain relief compared with the same analgesic given post-incision (after the surgeon has cut the skin) (Kissin 2000). Preventive analgesia extends this definition to include increasing the intensity and duration of pre-emptive analgesic interventions until final wound healing (Dahl 2011).

How the intervention might work

Surgical incision promotes changes in both the central and peripheral nervous system, called sensitization. Such sensitization can cause biochemical changes which manifest as hyperalgesia (the same pain stimulus causing increased pain), and allodynia (normal sensations causing pain). It is thought that by initiating analgesia before surgical incision, both peripheral and central sensitization can be reduced, resulting in reductions in intra-operative nociception, and later, both acute and chronic postoperative pain. Preventive analgesia extends this reduction in sensitization to include the postoperative period. This enhanced definition came from an increased understanding of the development of persistent postsurgical pain, which is associated with postoperative sensitization. Postoperative sensitization may only be reduced by continuing analgesia longer into the postoperative period (Dahl 2011). As opioids are commonly used to treat pain postoperatively (Benhamou 2008), any reductions in opioid use may also result in a reduction in opioid adverse events (Doleman 2015b; Zhao 2004), and improve the patient experience.

Why it is important to do this review

Due to both its common occurrence (Apfelbaum 2003; Gerbershagen 2014), and potential deleterious effects during the postoperative period, reducing postoperative pain is an important clinical issue. A simple change in clinical practice, such as changing the timing of administration of analgesics, could have important implications for postoperative pain management. Moreover, such a change is cost-neutral and therefore may benefit both anaesthetists in low-income countries and those working within healthcare systems with finite resources (such as the National Health Service (NHS) in the United Kingdom).

The first review to examine the clinical effects of pre-emptive analgesia showed pre-emptive NSAIDs were ineffective in reducing pain scores or analgesic consumption in most of the included trials when compared to post-incision NSAIDs (Møiniche 2002). A second review, published a few years later, demonstrated a lower analgesic consumption and delayed time to first analgesic request with pre-emptive NSAIDs (Ong 2005). However, these reviews are now outdated and, importantly, did not evaluate reductions in opioid side effects (from reduced postoperative opioid consumption) and potential NSAID adverse events. This mandates an updated review of the evidence.

OBJECTIVES

To evaluate in adult participants undergoing all types of surgery, the effects of pre-emptive and preventive nonsteroidal anti-inflammatory drugs (NSAIDs) compared with post-incision NSAIDs for reducing postoperative pain and opioid consumption.

METHODS

Criteria for considering studies for this review

Types of studies

We included parallel-group, randomized controlled trials (RCTs) only. We considered studies that did and did not use a double-dummy placebo (for example, intervention group receives active drug before incision and placebo after incision; control group receives placebo before incision and active drug after incision).

We excluded studies that included paediatric participants and pharmacokinetic studies not reporting any clinical outcomes.

Types of participants

Adult patients (18 years and above), both male and female, undergoing any type of surgery. We did not include studies that included both adult and paediatric participants.

Types of interventions

We compared both pre-emptive nonsteroidal anti-inflammatory drugs (NSAIDs) and preventive NSAIDs (intervention groups) with post-incision NSAIDs (control group). We defined:

1. pre-emptive NSAIDs as NSAIDs initiated before incision but not continued postoperatively;
2. preventive NSAIDs as NSAIDs initiated before surgical incision and continued postoperatively; and
3. post-incision NSAIDs as the same analgesic intervention initiated after surgical incision, whether single dose (as comparator with pre-emptive analgesia) or continued postoperatively (as comparator with preventive analgesia) (control group).

We only compared interventions if identical analgesics with identical dosages were used. In addition, we only included studies if concurrent use of other multimodal analgesic agents during the peri-operative period were identical, in order to avoid confounding. If the studies reported multiple intervention subgroups that had comparable control groups (identical interventions), we combined these into one group using recommended methods (Higgins 2011a). We included all types of non-selective NSAIDs and COX-2 inhibitors, at any dose, via any route of systemic administration (oral and parenteral but not topical administration) and all types of regimen (pre-emptive or preventive) in the analysis.

Types of outcome measures

Primary outcomes

1. Early acute postoperative pain (measured within six hours postoperatively using a validated pain scale; converted to a 0 to 10 scale where a 0 to 100 scale was used; and where multiple time points were reported, we included the earliest time point reported after post-incision dosing).
2. Adverse events (reoperation for major bleeding within 30 days (yes/no)); acute kidney injury within 48 hours (defined using published criteria (Mehta 2007) (yes/no)); gastrointestinal ulceration or bleeding requiring endoscopy within 30 days (yes/no); myocardial infarction within 30 days (defined as two of three of the following: chest pain, electrocardiogram (ECG) changes indicating ischaemia, or > 20% rise in high-sensitivity troponin (yes/no)). We reported these adverse events separately.

Secondary outcomes

1. Nausea and vomiting (self-reported by the patient or requirement for anti-emetic; we reported nausea and vomiting aggregated (yes/no)).
2. Late acute postoperative pain (measured at 24 to 48 hours postoperatively using a validated pain scale; converted to a 0 to 10 scale where a 0 to 100 scale was used; and where multiple time points were reported, we included the earliest time point reported).
3. 24-hour morphine consumption (mg) (if alternative opioids were used, we converted these to morphine-equivalents using standard conversion factors (Doleman 2018a)).
4. Time to first analgesic request (minutes).
5. Pruritus (self-reported by the patient (yes/no)).
6. Sedation (as defined in the individual studies (yes/no)).
7. Patient satisfaction (overall satisfaction self-reported by the patient within 24 hours; converted to a 0 to 10 scale where a 0 to 100 scale was used).
8. Chronic pain (yes/no, measured three to six months postoperatively using a validated scale, such as the Visual Analogue Scale or the McGill Pain Questionnaire; we included the earliest time point closest to three months). We reported this outcome as a separate dichotomous and continuous outcome.
9. Time to first bowel movement (hours).

For the secondary outcomes where time points were not specified, we used the end point closest to two hours (one to six hours) to assess immediate short-term effects, and the end point closest to 24 hours (six to 48 hours) to assess longer-term effects. Outcomes did not form part of the study eligibility assessment, and so we included studies that met the participant, intervention and comparison criteria for inclusion in the review even if they reported no relevant outcomes. For the continuous outcomes, we considered the following to be minimal clinically important differences:

• Acute postoperative pain: 1.5 on a 0-10 scale (Gallagher 2001; Myles 2017)

• 24-hour morphine consumption: 10 mg reduction (Doleman 2015a)

• Time to analgesic request: one hour

• Time to first bowel movement: 12 hours.

Search methods for identification of studies

Electronic searches

We identified RCTs through literature searching designed to identify relevant trials as outlined in Chapter 4 of the *Cochrane Handbook of Systematic Reviews of Interventions* (Lefebvre 2019). We searched relevant systematic reviews for further trials (Møiniche 2002; Ong 2005). We did not apply restrictions due to language, publication status or publication year. We searched the following databases for relevant trials (Figure 1).

Figure 1. Study flow diagram.

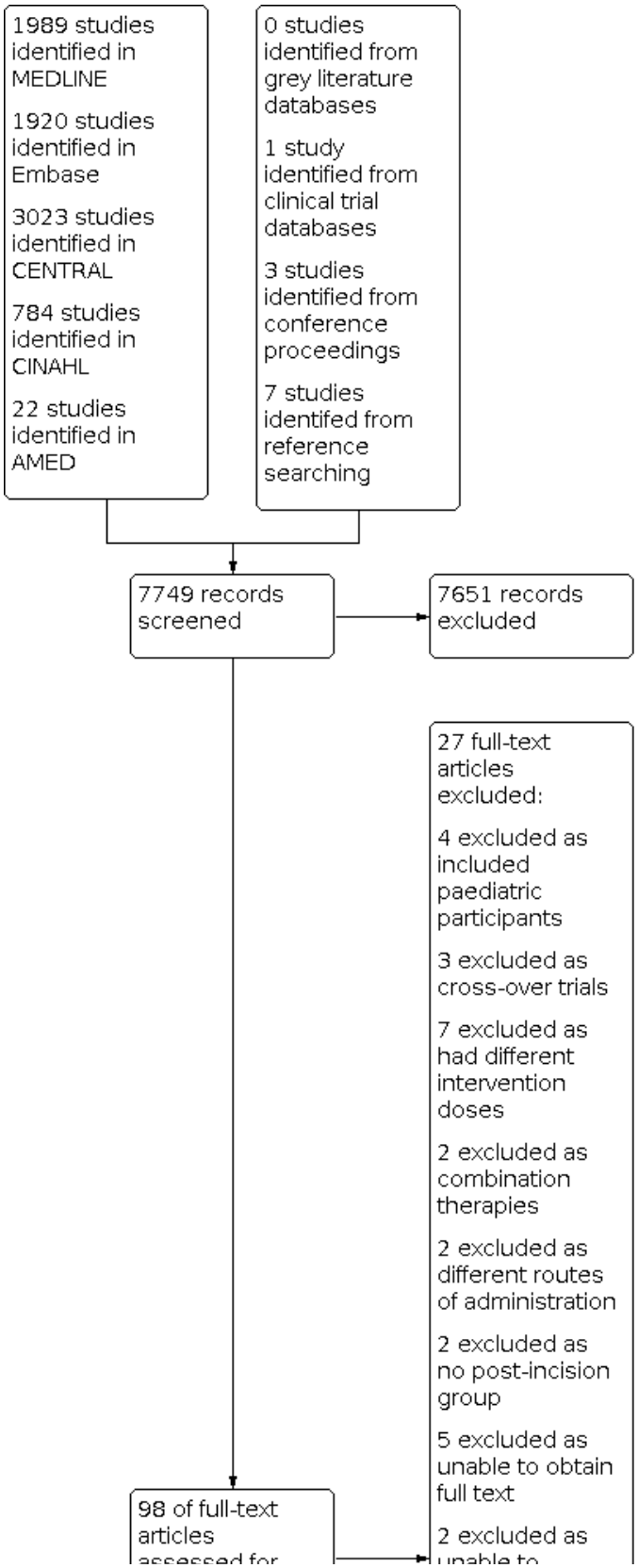
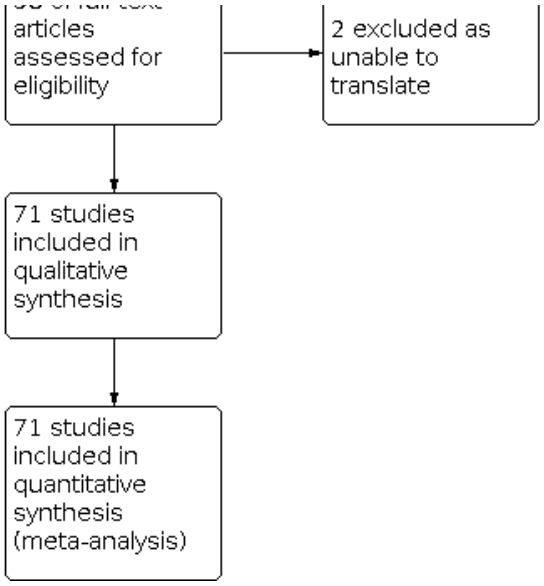


Figure 1. (Continued)



1. Cochrane Central Register of Controlled Trials (CENTRAL, latest Issue) in the Cochrane Library.
2. MEDLINE (Ovid SP, 1946 to June 2020).
3. Embase (Ovid SP, 1974 to June 2020).
4. CINAHL (1982 to June 2020).
5. AMED (1985 to June 2020).

We developed a draft search strategy for MEDLINE. We used this as the basis for the search strategies in the other databases listed (Appendix 1).

We scanned the following trials registries for ongoing and unpublished trials.

1. World Health Organization International Clinical Trials Registry Platform (www.who.int/ictrp/en);
2. ClinicalTrials.gov (clinicaltrials.gov).

Searching other resources

We conducted a search of the OpenSIGLE database to identify grey literature sources. We scanned the reference lists and citations of included trials and systematic reviews identified for further references to additional trials. When necessary, we contacted trial authors for additional information. In addition, we searched the following conference proceedings to identify further unpublished studies (all years considered).

1. World Congress on Pain (International Association for the Study of Pain).
2. Anaesthetic Research Society Meetings.
3. Association of Anaesthetists of Great Britain and Ireland Winter Symposium and Annual Congress.
4. American Society of Anesthesiologists Annual Meeting.
5. European Society of Anaesthesiologists Euroanaesthesia Conference.

The search strategy was developed in consultation with the Cochrane Anaesthesia Information Specialist.

Data collection and analysis

Selection of studies

We used two review authors (BD and JPW) to independently screen the identified studies using the inclusion criteria to assess eligibility. BD and JPW resolved any disagreements by consensus. If disagreement still existed following discussion, we consulted a third review author (JLB). BD and JPW used the information from the retrieved reports to help identify any duplicate publications, such as author name, study centre, type and dose of interventions used, and study dates. We linked any duplicate publications. We inputted details of all potentially eligible studies into PubMed to identify any retracted publications and we excluded these (Eisenach 2009).

Data extraction and management

We extracted data onto an electronic database using standardized data extraction forms (Appendix 2). We performed this independently using two review authors (BD and TH/HBC/LC), and resolved any disagreements by consensus. If disagreement still existed, we consulted a third review author (JPW). We performed the analysis using one review author (BD). Where possible, we translated non-English language studies and extracted data following translation. If data were not contained within the original research report, we contacted the corresponding author, irrespective of the age of publication. We extracted the following information:

1. Bibliographic data, including date of completion/publication.
2. Country.
3. Publication status.
4. Source of funding.
5. Trial design, e.g. parallel-group.
6. Study setting.
7. Number of participants randomized to each trial arm and number included in final analysis.

8. Eligibility criteria and key baseline participant data, including sex and age.
9. Details of treatment regimen received by each group.
10. Details of any co-interventions.
11. Primary and secondary outcome(s) (with definitions and, where applicable, time points).
12. Outcome data for primary and secondary outcomes (by group).
13. Duration of follow-up.
14. Number of withdrawals (by group) and number of withdrawals (by group) due to adverse events.
15. Adverse events.

Assessment of risk of bias in included studies

We assessed risk of bias in the included studies using the Cochrane tool for assessing risk of bias (Higgins 2011b). Two review authors (BD and JPW) independently undertook assessment of risk of bias and reached agreement by consensus. We assessed risk of bias for the domains of sequence generation, allocation concealment, blinding of participants, study personnel and outcome assessors, incomplete outcome data, selective outcome reporting and other sources of bias. We assessed each domain as being at low, unclear or high risk of bias (Higgins 2011b). We presented the results in both a risk of bias summary (Figure 2) and a risk of bias graph (Figure 3). We considered a study as being at low risk of bias if it was low risk for all domains (except selective reporting bias, as some studies were published before published protocols and clinical trial databases were standard) with no high-risk domains and as being at high risk of bias if it was high risk in any domain. Studies were assessed as being at unclear risk if they were not classified into either low or high risk.

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

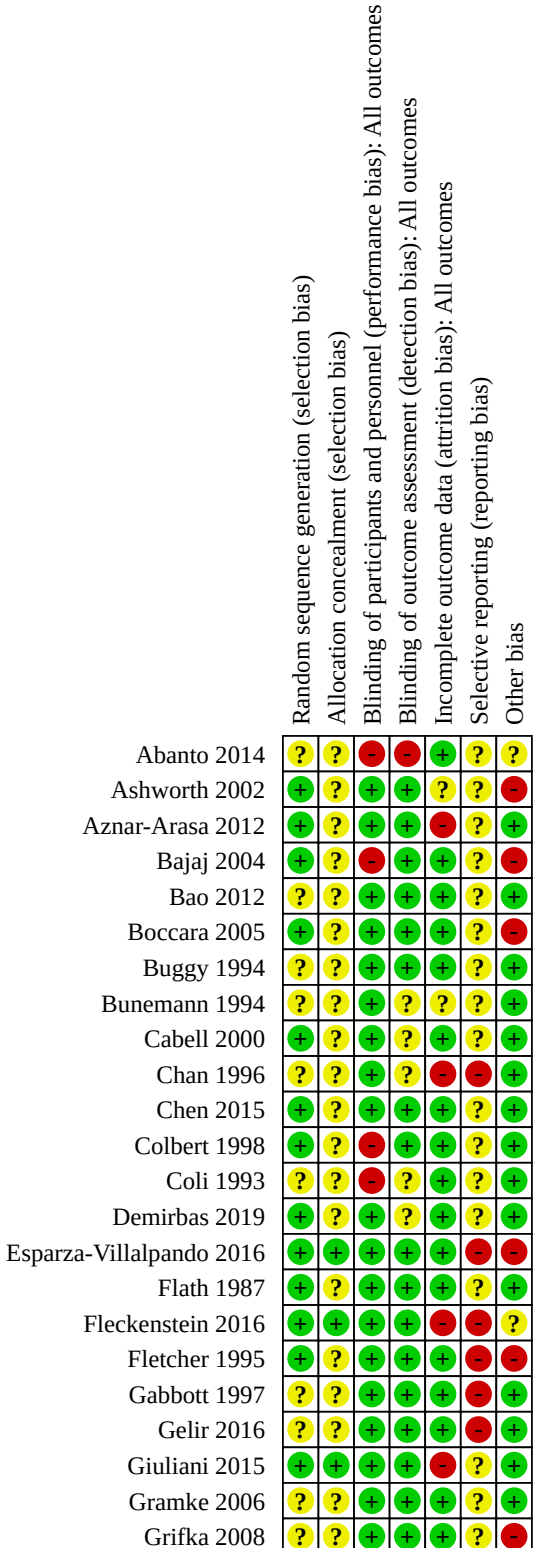


Figure 2. (Continued)

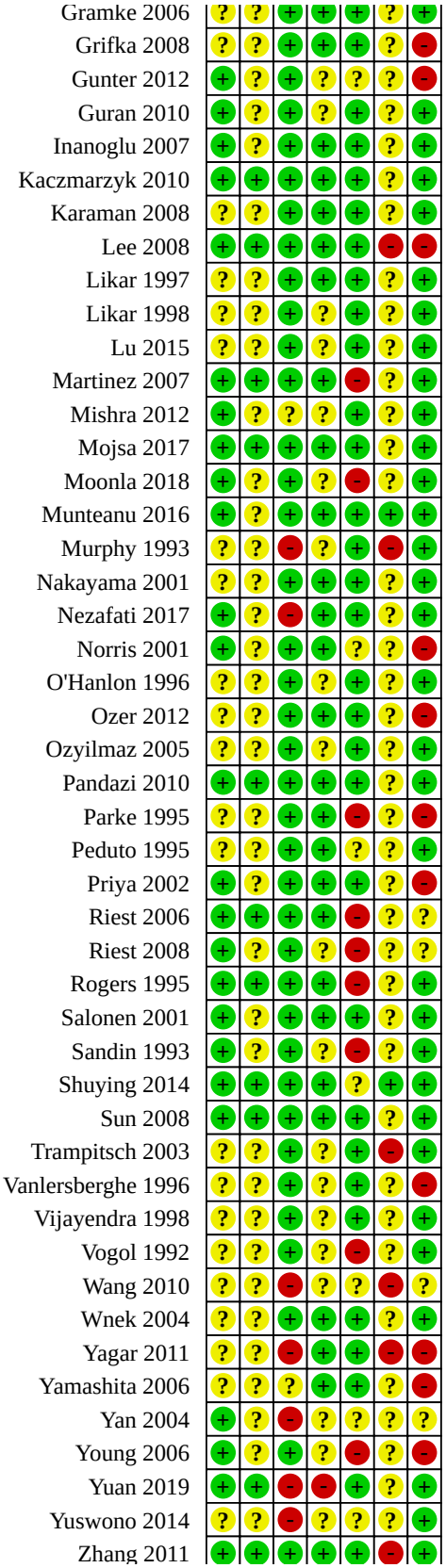


Figure 2. (Continued)

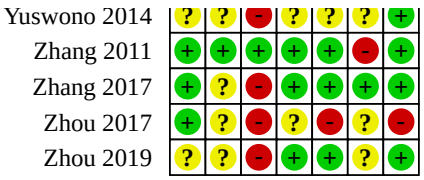
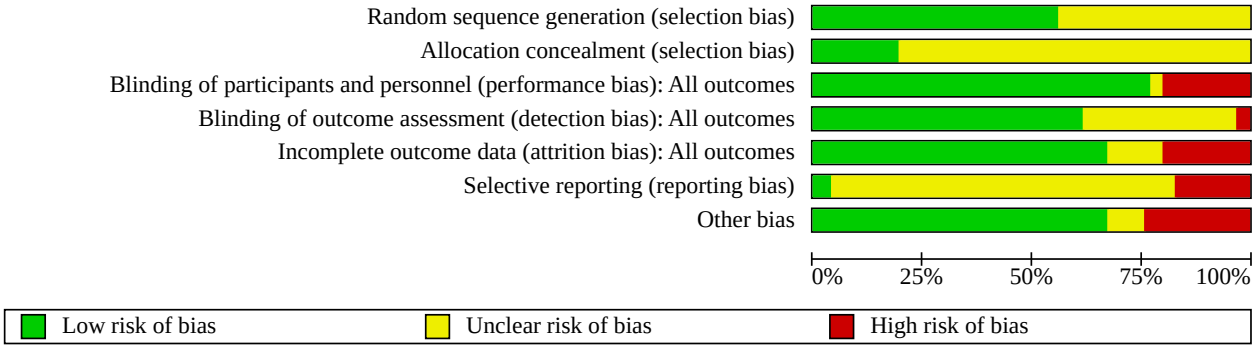


Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Measures of treatment effect

We presented dichotomous outcomes as risk ratios (RRs). For continuous outcomes, we presented these as mean differences (MDs). If non-comparable scales were used across studies but still presented as continuous data, which we expected may be the case for chronic pain and patient satisfaction, we would have presented these as standardized mean differences (SMDs). We aimed to present the outcomes of time to first analgesic and time to first bowel movement as hazard ratios (HRs) (Tierney 2007). We presented the precision of effect estimates using 95% confidence intervals (CIs).

Unit of analysis issues

As we included parallel-group RCTs only, unit of analysis issues were not a problem for the main analysis (Higgins 2011c). For the main results, we combined different dose subgroups into one treatment group, as suggested in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a). If it was not possible to combine groups (for example, for continuous outcomes where the combined standard deviation (SD) could not be estimated), we treated these as separate studies and distributed the control group participants between these treatment groups to avoid analysing them twice (Higgins 2011c).

Dealing with missing data

We contacted corresponding authors for any data missing from the original publication, irrespective of publication date. If we did not receive a response, we extracted data from published graphs. If SDs were not reported, we attempted to calculate these from other reported statistics. If this was not possible, we estimated SDs from other studies with similar means. We estimated means from medians (equal if the assumption of normality holds) and SD from interquartile range (IQR)/1.35 (Higgins 2011a) or range (Hozo 2005). We did this as our previous review identified studies where medians were reported, and were more likely to be 'negative' than those reporting means, which could introduce bias into the results (Doleman 2018b). However, we assessed the robustness of our estimates by excluding all studies where means or SDs were estimated in a sensitivity analysis.

Assessment of heterogeneity

We assessed clinical heterogeneity by examining study characteristics, such as the type of population, type of surgery and the intervention used. We assessed statistical heterogeneity using the I^2 statistic. We used the following recommended cut-off values in the interpretation of the I^2 statistic (Deeks 2011).

1. > 50% may represent moderate heterogeneity.
2. > 85% considerable heterogeneity.

In addition to the cut-off values, we examined the direction of the effect in the individual studies. For clinically meaningful magnitudes of the pooled effect, we explored heterogeneity using meta-regression when the criteria set out in Subgroup analysis and investigation of heterogeneity section were fulfilled.

Assessment of reporting biases

If we included 10 or more studies in the meta-analysis, we assessed publication bias graphically using funnel plots and quantitatively using an updated publication bias test which uses inverse sample size on the Y axis and performs better than Egger's linear regression test (Egger 1997) for outcomes dependent on baseline risk, such as pain and morphine consumption (Doleman 2020). This is due to correlation between standard errors and mean differences with

these outcomes causing artefactual funnel plot asymmetry with Egger's test, which the use of inverse sample size corrects. Due to the low power of this test, we regarded P < 0.1 as evidence of imprecise study effects and possible publication bias.

Data synthesis

We used Review Manager 5 to aggregate study data (Review Manager 2014). We conducted separate analyses for pre-emptive and preventive interventions. We aggregated data using the adapted DerSimonian and Laird random-effects model (for continuous and categorical outcomes), as currently available in Review Manager 5. This is because we expected the treatment effect to vary with respect to the different populations within each study, and, therefore, there was no single underlying effect to estimate, making the random-effects model more appropriate. We attempted to aggregate reported log hazard ratios and their associated standard errors using the generic inverse variance method, although no study adequately reported this.

Subgroup analysis and investigation of heterogeneity

If there were sufficient included studies, we conducted two separate subgroup analyses for the type of NSAIDs (non-selective NSAIDs versus COX-2 inhibitors) and trials with different baseline pain levels (mean pain scores in the control group of < 3 (mild), 3 to 6 (moderate) and > 6 (severe)) (Moore 2013). If we included 10 studies or more in a meta-analysis and the included studies had a sufficient number of events, we explored reasons for heterogeneity by performing a restricted maximum likelihood, random-effects meta-regression where covariates were entered into the model separately based on type of anaesthesia and type of surgery (univariate analysis) (Thompson 2002). For dummy variables, we used the least effective subgroup as the reference category. We presented the R^2 analogue with a corresponding P value for each covariate. We used the Knapp-Hartung method to calculate P values (as this method more appropriately uses the t-distribution for the between-study variance). We performed these analyses using the software STATA Version 16.1 (Stata 2020). If there was a low number of studies or events, or both, we only performed traditional subgroup analysis, and reported the P value for subgroup differences.

Sensitivity analysis

We performed a sensitivity analysis by restricting the analysis to studies at low risk of bias (defined as low risk for randomization and allocation concealment). As we judged studies that did not use a double-dummy design as being at high risk of bias for blinding, we assessed the impact of excluding these from the analysis. We also performed a further sensitivity analysis by excluding studies where means and SDs were estimated (both where SDs were estimated from other studies and where means and/or SDs were estimated from median and IQR). As a further sensitivity analysis, we repeated analysis assuming excluded participants suffered an event to assess the robustness of the findings. Furthermore, we performed sensitivity analyses by excluding studies with a low sample size (< 50 participants).

Summary of findings and assessment of the certainty of the evidence

We presented outcomes in a summary of findings table. We produced two summary of findings tables, one for each comparison.

1. Pre-emptive NSAIDs versus single dose post-incision NSAIDs.
2. Preventive NSAIDs versus continuous post-incision NSAIDs.

The outcomes presented in the summary of findings table for each comparison included: early acute postoperative pain; adverse events; nausea and vomiting; late acute postoperative pain; 24-hour morphine consumption and time to first analgesic request. We did not include chronic pain as no studies reported this outcome. We presented these outcomes using the GRADE approach (Schünemann 2011). We downgraded the certainty of evidence from high-certainty to moderate-, low- or very low-certainty. Downgrading was undertaken independently by two review authors (BD and JPW) and agreement reached by consensus. Characteristics of the evidence that caused downgrading included:

1. limitations in the design and implementation of available studies, suggesting a high likelihood of bias (for example, studies not using a double-dummy placebo design);
2. indirectness of evidence (indirect population, intervention, control or outcomes);
3. inconsistency of results (considerable heterogeneity not explained by meta-regression or subgroup analysis);
4. imprecision of results (wide confidence intervals);
5. evidence of publication bias from asymmetry of the funnel plot.

RESULTS

Description of studies

Results of the search

Searching of electronic databases yielded 7749 studies (Figure 1). We found another study from clinical trial databases, a further three studies from conference proceedings and seven from reference list searches. We reviewed 98 full-text articles and 27 were not included (Excluded studies).

Included studies

Following full-text review, we included 71 studies (Characteristics of included studies) which satisfied our inclusion criteria.

Participants and surgery

The types of surgery included were diverse. We included 10 studies performed in dental surgery, one study included hand surgery, four in general/colorectal surgery, four in total hip arthroplasty, one in total knee arthroplasty, four in laparoscopic cholecystectomy, three in laparoscopic gynaecological surgery, five in minor orthopaedic surgery, four in laparoscopic or open gynaecological procedures, three in breast surgery, seven in hysterectomy, six in spinal surgery, one in abdominal or thoracic surgery, one in laparoscopic hernia repair, five in joint arthroscopy, one in varicocelectomy, one in laparotomy, one in lung resection, one in thoracotomy, one in mandible open reduction and internal fixation (ORIF), one in diagnostic laparoscopy, two in septo/rhinoplasty, one in spinal, breast and orthopaedic surgery, one in tonsillectomy, one

in major plastic surgery and one in thyroid surgery. Seventeen studies included female participants only and one included male participants only. Most studies were conducted in low-risk participants who were American Society of Anesthesiologists grade (ASA) 1 or 2 and seven included ASA 1-3 participants, whilst others did not specify any exclusions on the basis of ASA grade.

Settings

Most studies were conducted in secondary care although other settings included dental clinics or dental medical schools. In terms of countries in which the trials were conducted, these included: one in Peru, four in the UK, one in Spain, four in India, 12 in China, three in France, two in Ireland, one in Denmark, six in the USA, three in Italy, one in Mexico, four in Germany, seven in Turkey, two in Romania, three in Poland, three in Austria, one in Australia, two in Japan, one in Iran, one in Canada, one in Northern Ireland, one in Greece, one in Finland, one in Sweden, one in Belgium, one in Indonesia, one in Thailand and two studies where the country was unclear.

Interventions

We included 52 studies which studied non-selective NSAIDs and 19 which studied COX-2 inhibitors. We included 45 studies which were pre-emptive (single-dose intervention not continued postoperatively) and 26 studies were preventive (intervention continued postoperatively).

Comparators

All included studies gave identical post-incision doses as those that did not were excluded. In terms of post-incision dose timing, 53 studies gave post-incision doses postoperatively or at the end of surgery and 18 studies gave doses intraoperatively.

Funding

Many studies did not report sources of funding or stated no funding; overall, the total was 56 studies. Eleven studies specified that they received non-industry funding and three studies reported industry funding. One study appeared to have authors who were pharmaceutical company employees.

Postoperative opioids and concurrent analgesia

The included studies used a diverse range of opioids for postoperative analgesia so we used conversion factors to calculate intravenous (IV) morphine equivalents. We included 16 studies which used no postoperative opioids or their use was not reported. Seventeen studies used patient controlled analgesia (PCA) morphine, one used nalbuphine, two used intramuscular (IM)/IV morphine, five used IV or IM pethidine, one used IV fentanyl and morphine, two used IV fentanyl, one used fentanyl PCA, one used buprenorphine, one used an IV morphine infusion, five used a tramadol PCA/IV, one used oral oxycodone, three used IV/PCA piritramide, two used oral or IV tramadol, one used IV and subcutaneous (SC) morphine, one used IV papaveretum, one used IV morphine and pethidine, one used IV fentanyl and codeine, one used cyclimorph and codeine, one used a diamorphine PCA, one used IV/IM oxycodone, one used dextropropoxyphene, one used sufentanil and tramadol, one used fentanyl, hydrocodone and morphine PCA, one used PCA butorphanol, one used a sufentanil PCA and one study used an unspecified analgesic.

In terms of concurrent analgesia, 52 studies reported no concurrent multimodal analgesia or did not mention any in the manuscript. Two studies used paracetamol and NSAIDs, two used NSAIDs which were different NSAIDs from the intervention, one used nurse-controlled NSAIDs which were the same as the intervention NSAID, one used metamizole, 10 used paracetamol, one used codeine and NSAIDs, one used paracetamol, tramadol and metamizole and one used paracetamol, NSAIDs and codeine.

Excluded studies

We excluded 20 studies (Characteristics of excluded studies) which did not satisfy our inclusion criteria. Three studies were excluded because they were cross-over trials. Seven studies included different doses of pre-emptive or preventive versus post-incision interventions. Two studies were excluded because they studied combination therapy rather than just NSAIDs/COX-2 inhibitors. Two studies were excluded as they did not have any post-incision group. Four studies were excluded as they included paediatric participants. Two studies were excluded as interventions had different routes of administration and were, therefore, not comparable.

Studies awaiting classification

There were seven studies (Characteristics of studies awaiting classification) awaiting classification. We were unable to translate two studies. We were unable to obtain the full text of another five studies via the British Library or contacting the study authors.

Risk of bias in included studies

Risk of bias assessments were conducted for the following domains.

Allocation

We included 31 studies which did not report details for randomization so were rated as having unclear risk. Nine studies used a random number chart or table, 27 used computer-generated randomization, two used a random draw of envelopes or lots, one used block randomization and one used a random number generator so all of these studies were deemed as having low risk of bias. In terms of allocation concealment, 44 studies did not report their method of allocation concealment and four studies did not include enough details so both were deemed as having unclear risk of bias. In addition, a further nine studies reported envelopes but not enough details on envelope safeguards so were also deemed as having unclear risk of bias. Nine studies used third parties for randomization or allocation was pharmacy-controlled so were deemed as having low risk of bias, whilst five studies reported sealed, sequentially numbered and opaque envelopes so were also deemed as having low risk of bias for allocation concealment.

Blinding

We included 14 studies which did not report the use of a double-dummy placebo so were regarded as having high risk of bias for blinding. Fifty-five studies used a double-dummy placebo so were deemed as having low risk of bias. In two studies, it was unclear if a double-dummy placebo had been used so they were considered as having unclear risk of bias for this domain.

In terms of blinding of outcome assessment, two studies were regarded as high risk from the lack of blinding of post-incision

dosing. Thirty-seven studies used blinded outcome assessment and were deemed at low risk. Twenty-five studies did not mention any outcome assessment blinding and were therefore deemed as having unclear risk of bias for this domain. Seven studies used participant self-report for outcome assessment or outcomes were likely blinded from the details given, so these were deemed as having low risk for blinding of outcome assessment.

Incomplete outcome data

We included 15 studies which had low dropout rates or dropouts equal in numbers and reasons which were, therefore, regarded as low risk and 30 studies analysed all enrolled participants so were also at low risk of bias. Nine studies had unclear risk as it was unclear which to which group dropouts belonged or the study did not mention dropouts. We included 13 studies which were at high risk of bias due to a high number of dropouts which could bias results or an extreme dropout which could change results. Three studies used intention-to-treat analysis so were deemed as having low risk of bias.

Selective reporting

We included 53 studies which did not have a published protocol or clinical trial registration so were regarded as having unclear risk for selective outcome reporting. Ten studies did not report outcomes mentioned in the methods and were therefore deemed at high risk of bias for selective outcome reporting. One study used retrospective registration so was deemed at unclear risk for selective outcome reporting. Two studies pre-registered the trial on a clinical trials database but did not fully report all prespecified outcomes so were deemed as having high risk of bias. Two studies with a protocol registration number that we could not locate were considered at unclear risk of bias and three studies reported all prespecified outcomes so were considered at low risk of bias.

Other potential sources of bias

We included five studies which had no details on baseline characteristics so were deemed at unclear risk of other bias and one study had industry funding but, because the extent of involvement was unclear, it was considered as having unclear risk of bias. Another 16 studies had disparities in baseline characteristics which could have affected pain so were deemed at high risk. We also judged one study as having high risk as the authors appeared to be pharmaceutical company employees. We included 48 studies which had no differences in baseline characteristics or industry funding so these were deemed at low risk of bias for other sources of bias.

Effects of interventions

See: **Summary of findings 1** Summary of findings; **Summary of findings 2** Summary of findings

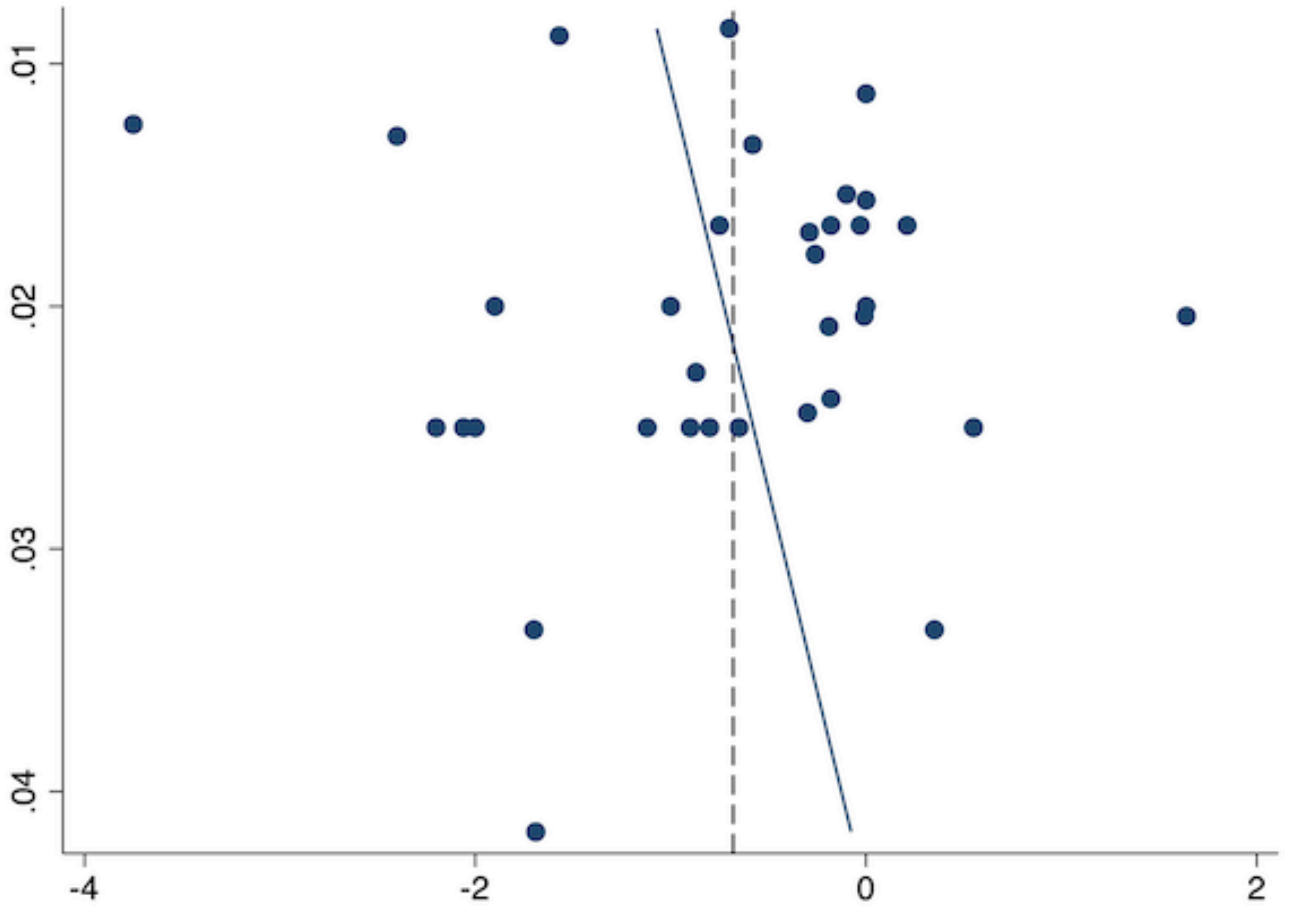
Pre-emptive NSAIDs versus post-incision NSAIDs

Primary outcomes

1. Early acute postoperative pain (measured within six hours postoperatively)

Thirty-six studies reported early acute postoperative pain for pre-emptive NSAIDs versus post-incision NSAIDs (Bajaj 2004; Bao 2012; Buggy 1994; Bunemann 1994; Cabell 2000; Chen 2015; Colbert 1998; Demirbas 2019; Esparza-Villalpando 2016; Fletcher 1995; Gelir 2016; Grifka 2008; Inanoglu 2007; Kaczmarzyk 2010; Karaman 2008; Lee 2008; Likar 1997; Lu 2015; Mojsa 2017; Nezafati 2017; O'Hanlon 1996; Ozer 2012; Ozyilmaz 2005; Peduto 1995; Priya 2002; Sandin 1993; Shuying 2014; Vanlersberghe 1996; Vijayendra 1998; Wang 2010; Yagar 2011; Yamashita 2006; Yan 2004; Zhang 2011; Zhang 2017; Zhou 2019). There is probably a reduction in early postoperative pain with pre-emptive NSAIDs (MD -0.69, 95% CI -0.97 to -0.41; participants = 2032; I^2 = 96%; Analysis 1.1). The certainty of evidence was downgraded to moderate owing to concerns over risk of bias (one level), mainly for allocation concealment. There was no evidence of publication bias both on observation of funnel plots (Figure 4) or quantitative testing (P = 0.27).

Figure 4. Funnel plot with mean difference on the X-axis and inverse sample size on the Y-axis for pre-emptive early acute postoperative pain



On subgroup analysis of non-selective NSAIDs versus COX-2 specific agents, there was no difference between the groups (COX-2: MD -1.14; 95% CI -1.78 to -0.5 versus NSAIDs: MD -0.57; 95% CI -0.89 to -0.25; P = 0.12; Figure 5). However, on subgroup analysis of baseline pain level (Doleman 2018a), there were greater reductions in pain with higher baseline pain levels (mild: MD -0.24; 95% CI -0.51 to 0.03, moderate: MD -1.19; 95% CI -1.52 to -0.86 and severe: MD -1.44; 95% CI -2.28 to -0.59; P < 0.001; Figure 6), although statistical heterogeneity was still high in these subgroups (I^2 = 86-90%). On meta-regression analysis, type of surgery (R^2 = 54%; P = 0.003) and type of anaesthesia (R^2 = 40%; P = 0.002) explained the majority of the between-study heterogeneity. On sensitivity analysis, restricting analysis to studies with low risk for randomization and allocation concealment (Esparza-Villalpando 2016; Kaczmarzyk 2010; Mojsa 2017; Shuying 2014; Zhang 2011) showed a smaller reduction in pain (MD -0.20, 95% CI -0.43 to 0.04; participants = 318; studies = 5; I^2 = 13%). Restricting analysis to studies at low risk for blinding of participants and outcome assessors (Buggy 1994; Chen 2015; Esparza-Villalpando 2016; Fletcher 1995; Gelir 2016; Grifka 2008; Inanoglu 2007; Kaczmarzyk 2010; Karaman 2008; Lee 2008; Likar 1997; Mojsa 2017; Ozer 2012; Pandazi 2010; Priya 2002; Shuying 2014; Zhang 2011) produced similar results to the main analysis (MD -0.60, 95% CI -0.99 to -0.21; participants = 888; studies = 17; I^2 = 85%). Similarly, restricting analysis to studies where standard deviations were not estimated from IQR or other studies, or means were not estimated from medians (excluded studies: Bajaj 2004; Buggy 1994; Bunemann 1994; Cabell 2000; Demirbas 2019; Grifka 2008; Kaczmarzyk 2010; Lee 2008; Ozyilmaz 2005; Peduto 1995; Sandin 1993; Vanlersberghe 1996; Vijayendra 1998; Yagar 2011; Yamashita 2006; Zhang 2011) showed a similar reduction in pain to the main analysis (MD -0.62, 95% CI -0.98 to -0.27; participants = 1167; studies = 20; I^2 = 97%). Restricting analysis to studies with more than 50 participants gave similar results to the main analysis (MD -0.77, 95% CI -1.15 to -0.39; participants = 1355; I^2 = 97%).

Figure 5. Subgroup analysis for pre-emptive early postoperative pain (NSAID versus COX-2 inhibitor)

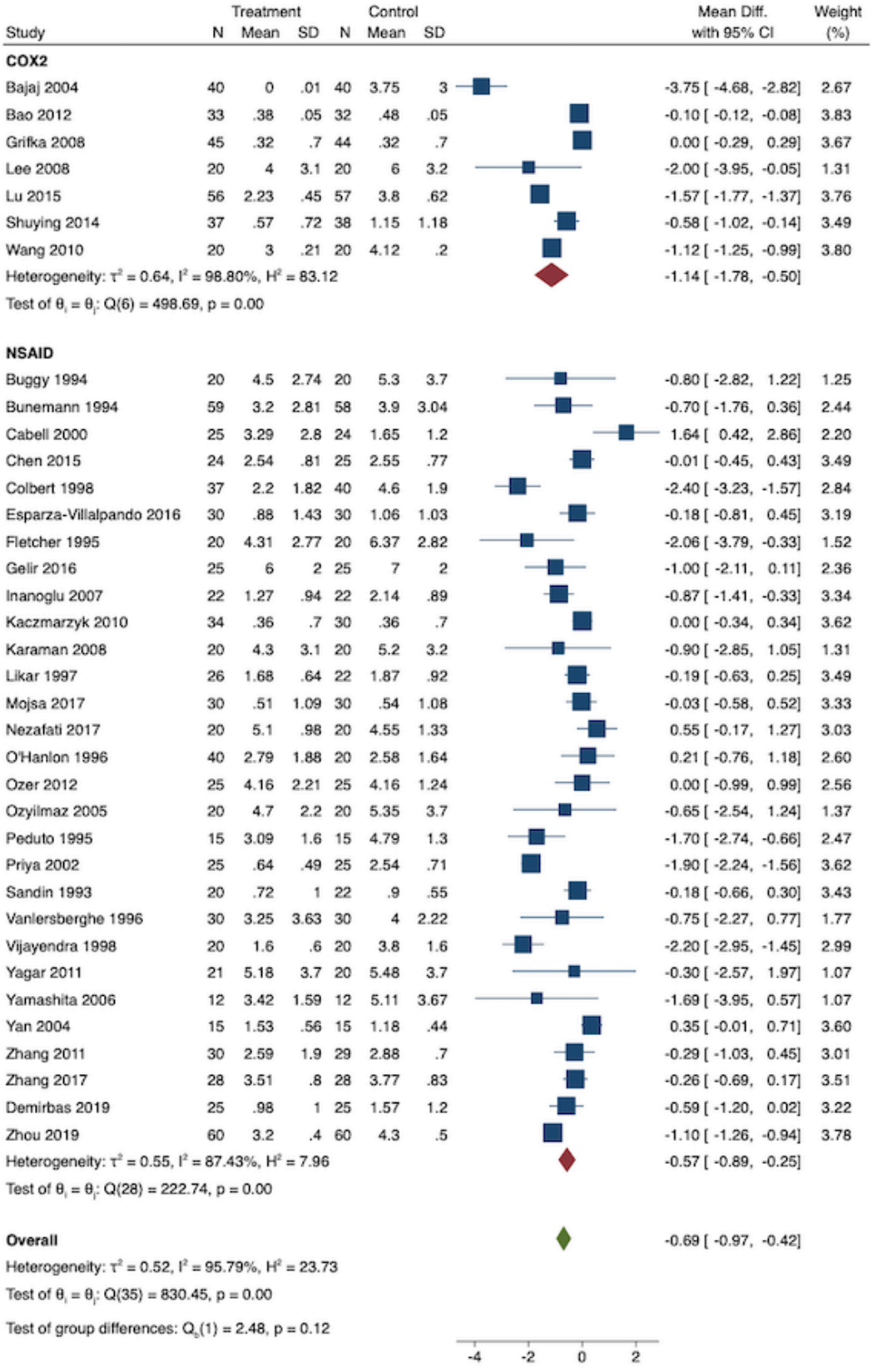


Figure 6. Subgroup analysis for pre-emptive early postoperative pain (baseline pain level). Subgroups are 1 (mild), 2 (moderate) and 3 (severe)

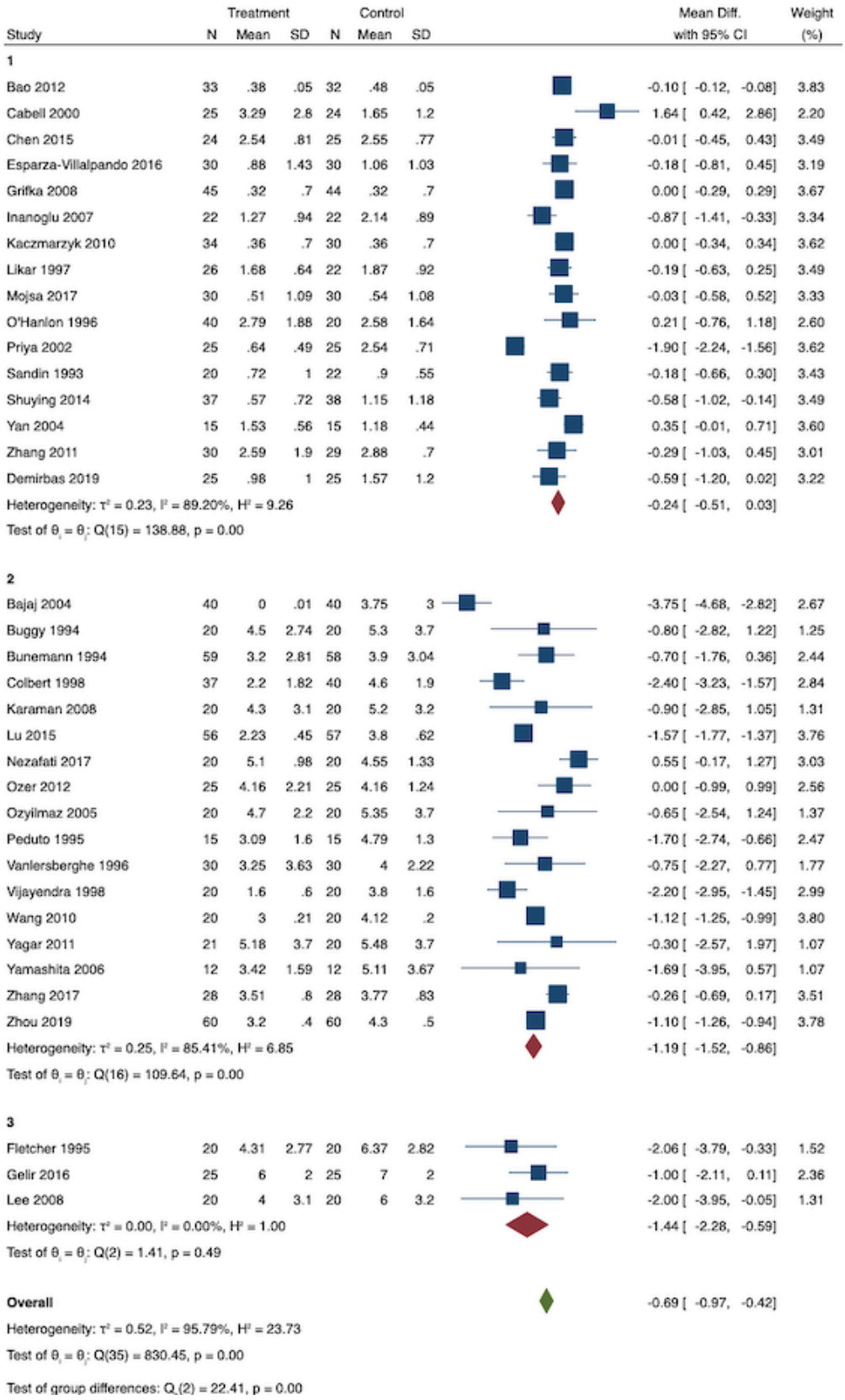


Figure 6. (Continued)

2. Adverse events (reoperation for major bleeding within 30 days, acute kidney injury within 48 hours, gastrointestinal ulceration or bleeding requiring endoscopy within 30 days, and myocardial infarction within 30 days)

No studies reported any adverse events for pre-emptive NSAIDs versus post-incision NSAIDs.

Secondary outcomes

1. Nausea and vomiting (self-reported by the patient or requirement for anti-emetic as composite outcome (yes/no))

Short-term nausea and vomiting

Two studies reported short-term nausea and vomiting (Lee 2008; Vanlersberghe 1996). Overall, there may be no difference between the pre-emptive and post-incision groups (RR 1.00, 95% CI 0.34 to 2.94; participants = 100; studies = 2; I^2 = 0%; Analysis 1.2). The certainty of evidence was downgraded to low owing to concerns over risk of bias, mainly selective outcome reporting (one level), and other bias and imprecision (one level).

We were unable to conduct assessment for publication bias or meta-regression due to the low number of included studies. On sensitivity analysis, none of the included studies were at low risk for randomization and allocation concealment. One study was at low risk for blinding (Lee 2008) which showed similar results to the main analysis (RR 0.85, 95% CI 0.52 to 1.38). Restricting analysis to studies with more than 50 participants gave similar results (RR 0.75, 95% CI 0.18 to 3.07; participants = 60).

Long-term nausea and vomiting

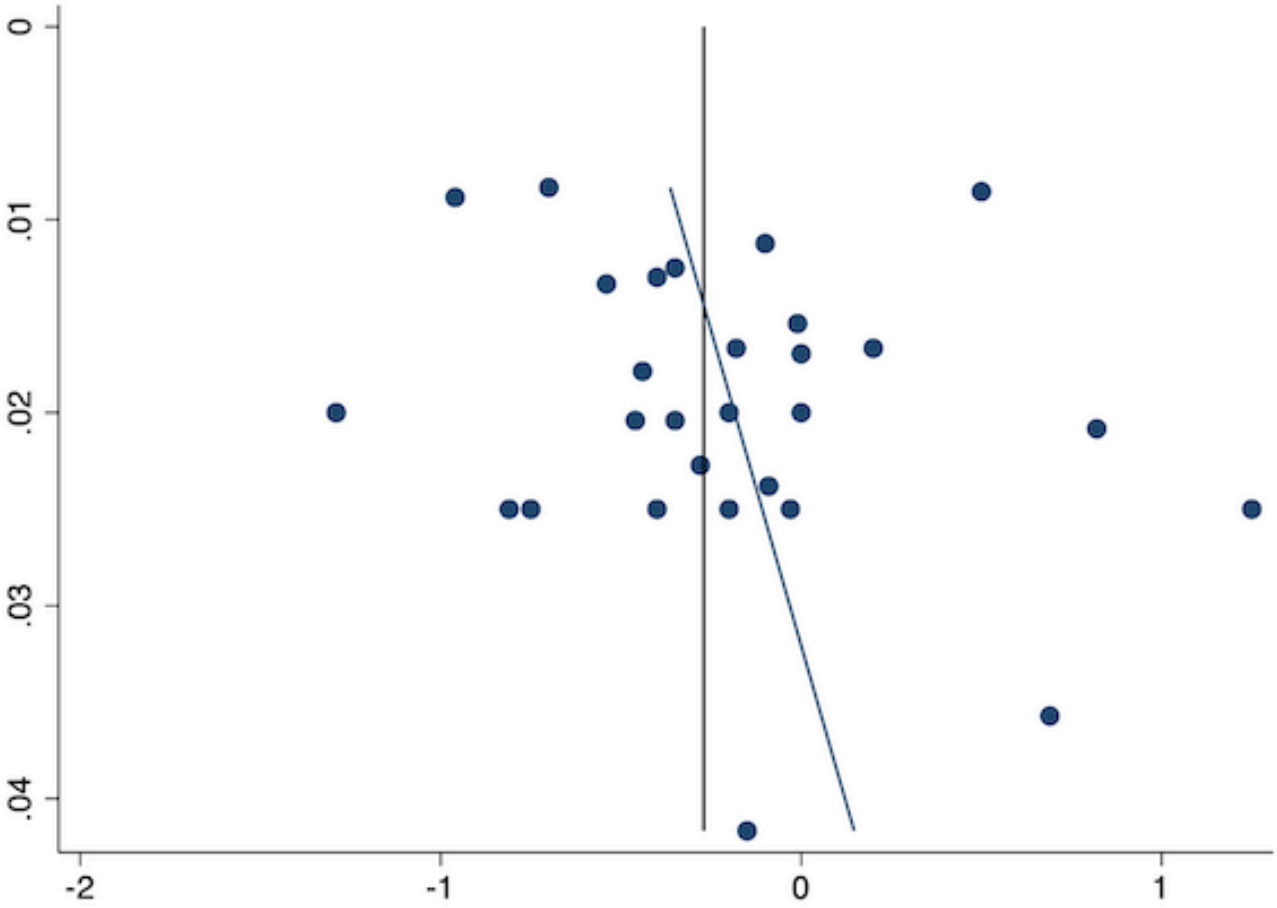
For long-term nausea and vomiting, five studies were included (Fletcher 1995; Karaman 2008; Lee 2008; Priya 2002; Rogers 1995). There may be no difference between the groups in the number of participants suffering from long-term nausea and vomiting (RR 0.85, 95% CI 0.52 to 1.38; participants = 228; studies = 5; I^2 = 29%; Analysis 1.3). The certainty of evidence was downgraded to low owing to concerns over risk of bias, mainly selective outcome reporting (one level), and other bias and imprecision (one level).

We were unable to conduct assessment for publication bias or meta-regression due to the low number of included studies. On sensitivity analysis, restricting analysis to one study that was at low risk of bias for randomization and allocation concealment (Rogers 1995) produced similar results to the main analysis (RR 1.28, 95% CI 0.61 to 2.72; participants = 58). All the studies were at low risk of bias for blinding so results were identical to the main analysis. Restricting analysis to studies with more than 50 participants gave similar results (RR 0.69, 95% CI 0.20 to 2.42; participants = 108; I^2 = 79%). Only one study (Rogers 1995) excluded participants, although it was unclear when, as each was excluded after receiving analgesia.

2. Late acute postoperative pain (measured at 24 to 48 hours)

Twenty-eight studies reported early acute postoperative pain for pre-emptive NSAIDs versus post-incision NSAIDs (Bajaj 2004; Bao 2012; Bunemann 1994; Cabell 2000; Chen 2015; Demirbas 2019; Flath 1987; Fletcher 1995; Gelir 2016; Grifka 2008; Inanoglu 2007; Karaman 2008; Lee 2008; Likar 1997; Lu 2015; Mojsa 2017; Nezafati 2017; O'Hanlon 1996; Ozer 2012; Parke 1995; Sandin 1993; Shuying 2014; Vijayendra 1998; Wang 2010; Yamashita 2006; Zhang 2011; Zhang 2017; Zhou 2019). There may be a slight difference between the groups (MD -0.22, 95% CI -0.44 to 0.00; participants = 1645; I^2 = 97%; Analysis 1.4). The certainty of evidence was downgraded to low due to concerns over risk of bias, mainly in allocation concealment (one level), and unexplained heterogeneity (one level). There was no evidence of publication bias both on visual inspection of funnel plots (Figure 7) or quantitative testing (P = 0.35).

Figure 7. Funnel plot with mean difference on the X-axis and inverse sample size on the Y-axis for pre-emptive late acute postoperative pain



On subgroup analysis of non-selective NSAIDs versus COX-2 agents, there was no significant difference between the groups (P = 0.16; Figure 8). When conducting subgroup analysis for different baseline pain levels, there were greater reductions in pain with higher baseline pain levels (Doleman 2018a) (mild: MD -0.14; 95% CI -0.37 to 0.10, moderate: MD -0.77; 95% CI -1.08 to -0.47; P < 0.001; Figure 9). On meta-regression analysis, although type of surgery explained some of the between-study heterogeneity, the result was not statistically significant (R^2 = 28%; P = 0.22). Type of anaesthesia did not predict any between-study heterogeneity (R^2 = 0%; P = 0.97). On sensitivity analysis, restricting analysis to the three studies that were at low risk of bias for randomization and allocation concealment (Mojsa 2017; Shuying 2014; Zhang 2011) showed a greater reduction in late acute postoperative pain (MD -0.52, 95% CI -0.65 to -0.40; participants = 194; I^2 = 0%). When restricting analysis to studies at low risk for blinding, 14 studies were included (Chen 2015; Flath 1987; Fletcher 1995; Gelir 2016; Grifka 2008; Inanoglu 2007; Karaman 2008; Lee 2008; Likar 1997; Mojsa 2017; Ozer 2012; Parke 1995; Shuying 2014; Zhang 2011) and showed similar results to the main analysis (MD -0.14, 95% CI -0.39 to 0.11; participants = 749; I^2 = 74%). When restricting analysis to studies where standard deviations were not estimated from IQR or other studies, or means were not estimated from medians (excluded studies: Bajaj 2004; Bunemann 1994; Cabell 2000; Demirbas 2019; Flath 1987; Grifka 2008; Lee 2008; Parke 1995; Sandin 1993; Vijayendra 1998; Yamashita 2006; Zhang 2011), 15 studies showed similar results to the overall analysis (MD -0.19, 95% CI -0.47 to 0.09; participants = 950; I^2 = 98%). Restricting analysis to studies with more than 50 participants gave similar results (MD -0.16, 95% CI -0.41 to 0.08; participants = 999; I^2 = 93%).

Figure 8. Subgroup analysis for pre-emptive late postoperative pain (NSAID versus COX-2 inhibitor)

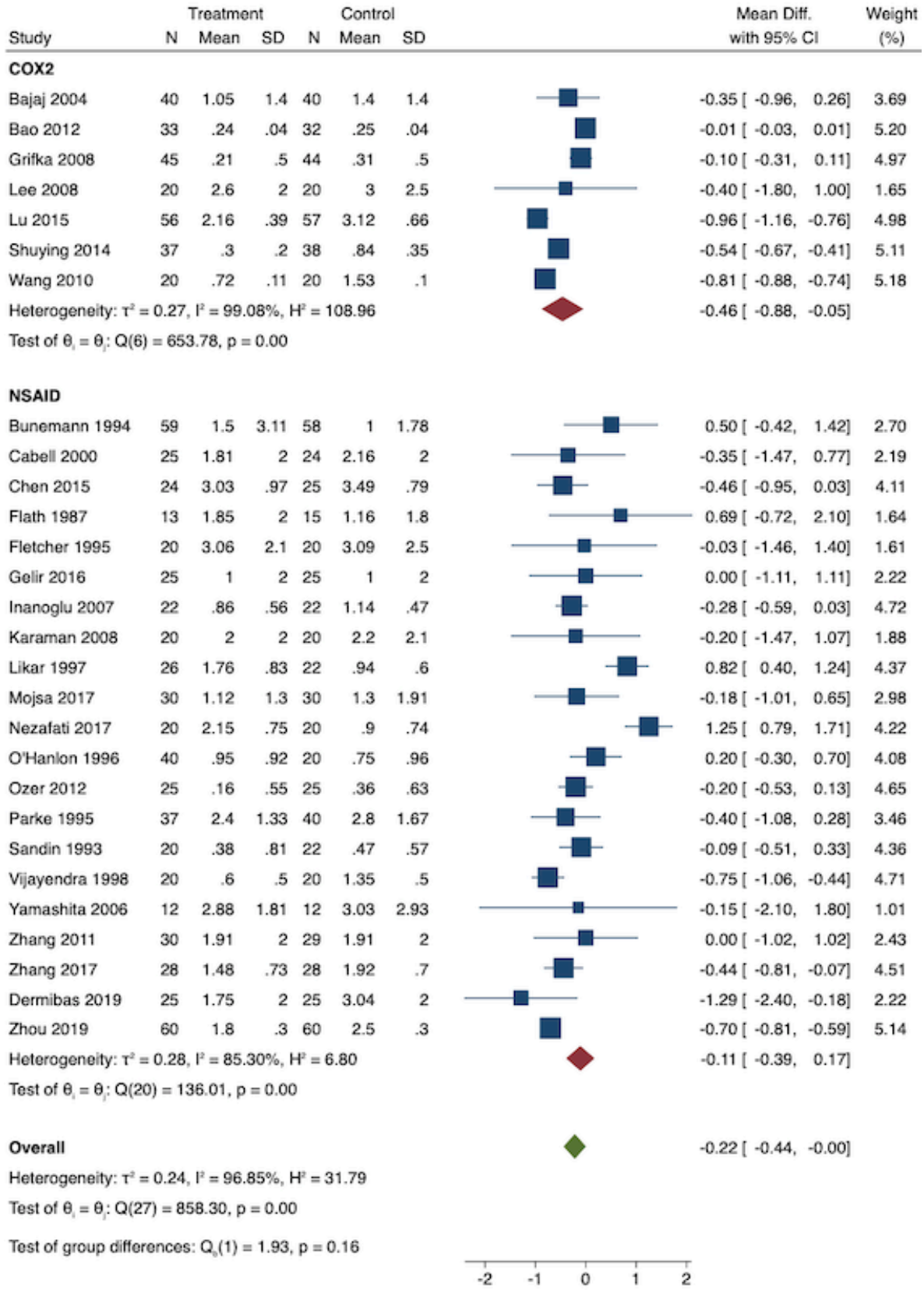
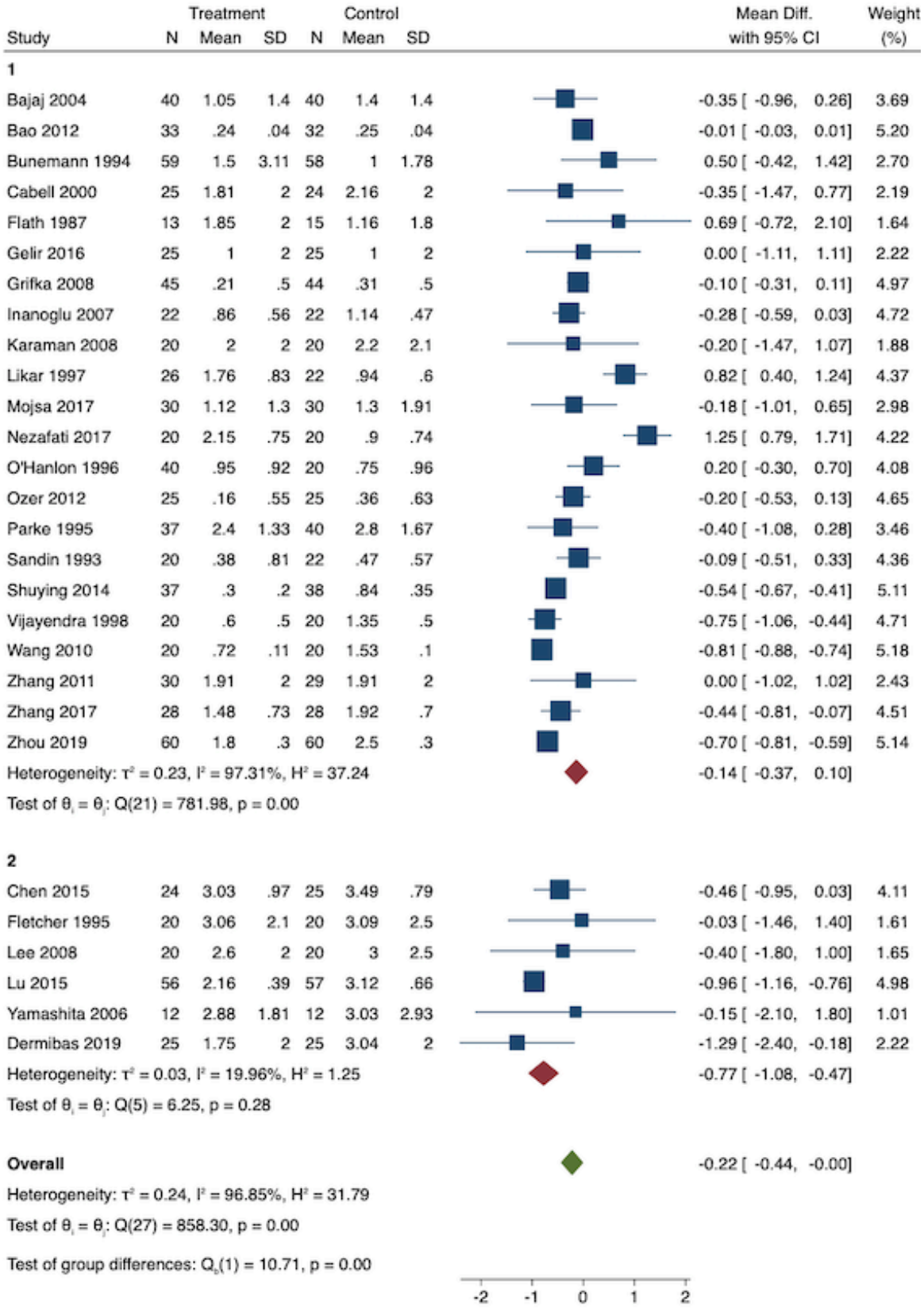


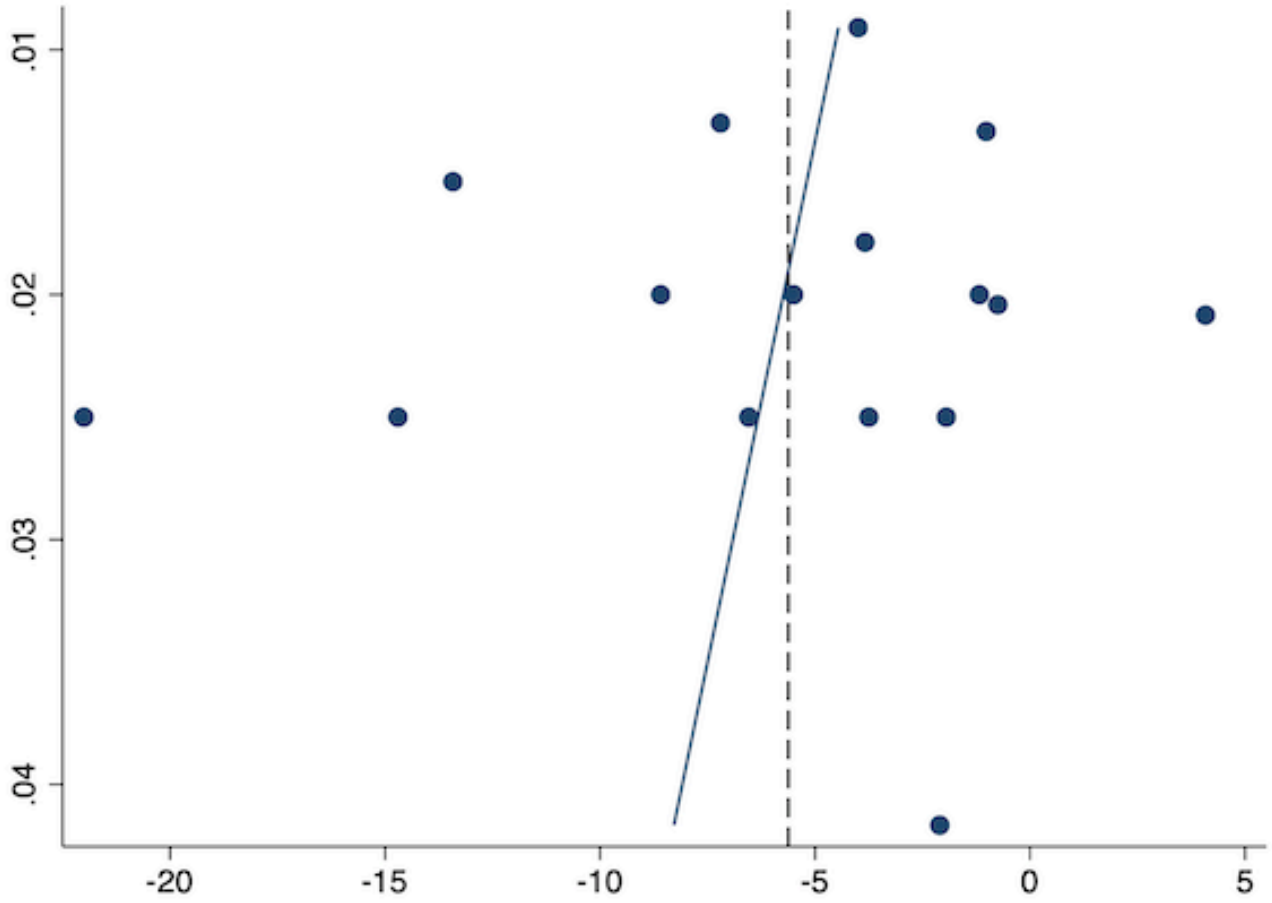
Figure 9. Subgroup analysis for pre-emptive late postoperative pain (baseline pain). Subgroups are 1 (mild) and 2 (moderate)



3. Twenty-four-hour morphine consumption (mg)

Sixteen studies reported 24-hour morphine consumption for pre-emptive NSAIDs versus post-incision NSAIDs (Bao 2012; Chen 2015; Coli 1993; Fletcher 1995; Gelir 2016; Karaman 2008; Likar 1997; Munteanu 2016; Ozer 2012; Ozyilmaz 2005; Parke 1995; Shuying 2014; Vijayendra 1998; Wang 2010; Yamashita 2006; Zhang 2017). There may be a reduction in 24-hour morphine consumption with pre-emptive versus post-incision NSAIDs (MD -5.62 mg, 95% CI -9.00 mg to -2.24 mg; participants = 854; studies = 16; I^2 = 99%; Analysis 1.5). The certainty of evidence was downgraded to low owing to concerns over risk of bias, mainly in randomization and allocation concealment (one level), and unexplained heterogeneity (one level). There was no evidence of publication bias both on visual inspection of funnel plots (Figure 10) or quantitative testing (P = 0.61).

Figure 10. Funnel plot with mean difference on the X-axis and inverse sample size on the Y-axis for pre-emptive 24-hour morphine consumption



On subgroup analysis of non-selective NSAIDs versus COX-2 specific agents, there was no difference between the groups (P = 0.25; Figure 11). When conducting subgroup analysis by baseline consumption of morphine (< 20 mg: low, 20-50 mg: moderate and > 50 mg: high; Doleman 2018a), there was no evidence of a difference although subgroup results were imprecise (MD -2.66 mg; 95% CI -4.54 mg to -0.79 mg for low and -15.22 mg; 95% CI -29.67 mg to -0.77 mg for moderate; P = 0.16; Figure 12). On meta-regression, type of surgery did not predict any of the between-study heterogeneity (R^2 = 0%; P = 0.66). Similarly, type of anaesthesia did not predict any between-study heterogeneity (R^2 = 0%; P = 0.72). On sensitivity analysis, restricting analysis to the one study that was at low risk of bias for randomization and allocation concealment (Shuying 2014) (MD -1.02 mg, 95% CI -2.16 mg to 0.12 mg; participants = 75) demonstrated a lower reduction in morphine consumption. Nine studies were at low risk of bias for blinding (Chen 2015; Fletcher 1995; Gelir 2016; Karaman 2008; Likar 1997; Munteanu 2016; Ozer 2012; Parke 1995; Shuying 2014). The results for these studies showed a smaller reduction in morphine consumption (MD -1.14 mg, 95% CI -2.29 mg to 0.01 mg; participants = 539; I^2 = 62%). When restricting analysis to studies where means and standard deviations were not estimated, 12 studies remained (Bao 2012; Chen 2015; Fletcher 1995; Gelir 2016; Karaman 2008; Likar 1997; Munteanu 2016; Ozer 2012; Ozyilmaz 2005; Parke 1995; Shuying 2014; Zhang 2017). Results were similar to the main analysis (MD -4.76 mg, 95% CI -8.79 mg to -0.73 mg; participants = 700; I^2 = 99%). Restricting analysis to studies with more than 50 participants gave similar results (MD -5.31 mg, 95% CI -8.61 mg to -2.02 mg; participants = 533; I^2 = 93%).

Figure 11. Subgroup analysis for pre-emptive 24-hour morphine consumption (NSAID versus COX-2)

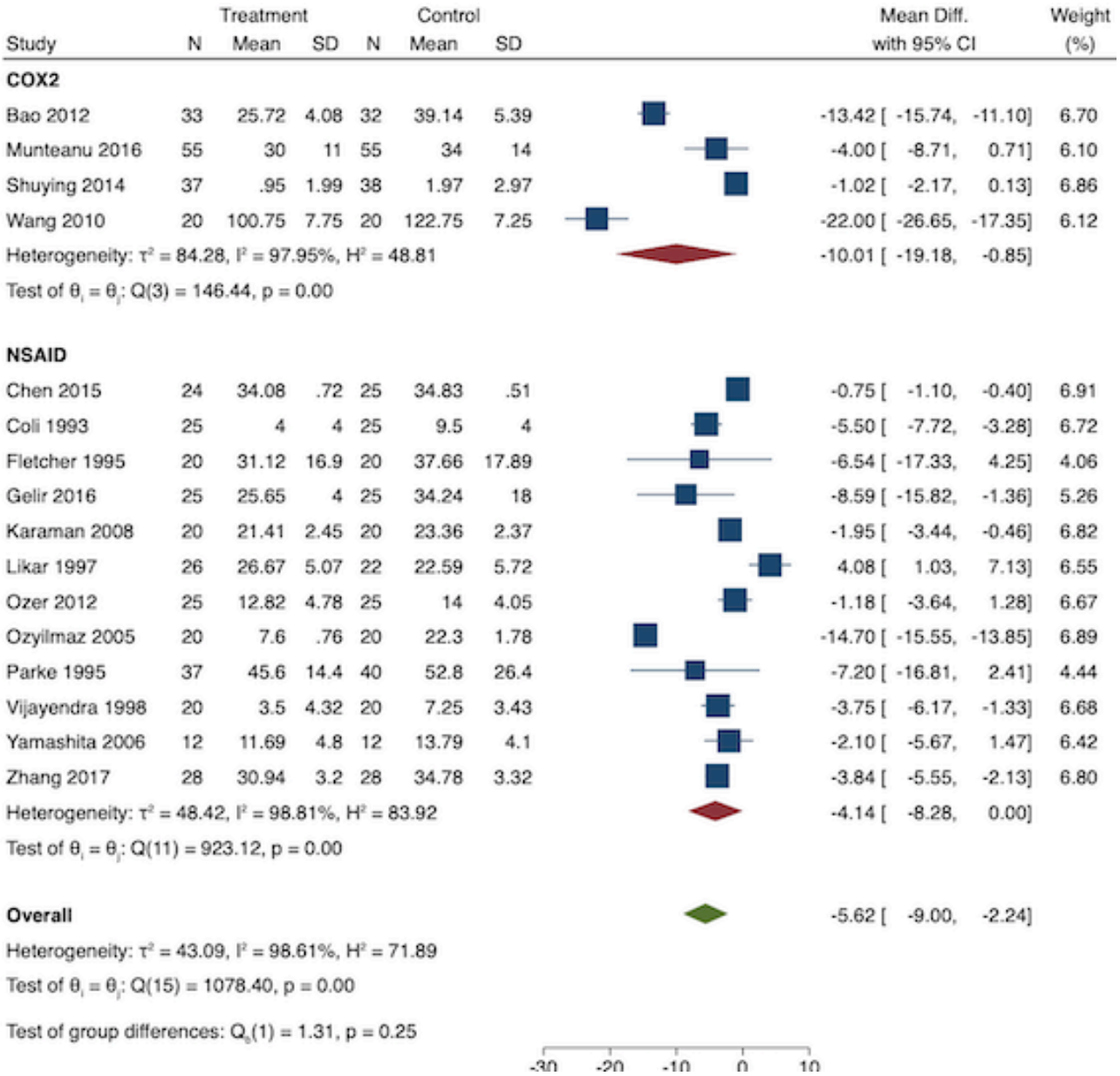
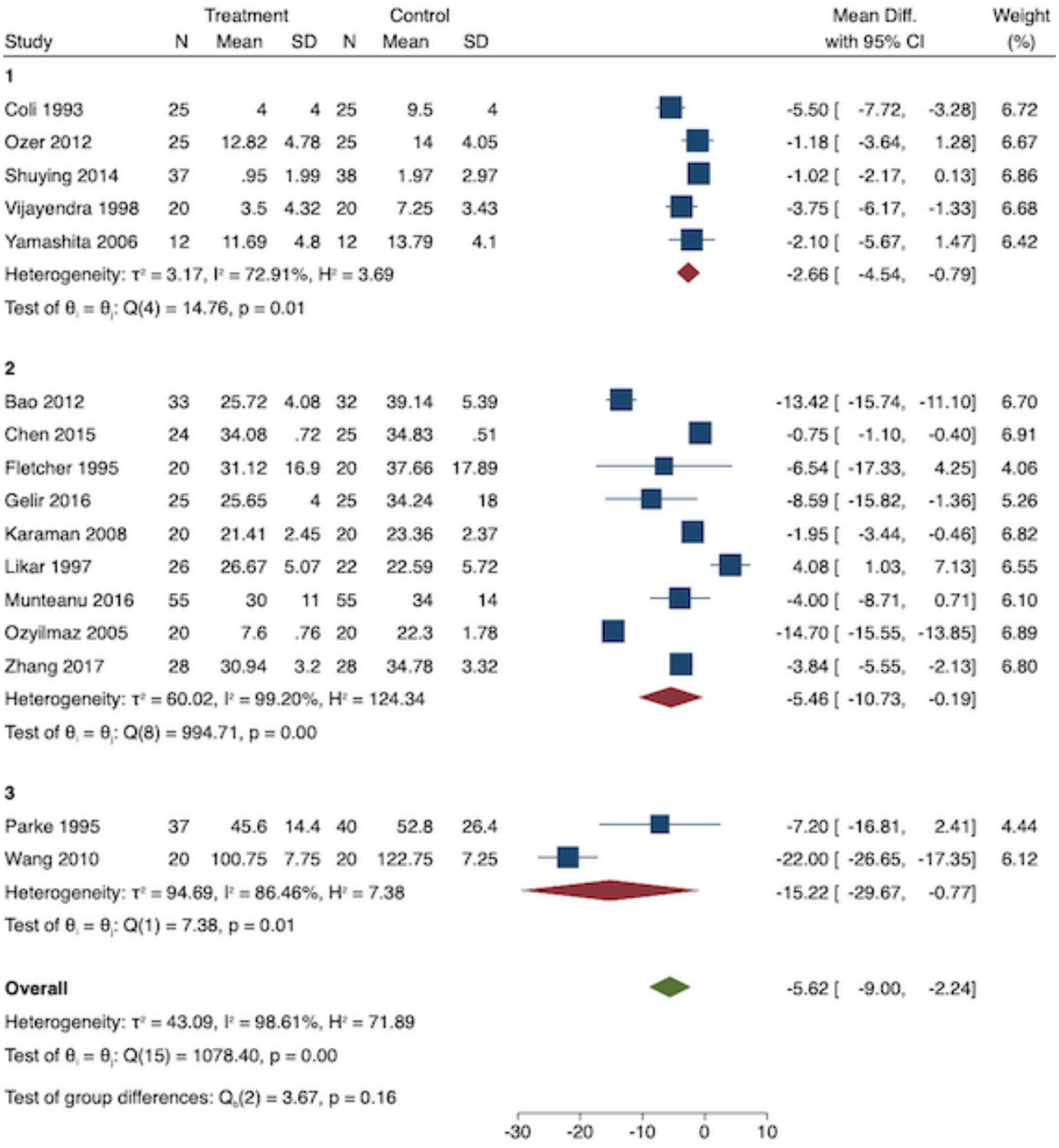


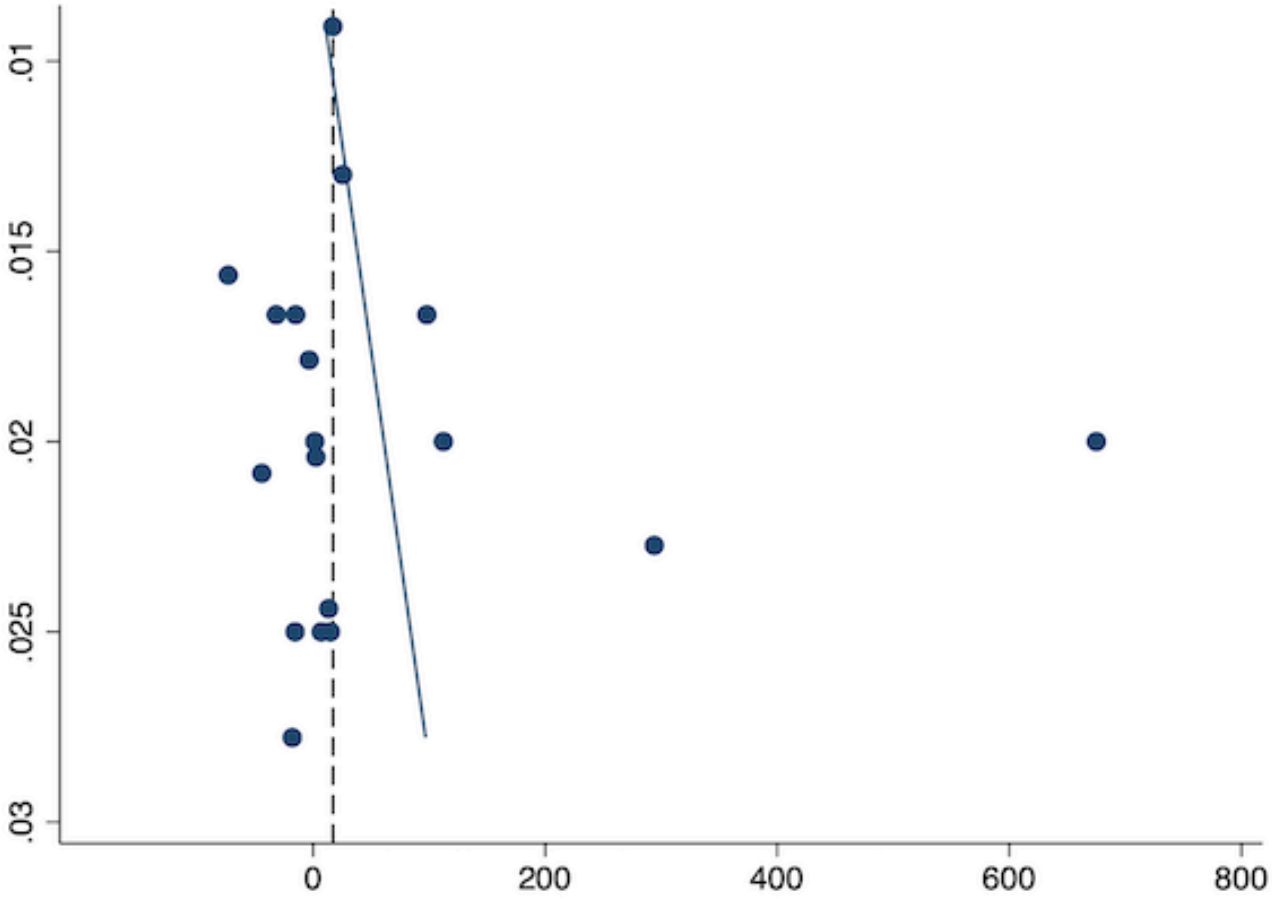
Figure 12. Subgroup analysis for pre-emptive 24-hour morphine consumption (baseline consumption). Subgroups are 1 (low), 2 (medium) and 3 (high)



4. Time to first analgesic request (minutes)

Eighteen studies reported time to analgesic request for pre-emptive NSAIDs versus post-incision NSAIDs (Buggy 1994; Chen 2015; Colbert 1998; Coli 1993; Esparza-Villalpando 2016; Gelir 2016; Inanoglu 2007; Kaczmarzyk 2010; Likar 1997; Munteanu 2016; Nezafati 2017; O'Hanlon 1996; Priya 2002; Vanlersberghe 1996; Vijayendra 1998; Vogol 1992; Yagar 2011; Zhang 2017). There may be an increase in the time to analgesic request with pre-emptive NSAIDs (MD 17.04 minutes, 95% CI 3.77 minutes to 30.31 minutes; participants = 975; studies = 18; I^2 = 95%; Analysis 1.6). The certainty of evidence was downgraded to low owing to concerns over risk of bias, mainly allocation concealment (one level), and unexplained heterogeneity (one level). There was no evidence of publication bias both on visual inspection of funnel plots (Figure 13) or quantitative testing (P = 0.52).

Figure 13. Funnel plot with mean difference on the X-axis and inverse sample size on the Y-axis for pre-emptive time to analgesic request



We did not conduct subgroup analysis as there was only one study in one of the subgroups. On meta-regression analysis, neither type of surgery (R^2 = 28%; P = 0.14) nor type of anaesthesia (R^2 = 0%; P = 0.98) was a significant predictor of between-study heterogeneity. On sensitivity analysis, restricting analysis to the two studies that were at low risk of bias for randomization and allocation concealment (Esparza-Villalpando 2016; Kaczmarzyk 2010), results were opposite to the main analysis, with a reduction in time to analgesia (MD -70.25 minutes, 95% CI -101.28 minutes to -39.21 minutes; participants = 124; I^2 = 0%). Nine studies were at low risk of bias for blinding (Buggy 1994; Chen 2015; Esparza-Villalpando 2016; Gelir 2016; Inanoglu 2007; Kaczmarzyk 2010; Likar 1997; Munteanu 2016; Priya 2002) which showed a prolonged duration of time to analgesia in the pre-emptive NSAIDs group (MD 56.84 minutes, 95% CI 13.27 minutes to 100.42 minutes; participants = 515; I^2 = 97%). When restricting analysis to the five studies that did not estimate standard deviations or means (Buggy 1994; Coli 1993; Vanlersberghe 1996; Vijayendra 1998; Yagar 2011), the results were similar to the main analysis (MD 17.93 minutes, 95% CI 1.09 minutes to 34.78 minutes; participants = 744; studies = 18; I^2 = 96%). Restricting analysis to studies with more than 50 participants gave broadly similar results (MD 33.66 minutes, 95% CI 14.12 minutes to 53.19 minutes; participants = 637; I^2 = 97%). One study included data as time to an event (Mojsa 2017), but only reported data with reference to a control group so could not be included in the meta-analysis.

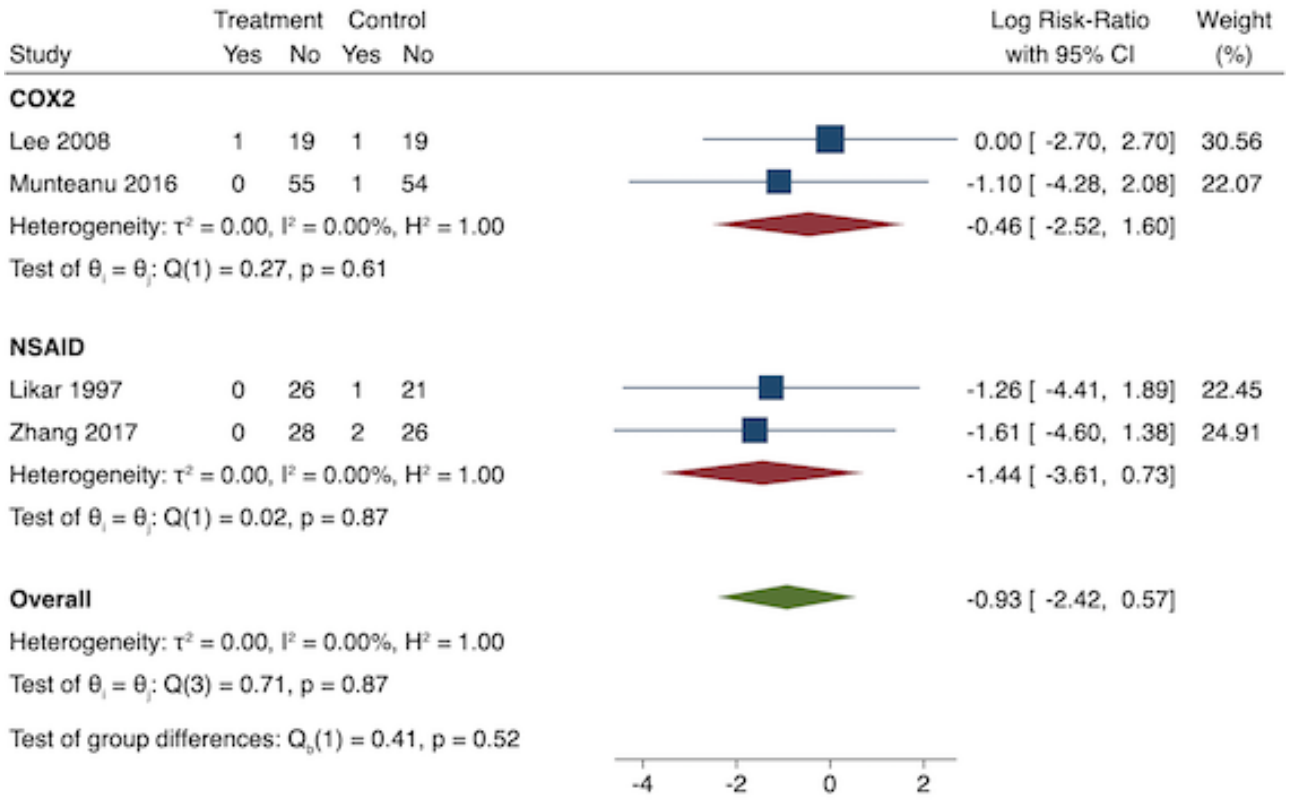
5. Pruritus (yes/no)

Four studies included data for long-term pruritus (Lee 2008; Likar 1997; Munteanu 2016; Zhang 2017). Overall, there may be no difference between pre-emptive and post-incision NSAIDs (RR 0.40, 95% CI 0.09 to 1.76; participants = 254; I^2 = 0%; Analysis 1.7). The certainty of evidence was downgraded to low owing to concerns over risk of bias, mainly in allocation concealment (one level), and imprecision (one level).

We were unable to assess publication bias or conduct meta-regression due to the low number of included studies. On subgroup analysis, non-selective NSAIDs versus COX-2 agents showed no difference between groups (P = 0.52; Figure 14). On sensitivity analysis, no study was at low risk of bias for randomization and allocation concealment. When restricting analysis to the three studies that were at low risk of bias for blinding (Lee 2008; Likar 1997; Munteanu 2016), results were similar to the main analysis (RR 0.50, 95% CI 0.09 to 2.78; participants = 198; I^2 = 0%). Restricting analysis to studies with more than 50 participants gave similar results (RR 0.25, 95% CI 0.03 to 2.25; participants = 166; I^2 = 0%). Assuming those participants who dropped out from Zhang 2017

suffered an event gave similar results (RR 0.50, 95% CI 0.15 to 1.62; participants = 258; studies = 4; I^2 = 0%).

Figure 14. Subgroup analysis for pre-emptive pruritus (NSAID versus COX-2). Effect estimate presented as log risk ratio

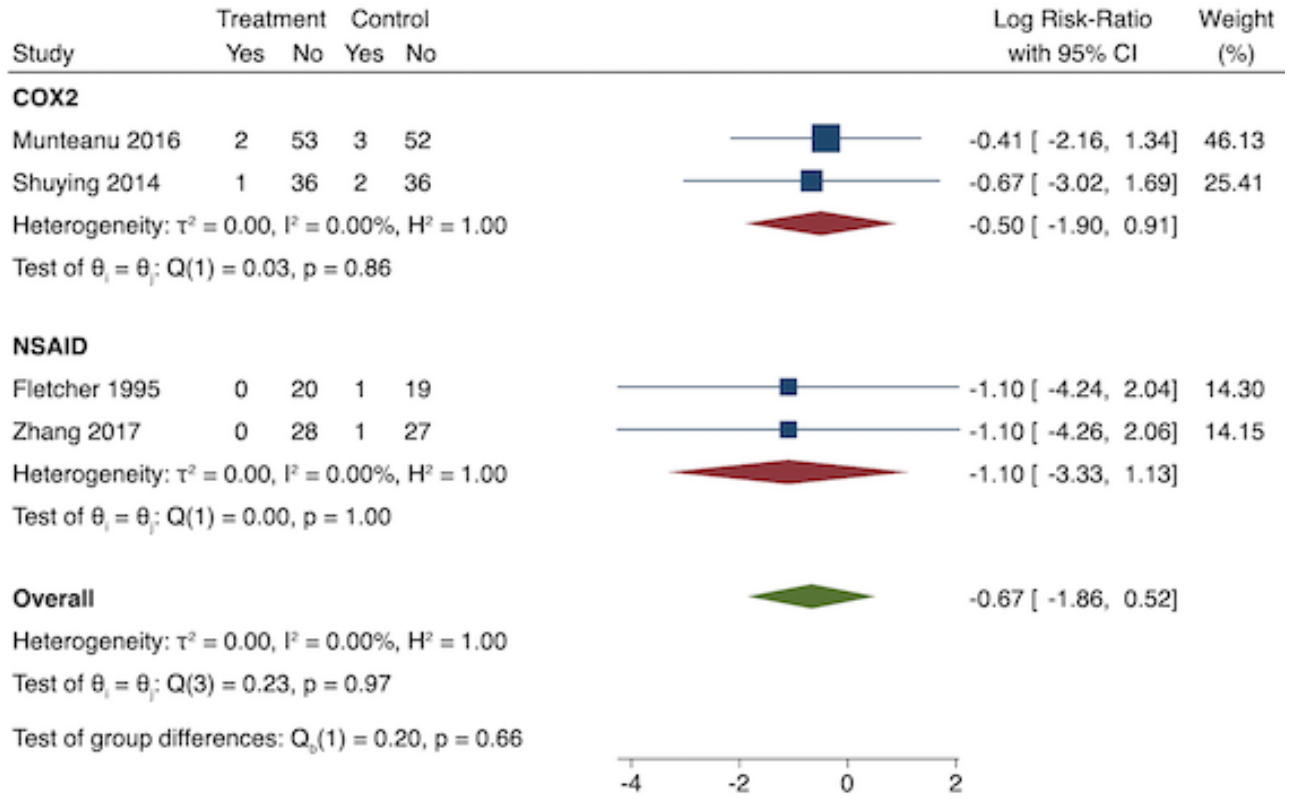


6. Sedation (yes/no)

Four studies reported sedation (long-term) (Fletcher 1995; Munteanu 2016; Shuying 2014; Zhang 2017). There may be no difference in sedation between the pre-emptive and post-incision NSAID groups (RR 0.51, 95% CI 0.16 to 1.68; participants = 281; I^2 = 0%; Analysis 1.8). The certainty of evidence was low owing to concerns over risk of bias, mainly in allocation concealment (one level), and imprecision (one level).

We were unable to assess publication bias or conduct meta-regression due to the low number of included studies. On subgroup analysis, there was no difference between the non-selective NSAID and COX-2 groups (P = 0.66; Figure 15). On sensitivity analysis, restricting analysis to the only study that was at low risk of bias for randomization and allocation concealment (Shuying 2014), results were similar to the main analysis (RR 0.51, 95% CI 0.05 to 5.42; participants = 75). Three studies were at low risk of bias for blinding (Fletcher 1995; Munteanu 2016; Shuying 2014) and results were again similar to the main analysis (RR 0.55, 95% CI 0.15 to 1.98; participants = 225; I^2 = 0%). Restricting analysis to studies with more than 50 participants gave similar results (RR 0.55, 95% CI 0.15 to 1.99; participants = 241; I^2 = 0%). When assuming participants who dropped out suffered events from two studies (Shuying 2014; Zhang 2017), the results were similar (RR 0.75, 95% CI 0.32 to 1.78; participants = 290; I^2 = 0%).

Figure 15. Subgroup analysis for pre-emptive sedation (NSAID versus COX-2). Effect estimate is log risk ratio



7. Patient satisfaction (< 24 hours)

No studies reported patient satisfaction within 24 hours.

8. Chronic pain (yes/no)

No studies reported chronic pain.

9. Time to first bowel movement (hours)

No studies reported time to first bowel movement.

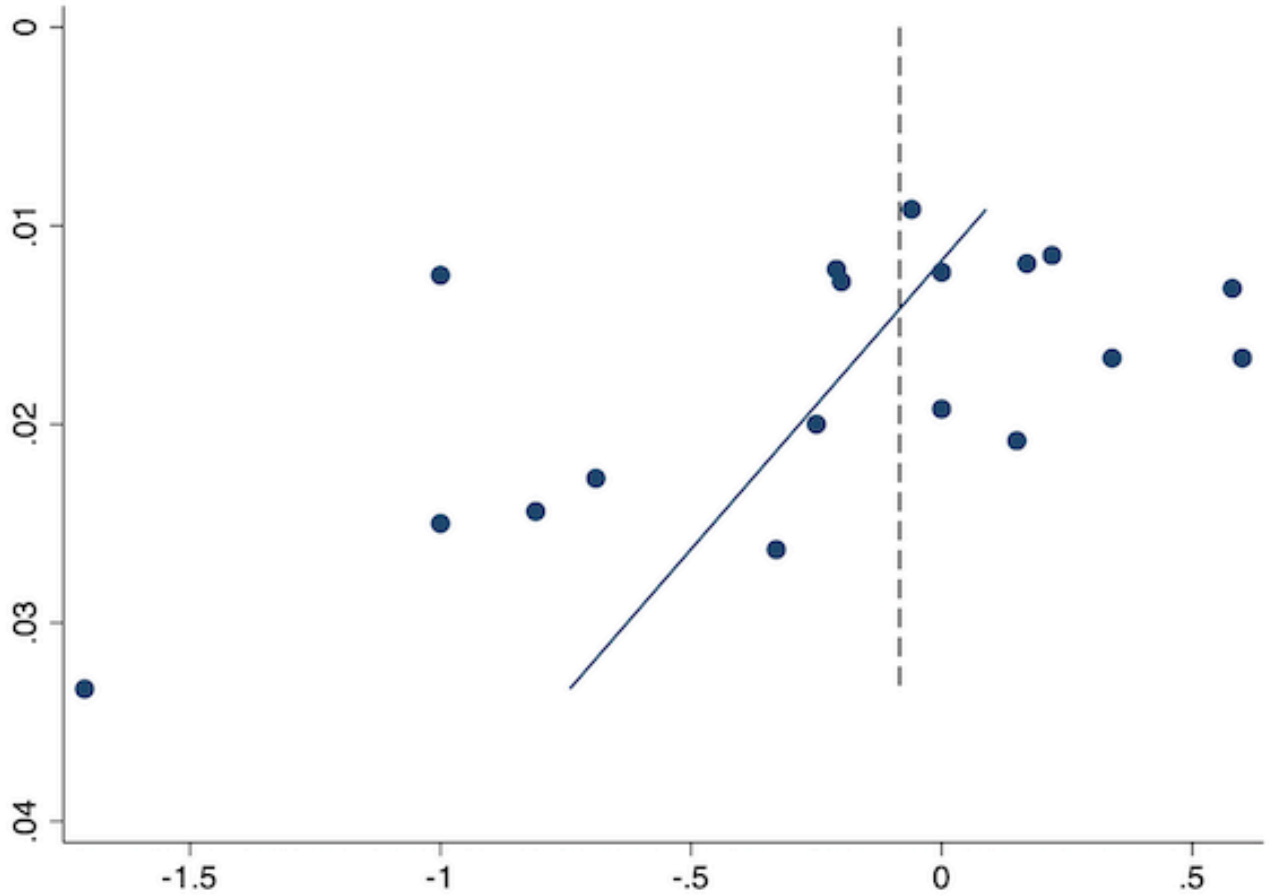
Preventive NSAIDs versus post-incision NSAIDs

Primary outcomes

1. Early acute postoperative pain (measured within six hours postoperatively)

Eighteen studies reported early acute postoperative pain for preventive NSAIDs versus post-incision NSAIDs (Abanto 2014; Ashworth 2002; Aznar-Arasa 2012; Boccara 2005; Giuliani 2015; Gramke 2006; Gunter 2012; Guran 2010; Likar 1998; Martinez 2007; Moonla 2018; Norris 2001; Pandazi 2010; Salonen 2001; Sun 2008; Trampitsch 2003; Wnek 2004; Young 2006). There may be no reduction in early acute postoperative pain with preventive NSAIDs (MD -0.14, 95% CI -0.39 to 0.12; participants = 1140; I^2 = 75%; Analysis 2.1). The certainty of evidence was downgraded to low owing to concerns over risk of bias, mainly in allocation concealment (one level), and unexplained heterogeneity (one level). There was some evidence of publication bias on visual inspection of funnel plots (Figure 16), although quantitative testing was not significant (P = 0.15).

Figure 16. Funnel plot with mean difference on the X-axis and inverse sample size on the Y-axis for preventive early acute postoperative pain



On subgroup analysis of non-selective NSAIDs versus COX-2 inhibitors, there was no difference between the groups (P = 0.32; Figure 17). When comparing groups with different baseline pain levels (Doleman 2018a), there was a significant difference between the groups (P = 0.01; Figure 18) with those in the severe group having greater reductions (MD -0.80; 95% CI -1.23 to -0.37) than those in the moderate (MD -0.24; 95% CI -0.92 to 0.45) and mild group (MD -0.04; 95% CI -0.31 to 0.24). On meta-regression analysis, neither type of surgery (P = 0.23) nor type of anaesthesia (P = 0.17) predicted reductions in early postoperative pain. On sensitivity analysis, when restricting analysis to the three studies that were at low risk of bias for randomization and allocation concealment (Martinez 2007; Pandazi 2010; Sun 2008), results were similar to the main analysis (MD -0.37, 95% CI -1.48 to 0.75; participants = 157; I^2 = 94%). Similarly, 11 studies were at low risk of bias for blinding (Ashworth 2002; Aznar-Arasa 2012; Boccara 2005; Giuliani 2015; Gramke 2006; Martinez 2007; Norris 2001; Pandazi 2010; Salonen 2001; Sun 2008; Wnek 2004) and showed similar results to the main analysis (MD -0.14, 95% CI -0.58 to 0.30; participants = 702; I^2 = 72%). When restricting analysis to studies where SD and means were not estimated, this left nine studies (Abanto 2014; Ashworth 2002; Aznar-Arasa 2012; Boccara 2005; Giuliani 2015; Moonla 2018; Norris 2001; Salonen 2001; Trampitsch 2003) and results were opposite to the main analysis (MD 0.17, 95% CI -0.06 to 0.40; participants = 621; I^2 = 10%). Restricting analysis to studies with more than 50 participants gave opposite results (MD 0.09, 95% CI -0.18 to 0.36; participants = 899; studies = 18; I^2 = 69%).

Figure 17. Subgroup analysis for preventive early postoperative pain (NSAID versus COX-2)

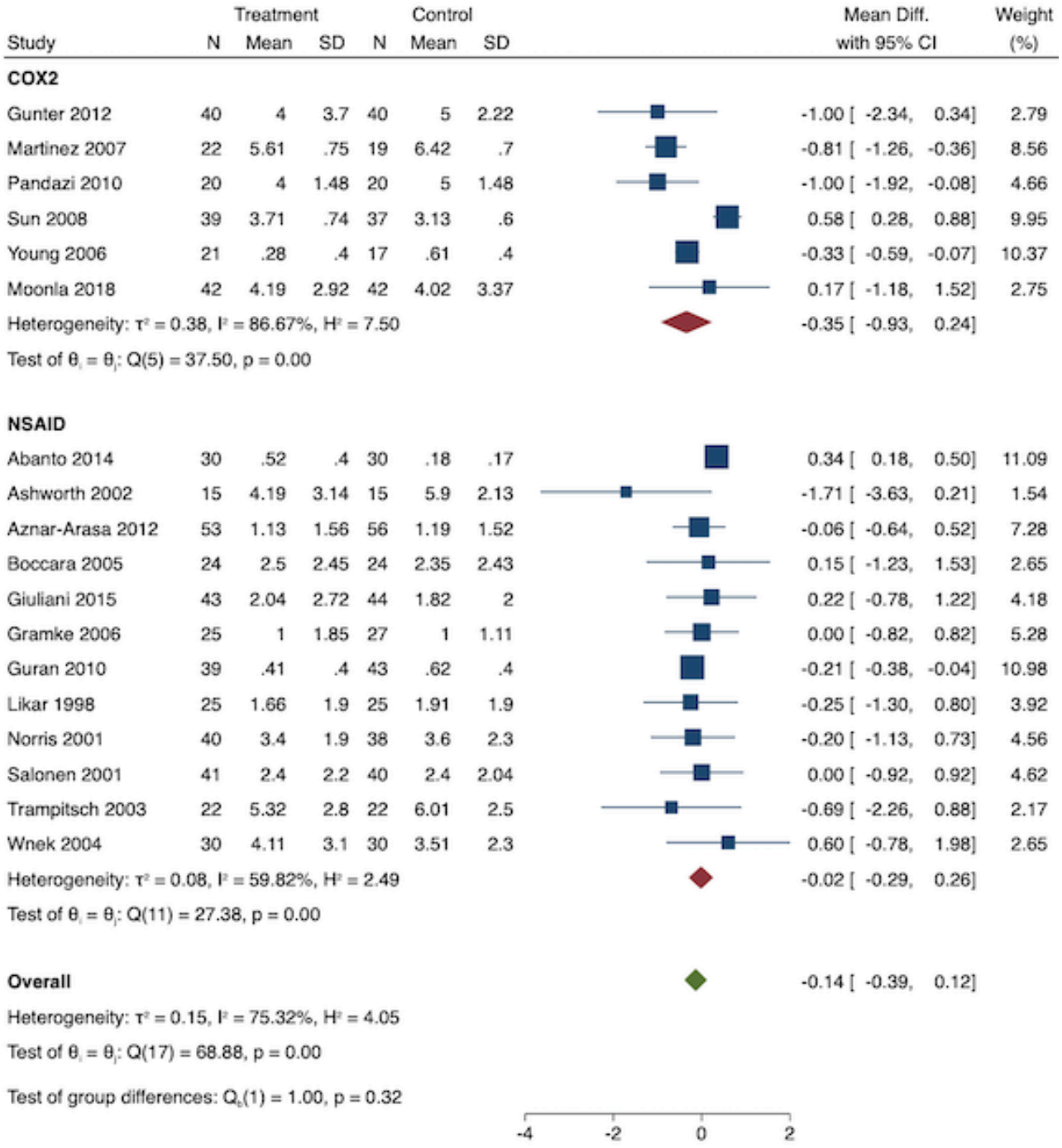
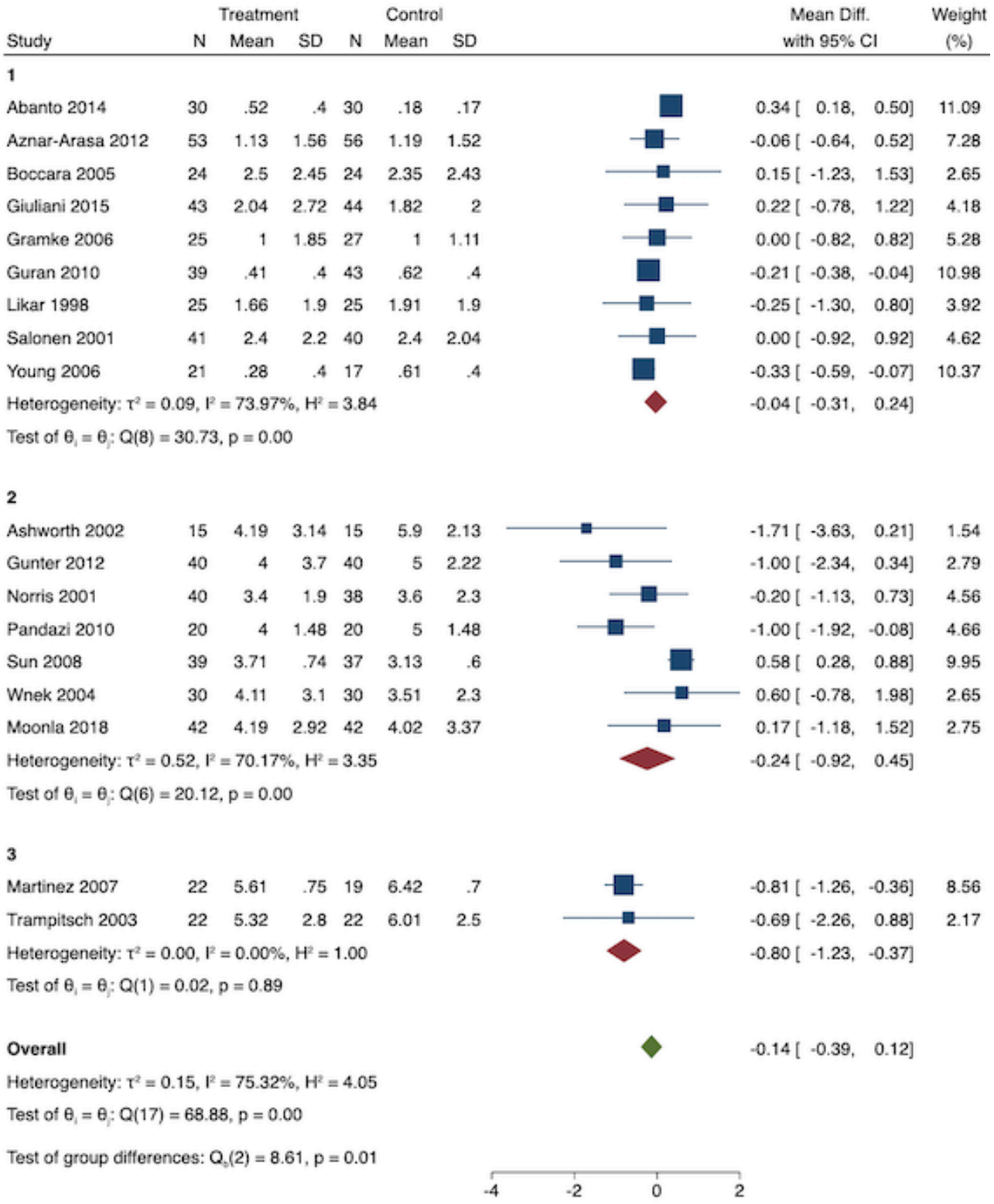


Figure 18. Subgroup analysis for preventive early postoperative pain (baseline pain). Subgroups are 1 (mild), 2 (moderate) and 3 (severe)



2. Adverse events (reoperation for major bleeding within 30 days, acute kidney injury within 48 hours, gastrointestinal ulceration

or bleeding requiring endoscopy within 30 days and myocardial infarction within 30 days)

No studies reported acute kidney injury, gastrointestinal ulceration or myocardial infarction for preventive NSAIDs versus post-incision NSAIDs. One study reported reoperation for bleeding following tonsillectomy (Salonen 2001). There may be no difference between preventive or post-incision NSAIDs (RR 1.95, 95% CI 0.18 to 20.68; participants = 81). The certainty of evidence was very low owing to concerns over imprecision, due to a low number of events (two levels), and indirectness of evidence (one level), as it was conducted in tonsillectomy only. Due to the inclusion of only one study, we could not conduct analysis for publication bias, investigation of heterogeneity or sensitivity analysis. No participants were excluded from this study (Salonen 2001).

Secondary outcomes

1. Nausea and vomiting (self-reported by the patient or requirement for anti-emetic as composite outcome (yes/no))

Short-term nausea and vomiting

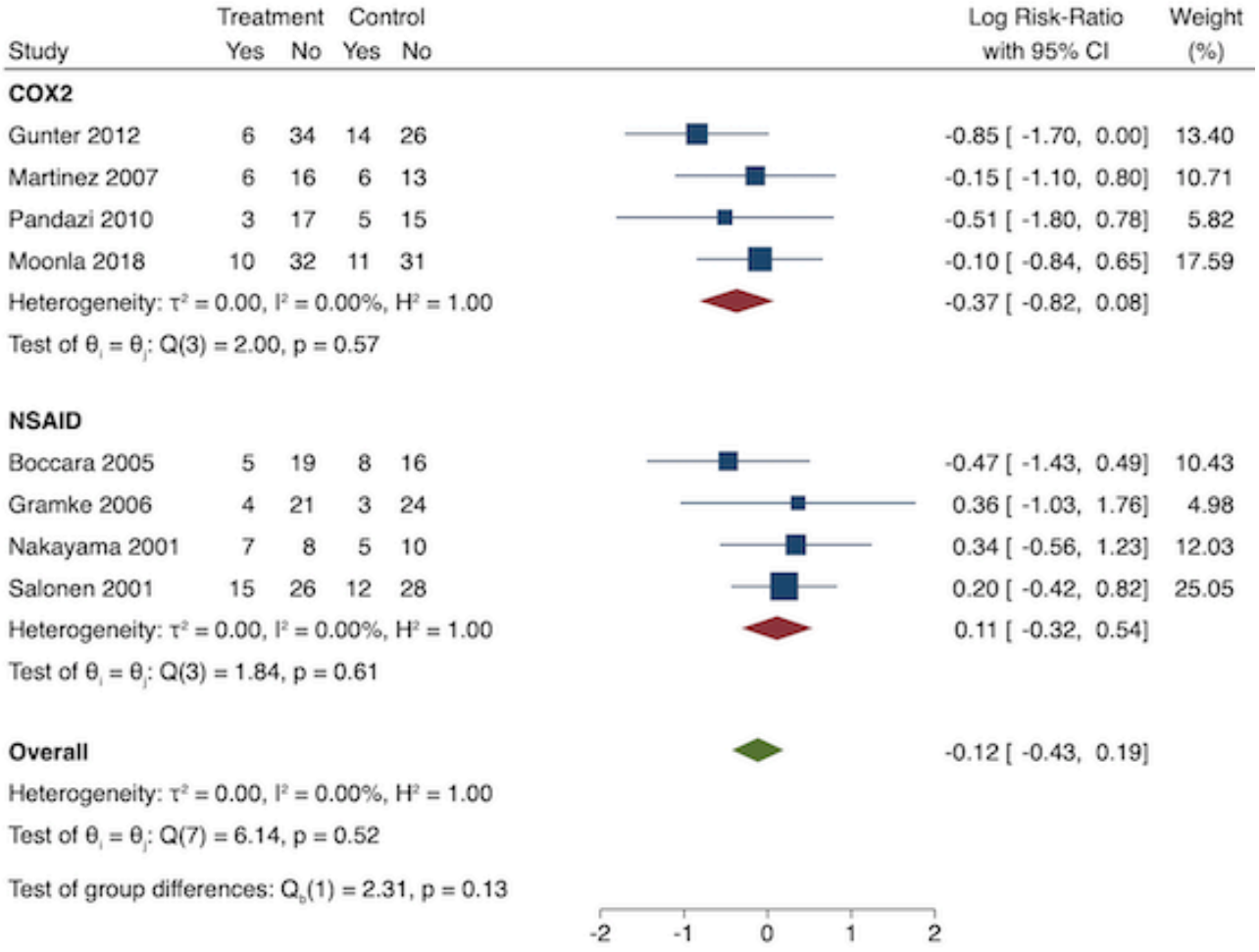
One study reported short-term nausea and vomiting (Sun 2008). There may be no difference in the number of events between preventive and post-incision NSAID groups (RR 1.26, 95% CI 0.49 to 3.30; participants = 76). The certainty of evidence was low owing to concerns over imprecision (one level) and indirectness (one level). Due to the inclusion of only one study, we could not conduct analysis for publication bias, investigation of heterogeneity or most sensitivity analyses. When assuming excluded participants suffered an event from Sun 2008, results were similar to the main analysis (RR 1.00, 95% CI 0.44 to 2.26).

Long-term nausea and vomiting

Eight studies reported long-term nausea and vomiting (Boccara 2005; Gramke 2006; Gunter 2012; Martinez 2007; Moonla 2018; Nakayama 2001; Pandazi 2010; Salonen 2001). There may be no difference between preventive and post-incision NSAIDs (RR 0.89, 95% CI 0.65 to 1.22; participants = 456; I^2 = 0%; Analysis 2.4). The certainty of evidence was low owing to concerns over risk of bias, mainly in allocation concealment (one level), and imprecision (one level).

There were too few studies to undertake assessment of publication bias or meta-regression analysis. On subgroup analysis, there was no difference between non-selective NSAIDs or COX-2 inhibitors (P = 0.13; Figure 19). On sensitivity analysis, restricting analysis to only studies with low risk for randomization and allocation concealment left two studies (Martinez 2007; Pandazi 2010) which gave similar results to the main analysis (RR 0.76, 95% CI 0.35 to 1.63; participants = 81; I^2 = 0%). Restricting analysis to only studies that were low risk for blinding left six studies (Boccara 2005; Gramke 2006; Martinez 2007; Nakayama 2001; Pandazi 2010; Salonen 2001). The results were similar to the main analysis (RR 1.02, 95% CI 0.70 to 1.48; participants = 292; I^2 = 0%). Restricting analysis to studies with more than 50 participants gave similar results (RR 0.89, 95% CI 0.54 to 1.46; participants = 297; studies = 8; I^2 = 30%). In Gunter 2012, it was unclear if excluded participants were analysed and, in Martinez 2007 and Moonla 2018, it was unclear to which group exclusions belonged. Assuming excluded participants suffered an event gave similar results (RR 0.89, 95% CI 0.64 to 1.24; participants = 376; studies = 7; I^2 = 0%).

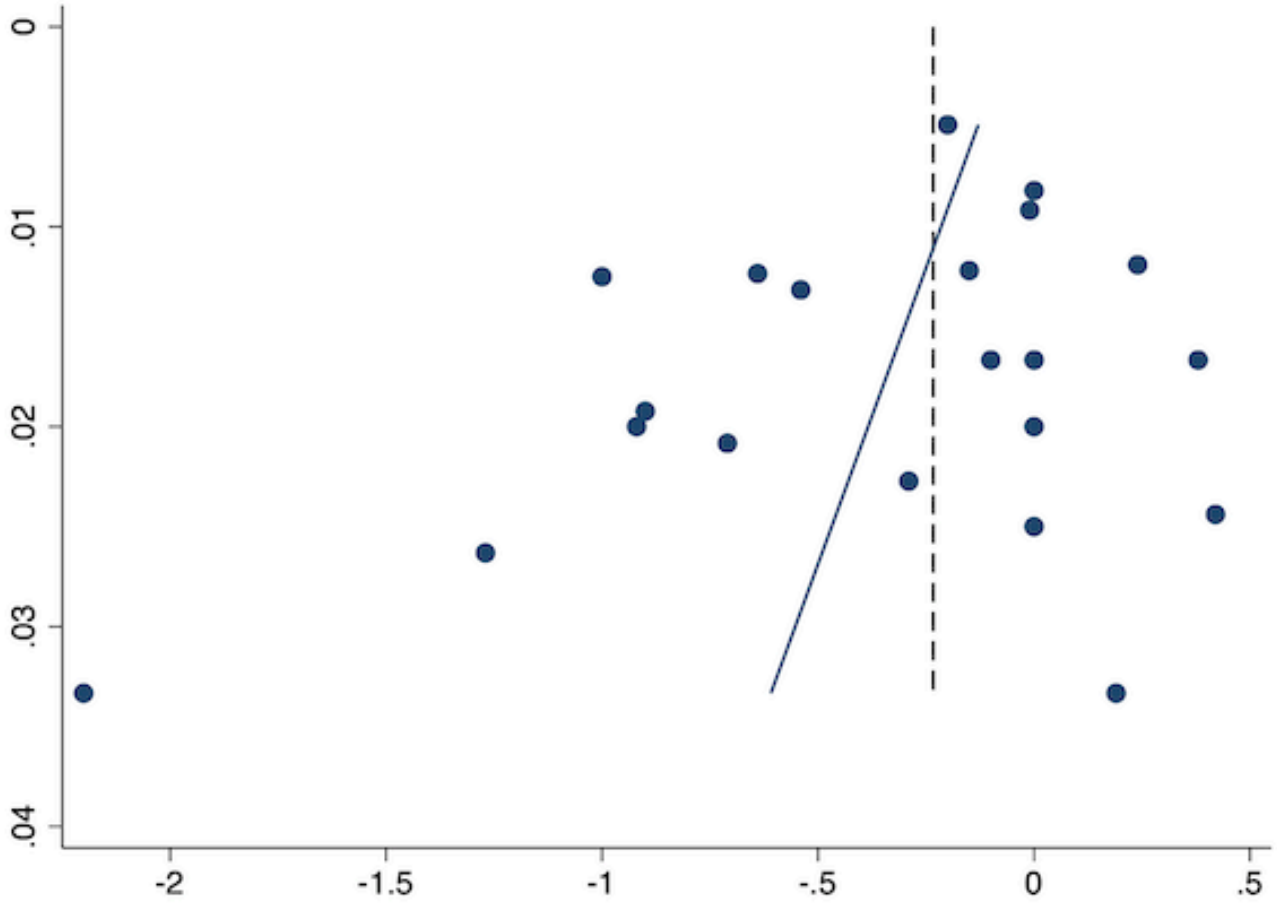
Figure 19. Subgroup analysis for preventive late nausea and vomiting (NSAID versus COX-2)



2. Late acute postoperative pain (measured at 24 to 48 hours)

Twenty-one studies reported late acute postoperative pain (Abanto 2014; Ashworth 2002; Aznar-Arasa 2012; Boccara 2005; Gramke 2006; Gunter 2012; Guran 2010; Likar 1998; Martinez 2007; Moonla 2018; Murphy 1993; Nakayama 2001; Norris 2001; Pandazi 2010; Salonen 2001; Sun 2008; Trampitsch 2003; Wnek 2004; Young 2006; Yuan 2019; Zhou 2017). There may be a reduction in late acute postoperative pain with preventive NSAIDs versus post-incision NSAIDs (MD -0.33, 95% CI -0.59 to -0.07; participants = 1441; I^2 = 81%; Analysis 2.5). The certainty of evidence was low owing to concerns over risk of bias, mainly in allocation concealment and blinding of outcome assessment (one level), and unexplained heterogeneity (one level). There was no evidence of funnel plot asymmetry on visual inspection (Figure 20) or on quantitative testing (P = 0.23).

Figure 20. Funnel plot with mean difference on the X-axis and inverse sample size on the Y-axis for preventive late acute postoperative pain



On subgroup analysis of non-selective NSAIDs versus COX-2 inhibitors, there was no difference between the groups (P = 0.63; Figure 21). When comparing groups with different baseline pain levels (Doleman 2018a), there was no difference between those with mild or moderate baseline pain levels (P = 0.69; Figure 22). On meta-regression analysis, type of anaesthesia (R^2 = 29%; P = 0.11) or type of surgery (R^2 = 0%; P = 0.95) did not predict between-study heterogeneity. On sensitivity analysis, restricting analysis to only three studies (Pandazi 2010; Sun 2008; Yuan 2019) that were at low risk of bias for randomization and allocation concealment showed similar results, although these were less precise (MD -0.28, 95% CI -0.63 to 0.07; participants = 320; I^2 = 64%). Eleven studies were at low risk of bias for blinding (Ashworth 2002; Aznar-Arasa 2012; Boccara 2005; Gramke 2006; Martinez 2007; Nakayama 2001; Norris 2001; Pandazi 2010; Salonen 2001; Sun 2008; Wnek 2004) and showed similar results (MD -0.35, 95% CI -0.61 to -0.09; participants = 627; I^2 = 32%). When restricting analysis to studies where SD and means were not estimated, 11 studies remained in the analysis (Abanto 2014; Ashworth 2002; Aznar-Arasa 2012; Boccara 2005; Moonla 2018; Murphy 1993; Nakayama 2001; Norris 2001; Salonen 2001; Trampitsch 2003; Yuan 2019). They showed similar effects, although these were less precise (MD -0.25, 95% CI -0.61 to 0.11; participants = 800; I^2 = 69%). Restricting analysis to studies with more than 50 participants gave similar results (MD -0.28, 95% CI -0.56 to -0.01; participants = 1170; studies = 21; I^2 = 76%).

Figure 21. Subgroup analysis for preventive late postoperative pain (NSAID versus COX-2)

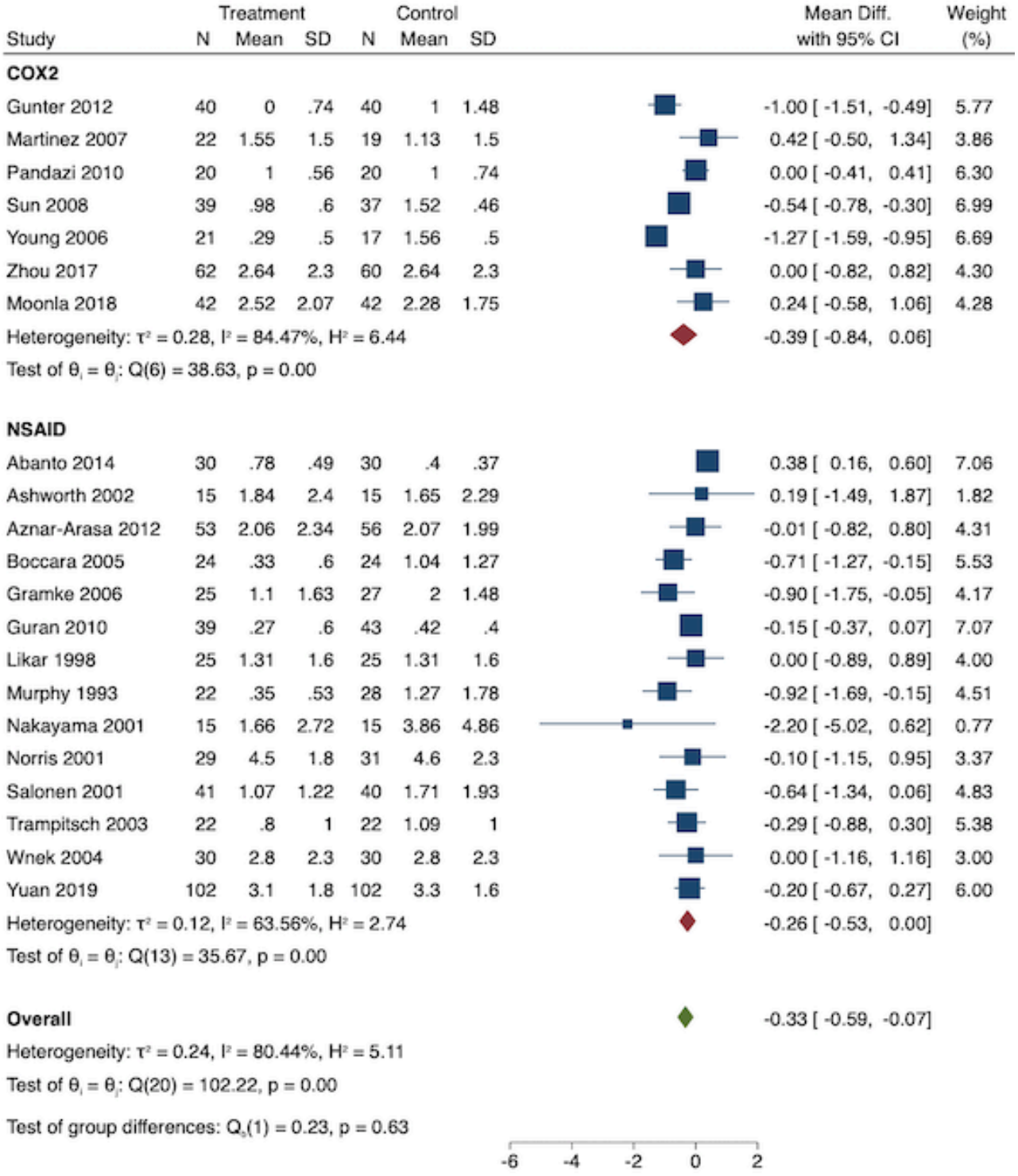
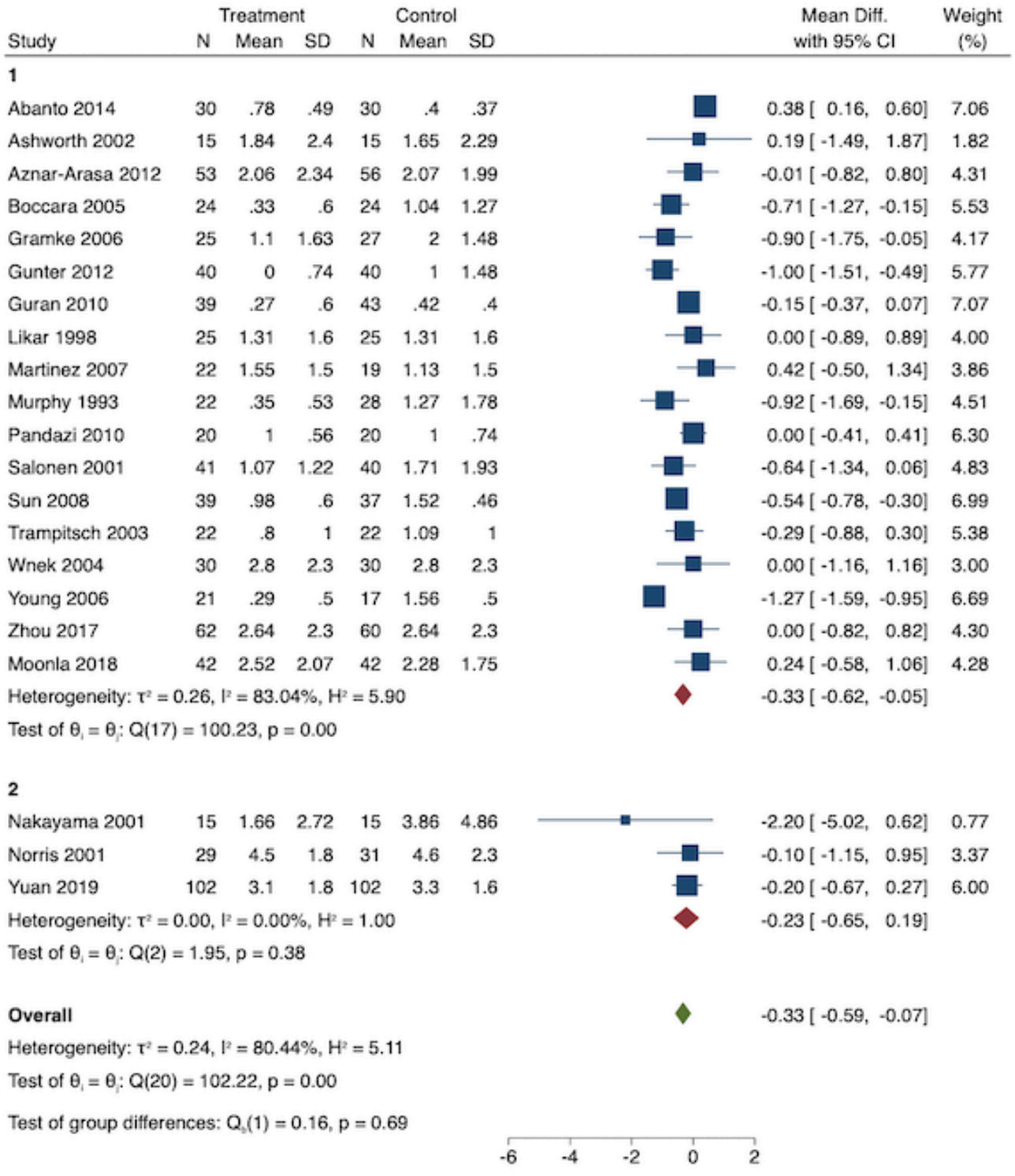


Figure 22. Subgroup analysis for preventive late postoperative pain (baseline pain). Subgroups are 1 (mild) and 2 (moderate)

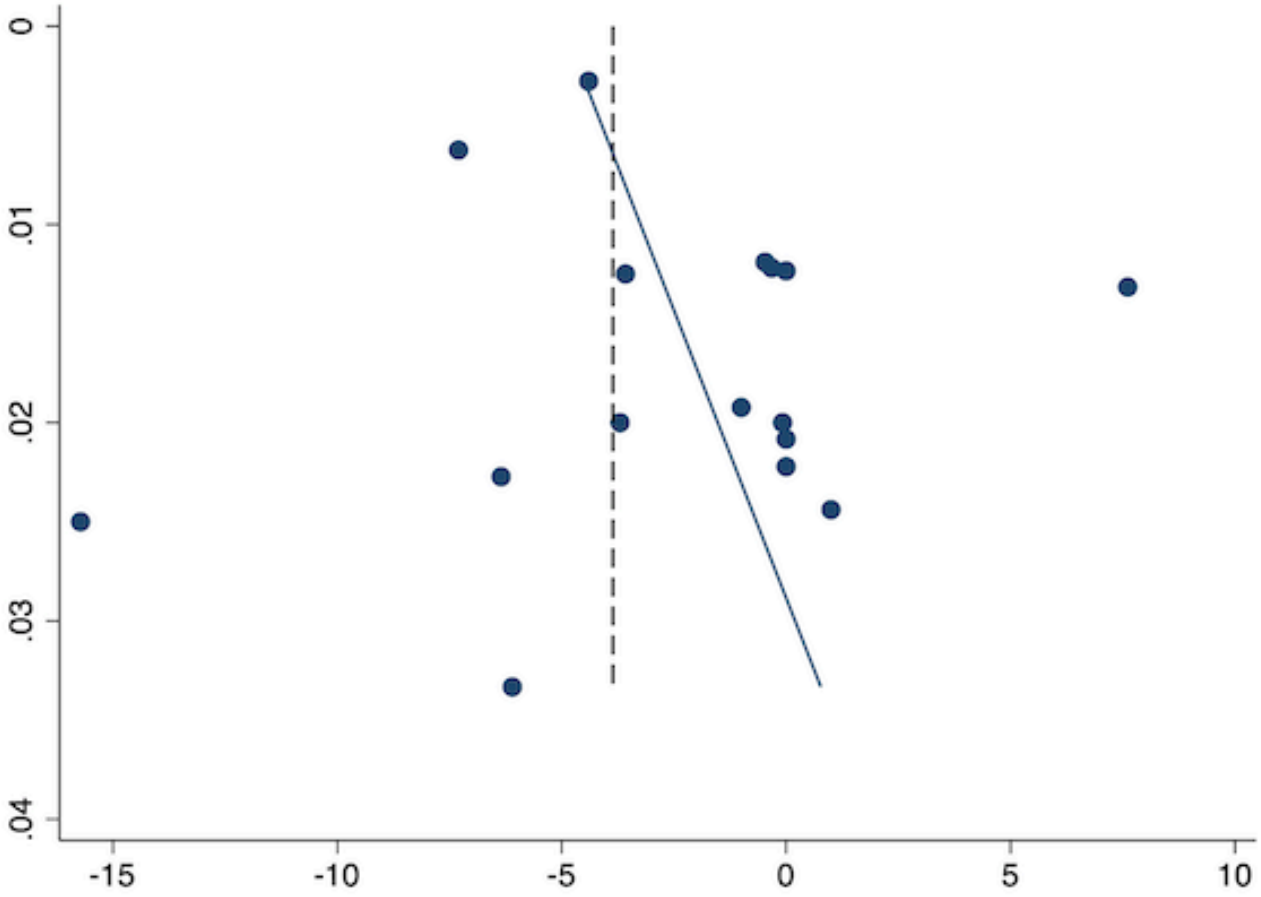


3. Twenty-four-hour morphine consumption (mg)

Sixteen 16 studies reported 24-hour morphine consumption (Ashworth 2002; Boccara 2005; Fleckenstein 2016; Gramke 2006; Gunter 2012; Guran 2010; Likar 1998; Martinez 2007; Moonla 2018; Murphy 1993; Pandazi 2010; Riest 2006; Riest 2008; Salonen 2001; Sun 2008; Trampitsch 2003). There is probably a reduction in 24-hour morphine consumption with preventive versus post-incision NSAIDs (MD -1.93 mg, 95% CI -3.55 mg to -0.32 mg; participants = 1323; I^2 = 49%; Analysis 2.6). The certainty of evidence was moderate, downgraded owing to concerns over risk of bias, mainly in allocation concealment (one level), and incomplete outcome data. There was no evidence of publication bias both on visual

inspection of funnel plots (Figure 23) or quantitative testing (P = 0.18).

Figure 23. Funnel plot with mean difference on the X-axis and inverse sample size on the Y-axis for preventive 24-hour morphine consumption



On subgroup analysis of non-selective NSAIDs versus COX-2 inhibitors, there was no difference between the groups (P = 0.06; Figure 24). When conducting subgroup analysis by baseline consumption of morphine (< 20 mg: low, 20-50 mg: moderate and > 50 mg: high; Doleman 2018a), those with higher baseline consumption had greater reductions in morphine consumption (moderate: MD -3.77 mg; 95% CI -7.27 mg to -0.26 mg versus low: MD -0.32 mg; 95% CI -0.40 mg to -0.24 mg; P = 0.05; Figure 25). On meta-regression analysis, type of surgery predicted all the between-study heterogeneity (R^2 = 100%; P = 0.1), although the number of studies in each group was limited. We could not conduct analysis for type of anaesthesia as all studies used general anaesthesia. On sensitivity analysis, restricting analysis to four studies (Fleckenstein 2016; Martinez 2007; Pandazi 2010; Riest 2006) that were low risk of bias for randomization and allocation concealment (MD -5.31 mg, 95% CI -12.36 mg to 1.73 mg; participants = 486; I^2 = 68%), the results were more imprecise although differed from the main analysis with a greater reduction in morphine consumption. Nine studies were at low risk for blinding (Ashworth 2002; Boccara 2005; Fleckenstein 2016; Gramke 2006; Martinez 2007; Pandazi 2010; Riest 2006; Salonen 2001; Sun 2008) and results were similar to the main analysis although confidence intervals crossed zero (MD -2.13 mg, 95% CI -5.55 mg to 1.29 mg; participants = 773; I^2 = 55%). When restricting analysis to studies that did not estimate means or SDs, there were eight studies in the analysis (Ashworth 2002; Boccara 2005; Guran 2010; Moonla 2018; Murphy 1993; Riest 2006; Riest 2008; Trampitsch 2003) and results were similar to the main analysis (MD -1.30 mg, 95% CI -2.80 mg to 0.19 mg; participants = 858; I^2 = 34%) although again confidence intervals crossed zero. Restricting analysis to studies with more than 50 participants were similar although less precise (MD -1.07 mg, 95% CI -2.33 mg to 0.19 mg; participants = 1075; studies = 16; I^2 = 28%).

Figure 24. Subgroup analysis for preventive 24-hour morphine consumption (NSAID versus COX-2)

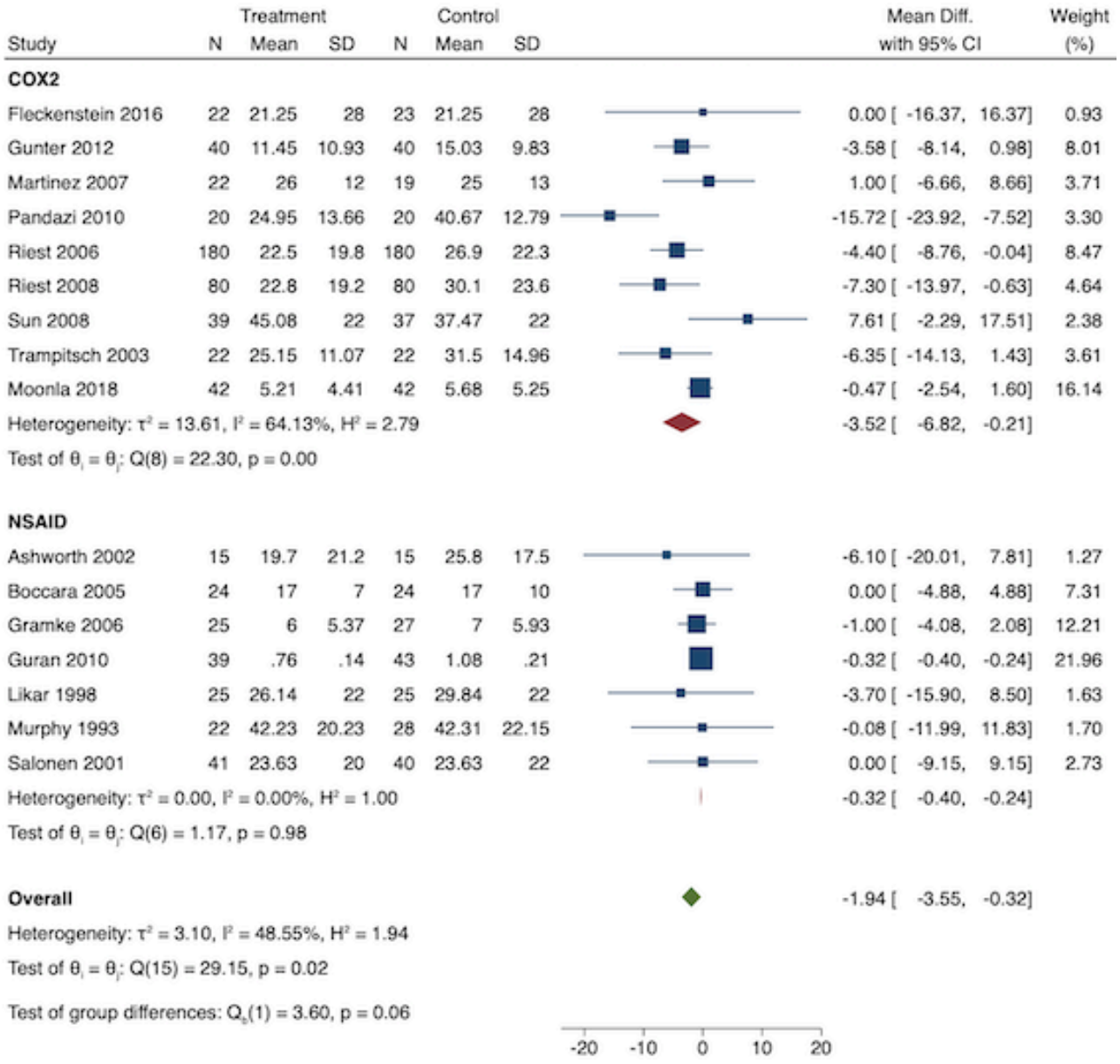
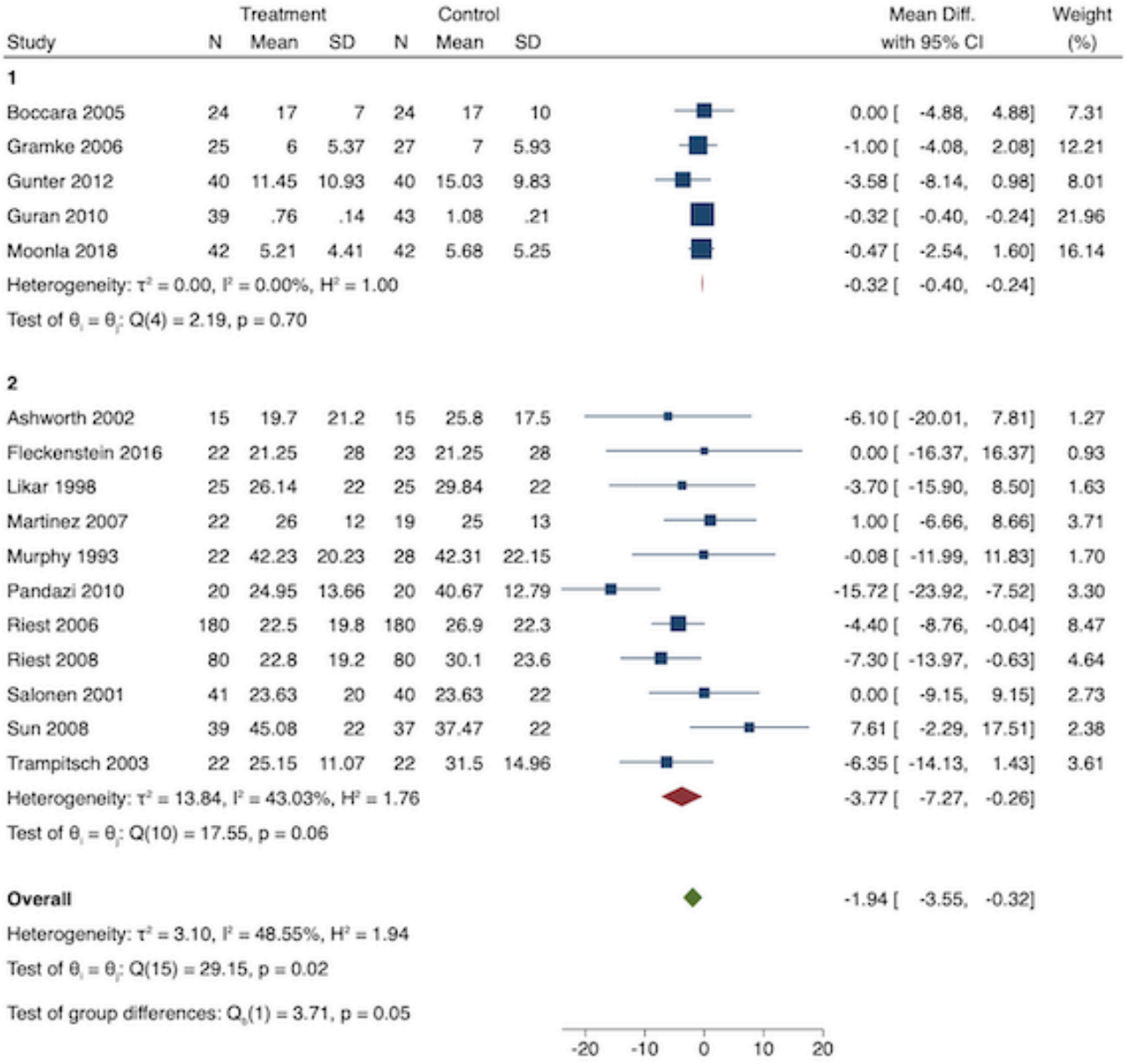


Figure 25. Subgroup analysis for 24-hour morphine consumption (baseline morphine consumption). Subgroups are 1 (low) and 2 (medium)



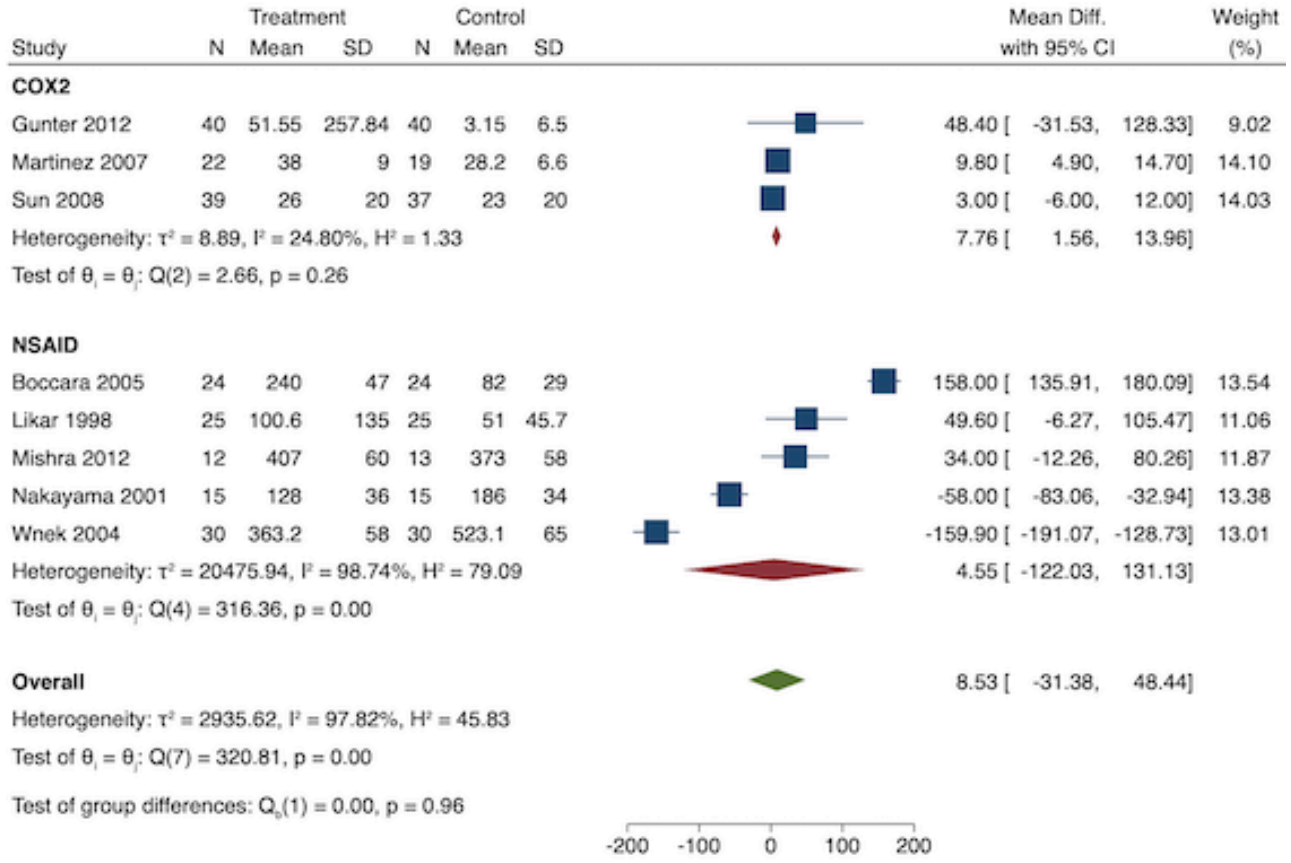
4. Time to first analgesic request (minutes)

Eight studies reported time to analgesic request for preventive versus post-incision NSAIDs (Boccara 2005; Gunter 2012; Likar 1998; Martinez 2007; Mishra 2012; Nakayama 2001; Sun 2008; Wnek 2004). There may be no difference between the groups in time to analgesic request (MD 8.51 minutes, 95% CI -31.24 minutes to 48.27 minutes; participants = 410; I^2 = 98%; Analysis 2.7). The certainty of evidence was very low owing to concerns over imprecision (one level), risk of bias, mainly in allocation concealment (one level), and other bias and unexplained heterogeneity (one level).

We could not conduct investigation for publication bias or meta-regression due to the low number of included studies. On subgroup analysis, there was no difference between non-selective NSAID and COX-2 groups (P = 0.96; Figure 26). On sensitivity analysis, when restricting analysis to two studies that were at low risk of bias for randomization and allocation concealment (Martinez 2007; Sun 2008), it showed similar effect estimates to the main analysis (MD 7.51 minutes, 95% CI 1.21 minutes to 13.81 minutes; participants = 117; I^2 = 42%). Five studies were at low risk of bias for blinding (Boccara 2005; Martinez 2007; Nakayama 2001; Sun 2008; Wnek 2004) which showed opposite effects to the main analysis (MD -7.94 minutes, 95% CI -57.28 minutes to 41.41 minutes; participants = 255; I^2 = 99%). When restricting analysis to studies where means or SDs were not estimated, four studies remained (Boccara 2005; Likar 1998; Nakayama 2001; Wnek 2004) which showed opposite effects to the main analysis (MD -2.71 minutes, 95% CI -155.26 minutes to 149.83 minutes; participants = 188; I^2 = 99%). Restricting analysis to studies with more than 50 participants again found opposite effects

to the main analysis (MD -17.62 minutes, 95% CI -115.94 minutes to 80.70 minutes; participants = 266; I^2 = 97%).

Figure 26. Subgroup analysis for preventive time to analgesic request (NSAID versus COX-2)



5. Pruritus (yes/no)

No studies reported short-term pruritus. Three studies reported long-term pruritus for preventive versus post-incision NSAIDs (Gunter 2012; Likar 1998; Salonen 2001). There may be no difference between the groups (RR 0.56, 95% CI 0.09 to 3.35; participants = 211; I^2 = 0%; Analysis 2.8). The certainty of evidence was low owing to concerns over risk of bias (one level) and imprecision (one level).

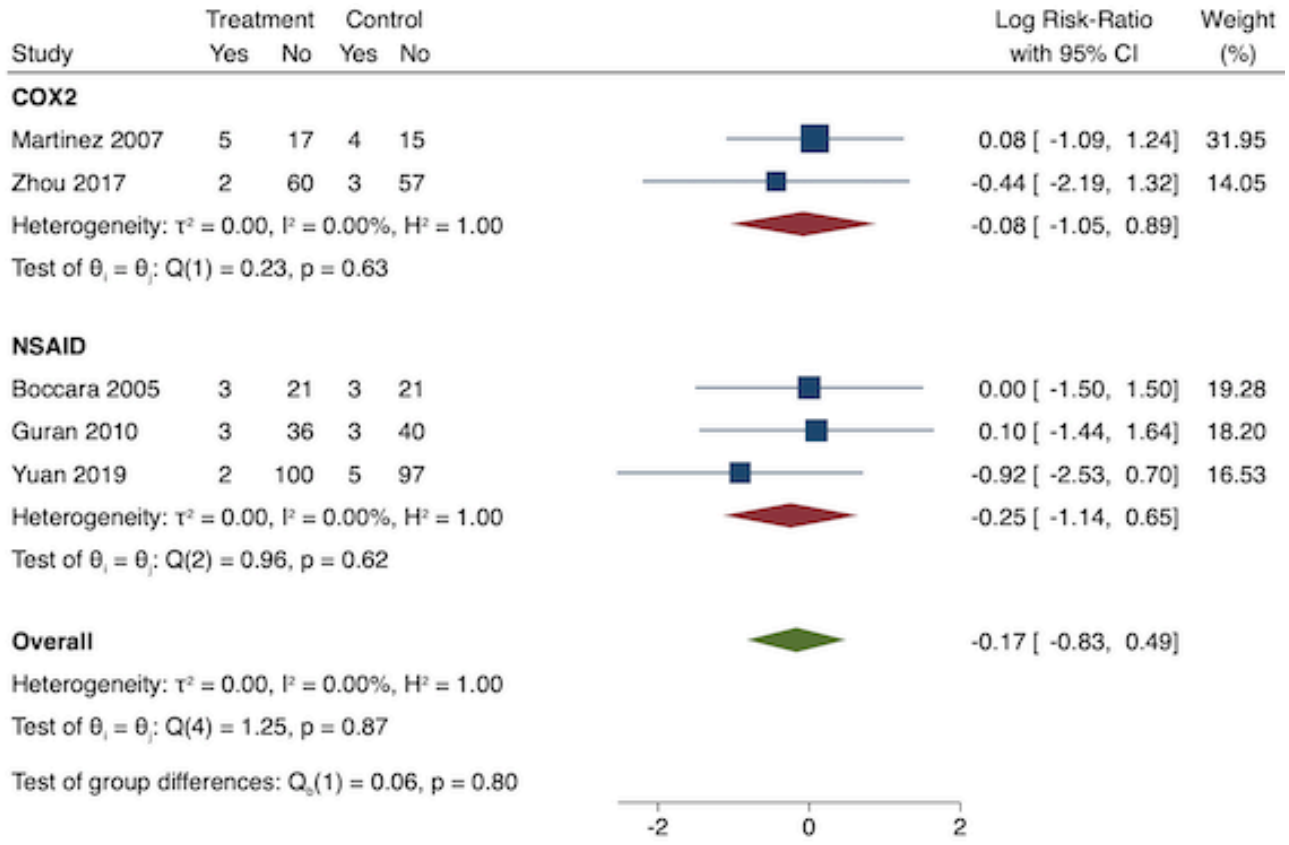
We were unable to conduct analysis for publication bias and meta-regression due to the low number of included studies. We did not conduct subgroup analysis as only one study used non-selective NSAIDs. On sensitivity analysis, restricting analysis to only one study that was at low risk of bias for randomization, allocation concealment and blinding (Sun 2008), it showed different, more imprecise effects to the main analysis (RR 2.93, 95% CI 0.12 to 69.83; participants = 81). No studies had fewer than 50 participants. In Gunter 2012, it was unclear if excluded participants were analysed. In Likar 1998, it was unclear which group exclusions belonged to. The other study (Salonen 2001) had no participants lost to follow-up.

6. Sedation (yes/no)

No studies reported short-term sedation. Five studies reported long-term sedation for preventive versus post-incision NSAIDs (Boccara 2005; Guran 2010; Martinez 2007; Yuan 2019; Zhou 2017). There may be no difference between the groups (RR 0.84, 95% CI 0.44 to 1.63; participants = 497; I^2 = 0%; Analysis 2.9). The certainty of evidence was low owing to concerns over risk of bias, mainly in allocation concealment (one level), and imprecision (one level).

We were unable to conduct analysis for publication bias and meta-regression due to the low number of included studies. On subgroup analysis, there was no difference between non-selective NSAID and COX-2 agents (P = 0.86; Figure 27). On sensitivity analysis, only two studies were at low risk of bias for randomization and allocation concealment (Martinez 2007; Yuan 2019) which gave similar results to the overall analysis (RR 1.08, 95% CI 0.34 to 3.45; participants = 41). Two studies were at low risk of bias for blinding (Boccara 2005; Martinez 2007) which again gave similar results to the main analysis (RR 0.77, 95% CI 0.30 to 1.98; participants = 245; I^2 = 0%). Restricting analysis to studies with more than 50 participants gave similar results (RR 0.67, 95% CI 0.26 to 1.72; participants = 408; studies = 5; I^2 = 0%). In Martinez 2007, it was unclear to which group exclusions belonged. Assuming excluded participants suffered an event in the other studies gave similar results (RR 0.95, 95% CI 0.58 to 1.58).

Figure 27. Subgroup analysis for preventive sedation (NSAID versus COX-2). Effect estimate is log risk ratio



7. Patient satisfaction (< 24 hours)

Only one study reported patient satisfaction for preventive versus post-incision NSAIDs (Giuliani 2015). There is probably no difference between the groups on a 10-point scale (MD -0.42, 95% CI -1.09 to 0.25; participants = 72; Analysis 2.10). The certainty of evidence was moderate owing to concerns over risk of bias (one level), mainly due to attrition bias. There were too few studies to undertake assessment for publication bias, investigation of heterogeneity and sensitivity analysis.

8. Chronic pain (yes/no)

No studies reported chronic pain.

9. Time to first bowel movement (hours)

Only one study reported time to bowel movement for preventive versus post-incision NSAIDs (Sun 2008). There is probably no difference between the groups (MD 0.00 hours, 95% CI -15.99 hours to 15.99 hours; participants = 76; Analysis 2.11). The certainty of evidence was moderate owing to concerns over imprecision (one level). There were too few studies to undertake assessment for publication bias, investigation of heterogeneity and sensitivity analysis.

DISCUSSION

Summary of main results

For pre-emptive NSAIDs, there is probably a decrease in early acute postoperative pain, although none of the included studies reported adverse events. There may be no difference between the groups in nausea and vomiting (short- or long-term). There may be a reduction in late acute postoperative pain. There may also be a reduction in 24-hour morphine consumption with pre-emptive NSAIDs and an increase in time to analgesic request. There may be no difference in opioid adverse events such as pruritus or sedation, although the number of included studies for these outcomes was small. No study reported patient satisfaction, chronic pain or time to first bowel movement. The certainty of evidence ranged from moderate to low mainly owing to concerns over risk of bias. However, investigation of heterogeneity showed that baseline pain or morphine consumption may result in more clinically significant reductions in agreement with previous research (Doleman 2018a).

For preventive NSAIDs, there may be no difference in early acute postoperative pain. One study (Salonen 2001) reported adverse events from NSAIDs (reoperation for bleeding) although the events were low which did not allow any meaningful conclusions to be drawn. There may be no difference in rates of nausea and vomiting (short- and long-term). There may be a reduction in late acute postoperative pain. There is probably a reduction in 24-hour morphine consumption. We are very uncertain if there is any effect on time to analgesic request. As with pre-emptive NSAIDs, there may be no difference in other opioid adverse events such as pruritus and sedation. There is probably no difference in patient satisfaction (Giuliani 2015). No study reported chronic pain. There is probably no difference in time to first bowel movement (Sun 2008). The certainty of evidence ranged from moderate to very low and there was some evidence that higher baseline pain or morphine consumption led to larger reductions in effects (Doleman 2018a).

None of the observed differences for both pre-emptive or preventive NSAIDs were clinically significant as defined in our protocol (1.5 reduction in pain, 10 mg reduction in morphine consumption or delay in analgesic request of one hour). However, these results need to be taken in the context of variable effects with baseline risk, that is, clinically significant effects may be observed at higher baseline risk (10 mg reduction in morphine consumption may be seen in studies with high morphine consumption in the control group; Doleman 2018a).

Overall, there may be some evidence of small, non-clinically significant reductions in acute postoperative pain and 24-hour morphine consumption with pre-emptive and preventive NSAIDs, with five out of six of these outcomes showing possible benefit. In addition, there was some evidence of better efficacy with higher baseline pain levels and morphine consumption (more painful operations or higher-risk patients; Doleman 2018a). However, only one study reported major adverse events for preventive NSAIDs (Salonen 2001). We found no difference in opioid adverse events from a limited number of included studies, further questioning the clinical significance of any observed differences.

Overall completeness and applicability of evidence

Our review had a wide ranging search strategy including electronic databases, grey literature sources, reference searches and searching of conference proceedings (Doleman 2019). This was important in order to reduce the risk of publication bias (Chong 2016). Indeed, when using more appropriate tests for publication bias, we found no evidence of publication bias (imprecise study effects). We excluded 20 studies mainly for reasons which would bias results, such as different doses in each group and different routes of administration (Characteristics of excluded studies). There are currently seven studies awaiting classification, two that we were unable to translate (Aoki 2002; Bai 1998) and five where we were unable to locate full texts despite contacting authors and the British Library (Beg 2001; Belzarena 1994; De Oliveira 1999; Jia 2011; Nicholson 2014). Of these studies, three found an improvement in pain with pre-emptive NSAIDs (Aoki 2002; Bai 1998; Jia 2011) while another two found no difference between the groups (De Oliveira 1999; Nicholson 2014). The other two results are unknown (Beg 2001; Belzarena 1994). Depending on their results, inclusion of these studies could potentially alter the conclusions of this review. This would be less likely for outcomes that include many studies (such as pain), due to the similar sample size of the missing studies (see Characteristics of studies awaiting classification) but more likely for outcomes with few included studies (nausea and vomiting).

We chose to include a range of time points for measurement of pain outcomes such as early acute postoperative pain (0-6 hours) and late acute postoperative pain (24-48 hours). This is due to the fact that postoperative pain trials tend to report a variety of different time points for pain (Doleman 2018a) and exclude others. If we had included more precise time points, this would lead to the exclusion of many studies for each of these outcomes. However, we recognise that including different studies with different time points within one outcome (e.g. one study measuring pain at 0 hours versus 6 hours) could affect pain levels, as these may improve with time. From our experience, this is less of an issue with opioid consumption (Doleman 2018a). We selected early pain as our primary outcome as this is when pain is likely to be at its maximal severity. It could be argued that opioid consumption may be a more appropriate primary outcome (and opioid adverse events more so) as the aim of multimodal analgesia is to reduce opioid consumption. Also, it may not be ethical to have two groups with differences in pain. We will consider this in future review updates.

A major limitation of our previous review on preventive opioids related to the reporting of central tendency as both means and medians in the included studies (Doleman 2018b). One analysis of 24-hour morphine consumption showed a difference on meta-analysis of means although nearly all studies that reported median values showed no significant difference. This raises two important issues, firstly, the likelihood of this leading to false conclusions on the efficacy of preventive opioids by review consumers not appreciating this subtle fact (especially those not reading the whole review) and the issues it raises in giving false positives on publication bias assessment (by excluding a large number of 'negative' studies). The options are to include median results in a narrative synthesis (Doleman 2018b) or estimate means from medians (Higgins 2011a). For the reasons described above, the narrative synthesis option has severe disadvantages. Although estimating means from medians risks making false assumptions about the data, it helps ensure all studies contribute data to the analysis. Moreover, even if studies report data as means and SDs, this does not ensure that the underlying data is not skewed. Therefore, we felt the ideal solution was to estimate means from medians and SD from IQR as stated in the *Cochrane Handbook* (Higgins 2011a) or the range from published research (Hozo 2005) so that all studies could be included. We then conducted a sensitivity analysis by excluding studies where these values had been estimated or imputed. This allows both scenarios to be compared and reduces the risks described previously. In most cases, results of the sensitivity analysis were similar to the main analysis (Effects of interventions).

In terms of the applicability of the evidence, the range of operations included in this review (Description of studies) were more diverse than in our opioid review (Doleman 2018b). Although this helps with external validity, it limited the meta-regression analysis as there were few studies in each surgical subgroup. Despite helping external validity, diverse types of surgery may raise issues surrounding clinical heterogeneity. However, our investigation of heterogeneity did not consistently identify type of surgery as a significant predictor of between-study heterogeneity. Moreover, our previous research has demonstrated that baseline risk models (our subgroup analysis) can account for differences between different surgical subtypes (Doleman 2018a). Another issue with respect to applicability is the inclusion of mainly low-risk participants, those without prior analgesic intake or chronic pain, and a lack of standardisation of postoperative opioids which may affect opioid consumption outcomes (Description of studies). Furthermore, some of our analyses included few studies from a limited set of surgical subtypes which may raise issues about whether these results can be applied to other operations. This also raises the issue around type of NSAIDs used and whether results from the use of certain NSAIDs can be applied to others. Despite our subgroup analysis suggesting no difference between non-selective NSAIDs and COX-2 inhibitors, we cannot rule out differences between agents within these classes, especially if different doses were used.

Quality of the evidence

The certainty of evidence for all outcomes ranged from moderate to very low, most commonly due to issues with risk of bias (Figure 2; Figure 3) although unexplained heterogeneity and imprecision were other common reasons. Issues with risk of bias were mainly due to a lack of reporting on allocation concealment and a lack of published protocols (unclear risk) which may result in selection bias and selective reporting bias, respectively. Moreover, 14 studies did not use a double-dummy placebo so were at high risk of bias for blinding which may affect a subjective outcome such as pain. Our previous research has identified that bias in domains of trial conduct, such as allocation concealment, can exaggerate effects so results from this review must be treated with caution (Doleman 2018a). However, when we conducted sensitivity analysis, there was no consistent effect of risk of bias and effect estimates were similar when we included only studies that scored low risk for either domains of random allocation or blinding (Risk of bias in included studies).

Similar to our previous research, when we conducted subgroup analysis based on differences in baseline pain/morphine consumption, we found larger effects with higher baseline pain/morphine consumption which may have contributed to the heterogeneity observed with these outcomes (Doleman 2018a). This may also be the mechanism by which subgroup differences observed with type of surgery may manifest. Furthermore, unexplained heterogeneity may have contributed to imprecision as our analysis was conducted using random-effects models where confidence intervals are wider if statistical heterogeneity exists in analyses. For our meta-regression analysis, type of surgery and type of anaesthesia were not significant predictors of between-study heterogeneity in most analyses. However, the limitations of such analysis should be considered when the number of included studies is 40 or less (López-López 2014).

Potential biases in the review process

Similar to our opioid review (Doleman 2018b), none of our review authors were involved in any of the included studies. However, some authors are involved in an ongoing study on preventive paracetamol (see Declarations of interest). Our previous research has identified issues with traditional meta-analysis when analysing outcomes dependent on baseline risk (Doleman 2018a), although we accounted for this when performing subgroup analysis and found that on most occasions this supported our previous findings. We have also conducted research that has identified type I errors when using Egger's linear regression test for this type of data using simulated meta-analyses. With this in mind, we have used our novel test which is based on inverse sample size rather than standard error and has been found to perform better than Egger's test due to lack of dependence between effect estimates and standard errors (Doleman 2020).

Agreements and disagreements with other studies or reviews

Although now over a decade old, the two previous reviews of pre-emptive and preventive NSAIDs found some similar and some different results to our review (Møiniche 2002; Ong 2005). The first review published in 2002 (Møiniche 2002) found that pre-incisional NSAIDs had no effect on acute pain (MD 0 mm; 95% CI -2 mm to 2 mm) with many studies also showing no benefit in reducing analgesic consumption. In contrast, we found some positive evidence for pre-emptive and preventive NSAIDs in reducing some measures of acute pain and opioid consumption, although we did find limitations in the certainty of evidence and clinical significance. A later review published in 2005 (Ong 2005) found no difference in acute pain, although it did find that pre-incisional NSAIDs reduced analgesic consumption and prolonged time to first analgesia. We found similar results with analgesic consumption, although we did find some reductions in acute pain in contrast to this review (Ong 2005).

AUTHORS' CONCLUSIONS

Implications for practice

We found some evidence of reductions in acute pain and analgesic consumption for both pre-emptive and preventive NSAIDs. However, these results were not consistent, not clinically significant and the certainty of evidence ranged from moderate to very low, limiting our certainty about these results. Moreover, although the number of included studies was small, we found no difference in postoperative opioid adverse events which further limits the clinical significance of our findings. We did find some evidence of improved efficacy in studies with higher baseline pain or analgesic consumption, although the limitations of such subgroup analysis must be considered. Importantly, we found only one study (Salonen 2001) reporting serious adverse events for the use of NSAIDs (reoperation for bleeding) with a limited number of events. It remains distinctly possible that administration of NSAIDs prior to surgery could increase surgical bleeding, gastrointestinal bleeding, myocardial infarction or acute kidney injury. This, despite some potential early benefits on pain, means any findings influencing clinical practice need to consider this possibility. Due to the large number of included studies in this review, it is unlikely that the studies awaiting classification will significantly change the conclusions of this review (Characteristics of studies awaiting classification).

Implications for research

Due to the limitations above, future research should aim to follow low risk of bias methodology to improve the certainty of evidence from these studies, particularly allocation concealment and adequate use of double-dummy placebo. Future studies should also aim to include larger numbers of participants in order to be adequately powered to identify whether pre-emptive or preventive NSAIDs reduce postoperative opioid adverse events and ensure they evaluate possible serious adverse events of pre-incision NSAIDs. Future research may also wish to study pre-emptive or preventive NSAIDs in operations with high baseline pain or analgesic consumption to improve absolute effects (Effects of interventions).

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CHARACTERISTICS OF STUDIES

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

Abanto 2014

Study characteristics	
Methods	Study design: parallel-group randomized controlled trial Sample size: 60 Country: Peru Setting: dental clinic Dates conducted: November 2013 to July 2014 Postoperative opioid used and delivery: none Pain score collection: researcher Concurrent postoperative analgesics: paracetamol or NSAID
Participants	**Inclusion criteria**

Abanto 2014 *(Continued)*

1. ASA 1
2. Aged 18 to 45 years old
3. Complete primary education
4. Undergoing simple dental extraction for dental caries and asymptomatic at the time of extraction with a previous history of extraction

Exclusion criteria

1. Refused study participation
2. Contraindication to extraction or study drugs
3. Pregnancy or breast-feeding
4. Patients receiving anaesthesia, sedatives, paracetamol, NSAIDs, tricyclic antidepressants, opioids, corticosteroids, anticonvulsants, phenothiazines, alcohol or caffeine 48 hours before the extraction
5. Intellectual disability
6. Procedure could not be performed
7. Exceeded two tubes of anaesthetic (> 3.6 mL) to achieve adequate anaesthesia
8. Pain more than 70 mm (on a 100 mm VAS) pre-extraction
9. Procedures exceeded 20 minutes
10. Participants who did not fill in the measuring instrument correctly
11. Participants who did not comply with the instructions, abandoned the study, did not attend postoperative control or those who presented with any of the following post-extraction complications: haemorrhage, infection, alveolitis, soft tissue lesions, bone or adjacent parts

Interventions	**Group Prophylactic (30 participants):** naproxen sodium 550 mg PO 30 minutes before the procedure, then every 12 hours for 4 doses **Group Continuous (30 participants):** naproxen sodium 550 mg PO 20 minutes after the procedure, then every 12 hours for 4 doses
Outcomes	1. Postoperative pain (0-100 mm VAS at 1, 8 and 24 hours) 2. Adverse effects (no details given)
Notes	Funding: not reported Declarations of interest: not reported Authors contacted: no Other: article in Spanish. Unpublished thesis.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unclear details. Quote: "Patients were randomly assigned".
Allocation concealment (selection bias)	Unclear risk	No mention
Blinding of participants and personnel (performance bias) All outcomes	High risk	No mention of double-dummy placebo. Quote: "Naproxen sodium 550 mg was administered orally 30 minutes before the procedure, then every 12 hours until the 4 doses".
Blinding of outcome assessment (detection bias) All outcomes	High risk	Likely unblinded from above information

Abanto 2014 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Three excluded for alveolitis unlikely to bias results as this would cause confounding from increased pain. Quote: "Three people were eliminated by alveolitis".
Selective reporting (reporting bias)	Unclear risk	No registration or protocol. Unpublished thesis
Other bias	Unclear risk	No detailed information on baseline characteristics

Ashworth 2002

Study characteristics	
Methods	Study design: parallel-group randomized controlled trial Sample size: 30 Country: UK Setting: secondary care Dates conducted: not reported Postoperative opioid used and delivery: IV morphine bolus then PCA Pain score collection: blinded nurse Concurrent postoperative analgesics: PO diclofenac
Participants	**Inclusion criteria** 1. Hand surgery lasting around one hour 2. ASA 1 or 2 **Exclusion criteria** 1. Renal disease 2. Asthma 3. Diabetes 4. Allergy to NSAIDs 5. On regular NSAID medication
Interventions	**Group Systemic Pre-surgery (15 participants):** 20 mg IV ketorolac before surgery and IV saline after surgery **Group Systemic Post-surgery (15 participants):** IV saline before surgery and 20 mg IV ketorolac after surgery
Outcomes	1. Postoperative pain (on a 0-100 mm VAS at 1, 2, 4, 6 and 24 hours after tourniquet deflation) 2. Morphine consumption (mg consumed at 1, 2, 4, 6 and 24 h after tourniquet deflation)
Notes	Funding: not reported Declarations of interest: not reported Authors contacted: no Other: data extracted from graph using software. Standard deviations calculated from reported confidence intervals. Only systemic pre-surgery and post-surgery compared. Included in preventive as diclofenac used postoperatively
Risk of bias	

Ashworth 2002 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number chart. Quote: "patients were assigned to one of three groups using a random number chart".
Allocation concealment (selection bias)	Unclear risk	No mention
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Triple-dummy placebo. Quote: "each group received an intravenous injection at three stages during the operation...each injection consisted of normal saline 20 ml with or without ketorolac 20 mg according to randomization. All groups received the injection".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded. Quote: "the nurses in the recovery room remained blind to the treatment group".
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	One participant excluded for respiratory depression but unclear which group and another excluded for extended procedure. Quote: "two patients were not studied: one had an extended procedure (> 1.5 h); the other had respiratory depression while using PCA, which was therefore discontinued".
Selective reporting (reporting bias)	Unclear risk	No protocol or trial registration
Other bias	High risk	More females in post-incision group and more patients in preventive group received fentanyl.

Aznar-Arasa 2012

Study characteristics	
Methods	Study design: parallel-group randomized controlled trial Sample size: 109 Country: Spain Setting: University hospital Dates conducted: February 2008 to October 2010 Postoperative opioid used and delivery: none Pain score collection: participant self-report Concurrent postoperative analgesics: metamizole PRN
Participants	**Inclusion criteria** 1. Impacted lower third molar that required surgical removal **Exclusion criteria** 1. Aged below 18 years or over 45 years 2. ASA 3 or 4 3. Pregnancy 4. Allergy to NSAIDs 5. Lactose intolerance 6. Gastrointestinal pathology 7. Presence of symptoms associated with the third molar the week prior to extraction

Aznar-Arasa 2012 *(Continued)*

	8. History of analgesic and/or anti-inflammatory drug intake 10 days before surgery
Interventions	**Group Experimental (53 participants):** PO ibuprofen 600 mg one hour before surgery followed by placebo just after the end of the operation **Group Control (56 participants):** placebo one hour before surgery and PO ibuprofen 600 mg just after the end of the operation
Outcomes	1. Postoperative pain (on a 0-100 mm VAS every 2 or 4 hours within the first 14 hours and then the patient measured pain intensity every 8 hours between 24 and 64 hours postoperatively) 2. Analgesic consumption (number of tablets at 72 hours) 3. Trismus (maximum mouth opening measured using calipers at 48 hours and 7 days) 4. Facial swelling (was determined by the following facial distances: gonion–lip commissure, gonion–external canthus of the eye and tragus–lip commissure at 48 hours and 7 days)
Notes	Funding: grant from the School of Dentistry of the University of Barcelona Declarations of interest: none declared Authors contacted: no Other: early pain score taken from two hours after surgery to allow postoperative dosing to take effect. Included in preventive as PRN metamizole is thought to be an NSAID

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated. Quote: "sequence of random numbers in blocks (generated in www.randomization.com)"
Allocation concealment (selection bias)	Unclear risk	Sequentially numbered envelopes although unclear if opaque and sealed. Quote: "sequentially numbered envelopes were used to conceal the allocation of patients to the two groups".
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-dummy placebo. Quote: "In the preoperative group, patients were administered 600 mg of ibuprofen (PO) 1 hour before the surgical procedure, followed by placebo just after the end of the operation".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded. Quote: "all patients, the statistician and the surgeons who performed the extraction and follow-up examinations were unaware of the medication given to each participant".
Incomplete outcome data (attrition bias) All outcomes	High risk	Large number of dropouts. Quote: "11 (7 in the experimental group and 4 in control group) were lost because they did not attend follow-up visits".
Selective reporting (reporting bias)	Unclear risk	No protocol or trial registration
Other bias	Low risk	Similar baseline characteristics and no conflicts of interest

Bajaj 2004

Study characteristics

Methods	Study design: parallel-group randomized controlled trial

Bajaj 2004 *(Continued)*

	Sample size: 80 Country: India Setting: secondary care Dates conducted: not reported Postoperative opioid used and delivery: unspecified rescue analgesic Pain score collection: researcher Concurrent postoperative analgesics: not reported
Participants	**Inclusion criteria** 1. Male and non-pregnant females 2. Aged 18-70 years old 3. Elective general surgery **Exclusion criteria** 1. Pregnant or breastfeeding 2. Sensitive to NSAIDs 3. Risk factors for gastrointestinal side effects 4. Bleeding history 5. Cirrhosis or oesophageal varices 6. Cardiac disease 7. Renal disease 8. Cerebrovascular disease 9. Malignancy 10.Uncontrolled systemic diseases
Interventions	**Group Pre-emptive (40 participants):** 40 mg parecoxib 30-45 minutes before surgery **Group Postoperative (40 participants):** 40 mg parecoxib when reported pain or awake from anaesthesia (whichever was earlier)
Outcomes	1. Postoperative pain (0-10 cm VAS at 0, 15 mins, 30 mins, 1, 2, 4, 6, 8, 12 and 24 hours) 2. Pain relief (0-3 scale at 0, 12 and 24 hours) 3. Safety (ascertained from tests and adverse events)
Notes	Funding: none reported Declarations of interest: none declared but authors appeared to be employees of Glenmark Pharmaceuticals Authors contacted: no Other: pain score taken from one hour to allow recovery from anaesthesia and postoperative dosing. Standard deviations estimated. Data extracted from graph using software

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer. Quote: "computer-generated randomisation"
Allocation concealment (selection bias)	Unclear risk	No mention
Blinding of participants and personnel (performance bias)	High risk	No double-dummy placebo. Quote: "to receive a single dose of 40 mg parecoxib either 30-45 minutes prior to induction....or in the postoperative period"

Bajaj 2004 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded. Quote: "...the study was assessor blinded".
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants analysed. Quote: "all patients enrolled in the study completed the trial".
Selective reporting (reporting bias)	Unclear risk	No protocol or trial registration
Other bias	High risk	Authors appeared to be employees of Glenmark pharmaceuticals.

Bao 2012

Study characteristics	
Methods	Study design: parallel-group randomized controlled trial Sample size: 65 Country: China Setting: secondary care Dates conducted: January 2008 to December 2011 Postoperative opioid used and delivery: morphine PCA Pain score collection: blinded staff Concurrent postoperative analgesics: none reported
Participants	**Inclusion criteria** 1. Aged 18–70 years old 2. ASA 1 or 2 3. Hip joint replacement **Exclusion criteria** 1. Severe cardiac, pulmonary or renal insufficiency 2. Use of analgesics during the week before surgery 3. History of peptic ulcer 4. Inflammatory bowel disease 5. Allergy to NSAIDs 6. Immunosuppressant drugs 7. Contraindication to parecoxib
Interventions	**Group Pre-incisional (33 participants):** 100 mL of normal saline with IV parecoxib 40 mg 30 minutes before skin incision and 100 mL normal saline IV 30 minutes after skin incision **Group Post-incisional (32 participants):** 100 mL of normal saline 30 minutes before skin incision and 100 mL normal saline with IV parecoxib 40 mg 30 minutes after skin incision
Outcomes	1. Postoperative pain at rest and with cough (0-100 mm VAS at 1, 6, 18 and 24 hours) 2. Morphine consumption (mg consumed at 1, 6, 18 and 24 hours) 3. Cytokines (IL-6, IL-8 and TNF-alpha at 30 minutes prior to surgery and 6 hours after surgery)

Bao 2012 *(Continued)*

Notes	Funding: none reported Declarations of interest: none declared Authors contacted: no Other: early pain score from 1 hour

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unclear how sequence generated. Quote: "by selection of sealed envelopes"
Allocation concealment (selection bias)	Unclear risk	Unclear if opaque envelopes used. Quote: "by selection of sealed envelopes"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-dummy placebo and surgical teams blinded. Quote: "The preincisional group received a solution of 100 ml normal saline with parecoxib 40 mg intravenously (IV) 30 min before skin incision and 100 ml normal saline IV 30 min after skin incision".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded. Quote: "the postanaesthesia care unit staff were blinded to the randomization".
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants analysed
Selective reporting (reporting bias)	Unclear risk	No protocol or trial registration
Other bias	Low risk	Similar groups and no conflicts of interest

Boccara 2005

Study characteristics

Methods	Study design: parallel-group randomized controlled trial Sample size: 48 Country: France Setting: secondary care Dates conducted: not reported Postoperative opioid used and delivery: nalbuphine Pain score collection: not reported Concurrent postoperative analgesics: paracetamol
Participants	**Inclusion criteria** 1. Aged 18–70 years old 2. ASA 1 or 2 3. Laparoscopic cholecystectomy **Exclusion criteria**

Boccara 2005 *(Continued)*

	1. Allergy to paracetamol, NSAIDs or opioids 2. Severe hepatic, renal, gastric or bleeding disorders 3. Received analgesic drugs within two weeks before surgery
Interventions	**Group K1 (24 participants):** IV ketoprofen 100 mg before induction and IV saline end of surgery and continued for 24 hours **Group K2 (24 participants):** IV saline before induction and IV ketoprofen 100 mg end of surgery and continued for 24 hours
Outcomes	1. Postoperative pain (0-100 mm VAS hourly for 24 hours) 2. Nalbuphine consumption (mg consumed at 8 and 24 hours) 3. Time to analgesic request (minutes if pain > 30 mm or > 50 mm) 4. Sedation (during postoperative period, yes/no if sedation score > 2) 5. Nausea and vomiting (yes/no during postoperative period) 6. Adverse events (gastralgia, bleeding and anaphylaxis, yes/no during the postoperative period) 7. Patient satisfaction (0-5 scale, reported as number of patients with score 4 or 5)
Notes	Funding: none reported Declarations of interest: not reported Authors contacted: yes Other: pain score converted to 0-10 scale, pain score data extracted from graph and taken from one hour to allow postoperative dosing to take effect. Authors contacted for raw patient satisfaction data

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated. Quote: "computer-generated random list"
Allocation concealment (selection bias)	Unclear risk	No mention
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-dummy placebo used. Quote: "in group K1, ketoprofen was administered before induction and saline after surgery".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded. Quote: "none of the patients, managing anaesthetists or nurses were aware of the randomization code".
Incomplete outcome data (attrition bias) All outcomes	Low risk	Exclusions unlikely to bias as equal in number. Quote: "Six patients were excluded from postoperative data analysis because four needed intraoperative laparotomy (one in K1, one in K2 and two in P1) and two for incomplete data (one in K1 and one in K2)".
Selective reporting (reporting bias)	Unclear risk	No protocol or trial registration
Other bias	High risk	More females in K2 group (Gerbershagen 2014)

Buggy 1994

Study characteristics	
Methods	Study design: parallel-group randomized controlled trial Sample size: 40 Country: Ireland Setting: secondary care Dates conducted: not reported Postoperative opioid used and delivery: IM morphine Pain score collection: blinded nurses Concurrent postoperative analgesics: none reported
Participants	**Inclusion criteria** 1. ASA 1 2. Elective laparoscopic tubal ligation **Exclusion criteria** 1. Peptic ulcer disease 2. Renal failure 3. Allergy to NSAIDs
Interventions	**Group 1 (20 participants):** IM diclofenac 75 mg as a 3 mL injection one to two hours before surgery and IM normal saline 3 mL immediately after surgery **Group 2 (20 participants):** IM normal saline 3 mL one to two hours before surgery and IM diclofenac 75 mg immediately after surgery
Outcomes	1. Postoperative pain (0-10 cm VAS and 4-point NRS at 30 minutes and 1, 3 and 6 hours postoperatively) 2. Morphine consumption (mg and number of doses postoperatively) 3. Time to analgesic request (minutes)
Notes	Funding: not reported Declarations of interest: not reported Authors contacted: no Other: median and IQR converted to mean and SD, morphine consumption data not included as study follow-up only appeared to be 6 hours

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No details. Quote: "patients were allocated randomly to two groups".
Allocation concealment (selection bias)	Unclear risk	No mention
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical double-dummy placebo. Quote: "each patient received two identical, coded, 3 ml injections: one containing diclofenac 75 mg, the other containing normal saline".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded outcome assessment. Quote: "...were recorded by nursing staff who were unaware"

Buggy 1994 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants analysed
Selective reporting (reporting bias)	Unclear risk	No protocol or trial registration
Other bias	Low risk	Similar baseline characteristics

Bunemann 1994

Study characteristics	
Methods	Study design: parallel-group randomized controlled trial Sample size: 117 Country: Denmark Setting: secondary care Dates conducted: not reported Postoperative opioid used and delivery: IV pethidine Pain score collection: in recovery (unclear who) and 24 hour self-report Concurrent postoperative analgesics: paracetamol
Participants	**Inclusion criteria** 1. ASA 1 or 2 2. Minor orthopaedic surgery **Exclusion criteria** 1. Allergy to NSAIDs 2. Pregnancy 3. NSAID treatment within 14 days 4. Opioids 5. Hypoglycaemics 6. Sedatives 7. Lithium 8. Psychiatric drugs 9. Peptic ulcer 10.Age < 18 and > 60 years old
Interventions	**Group TP (59 participants):** naproxen 1100 mg one hour before surgery and placebo immediately after surgery **Group PT (58 participants):** placebo one hour before surgery and naproxen 1100 mg immediately after surgery
Outcomes	1. Postoperative pain (0-100 mm VAS in PACU, discharge and at 24 hours) 2. Analgesia consumption (paracetamol and pethidine consumption in PACU and at 24 hours) 3. Side effects (no details reported on timing or actual side effects measured)
Notes	Funding: not reported Declarations of interest: not reported Authors contacted: no

Bunemann 1994 *(Continued)*

	Other: pain scores estimated from median and interquartile range; analgesic consumption not included as not just opioid consumed

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details reported
Allocation concealment (selection bias)	Unclear risk	No mention
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-dummy placebo. Quote: "naproxen sodium 1100 mg 1 h before surgery and placebo immediately after surgery"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No mention
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Six exclusions, although unclear which groups. Ten missing for 24-hour data. Quote: "six had to be excluded; three because they did not have an operation and three because they did not have general anaesthesia".
Selective reporting (reporting bias)	Unclear risk	No protocol or trial registration
Other bias	Low risk	Similar baseline characteristics

Cabell 2000

Study characteristics

Methods	Study design: parallel-group randomized controlled trial Sample size: 49 Country: USA Setting: secondary care hospital Dates conducted: not reported Postoperative opioid used and delivery: IV fentanyl and morphine Pain score collection: patient self-report Concurrent postoperative analgesics: paracetamol, codeine and NSAIDs PRN
Participants	**Inclusion criteria** 1. Female 2. ASA 1 or 2 3. 18-65 years old 4. Laparoscopic gynaecological procedures **Exclusion criteria** 1. Renal, hepatic or cardiovascular disease 2. ASA 3 or 4 3. Pregnancy or lactation

Cabell 2000 *(Continued)*

	4. Alcohol or drug abuse 5. Allergy to NSAIDs 6. Peptic ulcer or gastrointestinal problems
Interventions	**Group 1 (25 participants):** IV ketorolac 30 mg in operating room and 1 mL saline placebo at end of surgery **Group 2 (24 participants):** IV ketorolac 30 mg at end of surgery and 1 mL saline placebo on entering operating room
Outcomes	1. Postoperative pain (0-15 cm mechanical VAS at PACU admission, 15, 30, 45, 60, 90, 120 minutes and 24 hours) 2. Fentanyl and morphine consumption (quantity consumed during follow-up)
Notes	Funding: not reported Declarations of interest: not reported Authors contacted: no contact listed Other: Although 0-15 cm VAS, the stated text corresponded to a 0-10 scale. SD estimated. Analgesia consumption not reported. Included in pre-emptive as only 'several' participants received NSAIDs. Early pain score from 30 minutes to allow postoperative dosing to take effect

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated. Quote: "computer-generated"
Allocation concealment (selection bias)	Unclear risk	Not enough information about allocation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-dummy placebo used. Quote: "received IV ketorolac..and 1 ml IV isotonic sodium chloride"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No mention. Mostly patient self-report
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only two excluded, unlikely to cause bias. Quote: "2 were excluded...progressed to open laparotomy"
Selective reporting (reporting bias)	Unclear risk	No protocol
Other bias	Low risk	Similar baseline characteristics although absolute values not reported

Chan 1996

Study characteristics

Methods	Study design: parallel-group randomized controlled trial Sample size: 80

Chan 1996 *(Continued)*

	Country: UK Setting: secondary care hospital Dates conducted: not reported Postoperative opioid used and delivery: IV fentanyl Pain score collection: not reported Concurrent postoperative analgesics: not reported
Participants	**Inclusion criteria** 1. Aged 18 to 75 years old 2. ASA 1 or 2 3. Breast lump excision as day case **Exclusion criteria** 1. Asthma 2. Peptic ulcer or upper gastrointestinal pathology 3. Pregnancy or breastfeeding 4. Allergy to diclofenac or other NSAID 5. Contraindication to anaesthetic technique
Interventions	**Group A (20 participants):** IM diclofenac 75 mg before surgery, IM saline and wound infiltration with 0.5% plain bupivacaine at the end of surgery **Group B (20 participants):** IM saline before surgery, IM diclofenac 75 mg and bupivacaine infiltration at the end of surgery **Group C (20 participants):** IM diclofenac 75 mg before surgery, IM saline at the end of surgery and no bupivacaine infiltration **Group D (20 participants):** IM saline before surgery, IM diclofenac 75 mg at the end of surgery and no bupivacaine infiltration
Outcomes	1. Postoperative pain (0-10 cm VAS every 30 minutes until discharge) 2. Analgesic consumption (mcg fentanyl and oral tablets consumed after 48 hours) 3. Satisfaction with analgesia (not specified at 48 hours) 4. Side effects (not specified at 48 hours)
Notes	Funding: not reported Declarations of interest: not reported Authors contacted: yes Other: unable to use data as either not fully reported or reported as ordinal data

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details. Quote: "patients were divided".
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-dummy placebo used. Quote: "Syringes were filled by an independent anaesthetist according to a predetermined treatment schedule. Neither the patients nor the anaesthetist knew which injection was given at the aforemen-

Chan 1996 *(Continued)*

		tioned times...intramuscular diclofenac 75 mg before surgery, intramuscular saline (placebo)".
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No mention
Incomplete outcome data (attrition bias) All outcomes	High risk	High dropouts. Quote: "an additional 12 patients were initially enrolled in the study but failed to complete their pain relief questionnaires and have therefore been excluded from the results presented".
Selective reporting (reporting bias)	High risk	Satisfaction and side effects not reported
Other bias	Low risk	Similar baseline characteristics

Chen 2015

Study characteristics	
Methods	Study design: parallel-group randomized controlled trial Sample size: 49 Country: China Setting: secondary care Dates conducted: July 2011 to February 2014 Postoperative opioid used and delivery: fentanyl PCA Pain score collection: blinded anaesthetist Concurrent postoperative analgesics: none reported
Participants	**Inclusion criteria** 1. ASA 1 or 2 2. Aged 30-55 years old 3. Weight 50-75 kg 4. Transabdominal hysterectomy 5. Operation time of 55-80 minutes **Exclusion criteria** 1. Contraindication to epidural puncture 2. Allergy to local anaesthetics 3. Hypertension 4. Diabetes 5. Coronary heart disease 6. Consumption of opioids and NSAIDs preoperatively 7. Physiological and psychological disorders
Interventions	**Group P1 (24 participants):** IV 50 mg flurbiprofen and 1.0 μg/kg fentanyl with 0.25 mg/kg ketamine epidurally before surgery and 5 mL normal saline IV and 10 mL normal saline epidurally after surgery **Group P3 (25 participants):** 5 mL IV normal saline and 1.0 μg/kg fentanyl with 0.25 mg/kg ketamine epidurally before surgery and 50 mg IV flurbiprofen and 10 mL normal saline epidurally after surgery
Outcomes	1. Postoperative pain (0-10 cm VAS at 6, 12, 24 and 48 hours after surgery)

Chen 2015 *(Continued)*

	2. Time to analgesic request (hours) 3. Fentanyl consumption (mcg consumed at 24 hours) 4. Stress response (cortisol, glucose, IL-6 and TNF-alpha measured before surgery and 1-2 days postoperatively)
Notes	Funding: Wuxi Municipal Bureau of Science and Technology (government) Declarations of interest: none declared Authors contacted: no Other: fentanyl consumption converted to 70 kg weight then to morphine equivalents

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number table. Quote: "a random allocation number table was used for grouping the patients by two experienced chief physicians".
Allocation concealment (selection bias)	Unclear risk	No mention
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-dummy placebo used. Quote: "the participants, care providers, those assessing outcomes were blinded after assignment to interventions".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded. Quote: "the participants, care providers, those assessing outcomes were blinded after assignment to interventions".
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only one exclusion, unlikely to cause bias. Quote: "one patient in group P1 was excluded for hypopiesia and shock during operation".
Selective reporting (reporting bias)	Unclear risk	ChiCTR-IPR-15005848, although retrospectively registered
Other bias	Low risk	Similar baseline characteristics and government funding

Colbert 1998

Study characteristics

Methods	Study design: parallel-group randomized controlled trial Sample size: 77 Country: Ireland Setting: secondary care Dates conducted: July 1996 to December 1996 Postoperative opioid used and delivery: IM pethidine Pain score collection: blinded investigator Concurrent postoperative analgesics: diclofenac or paracetamol
Participants	**Inclusion criteria**

Colbert 1998 *(Continued)*

	1. ASA 1 or 2 2. Breast biopsy **Exclusion criteria** 1. Contraindications to NSAID use 2. Fine wire localised breast biopsy
Interventions	**Group A (37 participants):** 20 mg IV tenoxicam 30 minutes before surgery **Group B (40 participants):** 20 mg IV tenoxicam post-incision
Outcomes	1. Postoperative pain (0-100 mm VAS at 30, 60, 120 and 240 minutes after surgery) 2. Time to analgesic request (minutes) 3. Analgesic consumption (paracetamol, diclofenac and pethidine in the first 4 hours postoperatively)
Notes	Funding: not reported Declarations of interest: not reported Authors contacted: no Other: analgesic consumption not included as at 4 hours. Included as a pre-emptive intervention as not all participants received diclofenac postoperatively

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Table of random numbers. Quote: "table of random numbers"
Allocation concealment (selection bias)	Unclear risk	No mention
Blinding of participants and personnel (performance bias) All outcomes	High risk	No double-dummy placebo. Quote: "The patients in group A received 20 mg tenoxicam IV 30 mins pre-operatively and patients in group B received 20 mg tenoxicam IV post-incision".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded. Quote: "outcomes were assessed by an investigator without knowledge of the timing of tenoxicam administration".
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants analysed. Quote: "There were 37 patients in group A (20 mg tenoxicam and 30 min before surgery) and 40 patients in group B (20 mg tenoxicam post-incision)".
Selective reporting (reporting bias)	Unclear risk	No protocol or trial registration
Other bias	Low risk	Similar baseline characteristics. Quote: "There were no differences between the groups with respect to age, duration of surgery, length of the wound or the weight of the patient".

Coli 1993

Study characteristics

Coli 1993 *(Continued)*

Methods	Study design: parallel-group randomized controlled trial Sample size: 50 Country: Italy Setting: secondary care Dates conducted: not reported Postoperative opioid used and delivery: buprenorphine Pain score collection: not included as outcome Concurrent postoperative analgesics: none reported
Participants	**Inclusion criteria** 1. ASA 1 or 2 2. Weighing between 50 and 90 kg 3. Lumbar laminectomy **Exclusion criteria** 1. Aged < 18 and > 65 years old 2. Diabetes 3. Gastroduodenal ulcer 4. Alcoholism 5. Allergic to study medications 6. Psychiatric disorders 7. Renal and hepatic impairment 8. Anticoagulants or antiplatelets 9. Calcium channel blockers, beta-blockers or angiotensin-converting enzyme inhibitors 10. Clonidine 11. Psychotropic drugs 12. NSAIDs in the 12 hours pre-intervention
Interventions	**Group I (25 participants):** IV sodium naproxen 550 mg immediately after induction of anaesthesia **Group II (25 participants):** IV sodium naproxen 550 mg at the end of surgery
Outcomes	1. Analgesic consumption (mg of buprenorphine consumed at 24 hours) 2. Time to analgesic request (hours)
Notes	Funding: not reported Declarations of interest: not reported Authors contacted: no Other: article in Italian so translated. Buprenorphine consumption converted to mg intravenous morphine. Standard deviations estimated. Time to analgesic request data extracted from graph

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details
Allocation concealment (selection bias)	Unclear risk	No mention

Coli 1993 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	No double-dummy placebo. Quote: "group I received Naproxen sodium 550 mg intravenously immediately after induction of anesthesia; group II received sodium naproxen 550 mg intravenously at the beginning of the surgical suture".
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No mention
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants analysed
Selective reporting (reporting bias)	Unclear risk	No protocol or trial registration
Other bias	Low risk	Similar baseline characteristics. Quote: "The three groups were comparative to the distribution by age, weight, sex and duration of the intervention".

Demirbas 2019

Study characteristics	
Methods	Study design: parallel-group randomized controlled trial Sample size: 50 Country: Turkey Setting: secondary care Dates conducted: not reported Postoperative opioid used and delivery: none Pain score collection: not reported Concurrent postoperative analgesics: PRN paracetamol
Participants	**Inclusion criteria** 1. Surgical extraction of a full bony impacted mandibular third molar 2. Aged 18 to 50 years 3. No systemic disease (ASA 1) 4. No current medications 5. No allergies to any of the drugs 6. No local or systemic infection **Exclusion criteria** 1. Pregnant or breastfeeding patients 2. Allergic to ibuprofen or any other NSAIDs 3. Systemic diseases such as diabetes and uncontrolled hypertension 4. Opioid or illicit drug use
Interventions	**Group 1 (25 participants):** 800 mg of IV ibuprofen 60 minutes before surgery and IV placebo (100 mL of saline) after surgery **Group 2 (25 participants):** IV placebo (100 mL of saline) 60 minutes before surgery and 800 mg of IV ibuprofen 60 minutes after surgery

Demirbas 2019 *(Continued)*

Outcomes	1. Postoperative pain (0-100 mm VAS at 1, 2, 4, 6, 8, 12, and 24 hours) 2. Paracetamol consumption (mg at 1, 2, 4, 6, 8, 12, and 24 hours)
Notes	Funding: "Erciyes University Scientific Research Projects Unit, Turkey (project number: TSA-2018-7756)" Declarations of interest: "None of the authors have any relevant financial relationship(s) with a commercial interest". Authors contacted: no Other: Pain data extracted from graphs and SD estimated from other studies. Early pain taken at 2 hours to allow post-incision dosing to take effect

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated. Quote: "Patients who met the study criteria were divided randomly into equal groups using a random number generated by a computer".
Allocation concealment (selection bias)	Unclear risk	No mention
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-dummy placebo. Quote: "800 mg of IV ibuprofen 60 minutes before surgery and IV placebo (100 mL of saline) after surgery...Neither the surgeon nor the patient were informed of the group assignment throughout the entire study process".
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No mention who collected data
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants analysed. Quote: "No data were missing"
Selective reporting (reporting bias)	Unclear risk	No protocol
Other bias	Low risk	Non-industry funding and similar groups. Quote: "Erciyes University Scientific Research Projects Unit, Turkey (project number: TSA-2018-7756)...No differences were found among the 3 groups in terms of age (P = .2) or gender (P = .13)".

Esparza-Villalpando 2016

Study characteristics

Methods	Study design: parallel-group randomized controlled trial Sample size: 60 Country: Mexico Setting: secondary care Dates conducted: January to August 2015 Postoperative opioid used and delivery: none Pain score collection: self-report

Esparza-Villalpando 2016 *(Continued)*

	Concurrent postoperative analgesics: none reported
Participants	**Inclusion criteria** 1. Aged between 18 and 30 years of age 2. Clinical and radiographic diagnosis of asymptomatic mandibular impacted third molar 3. No intake of analgesic or anti-inflammatory drugs 12 hours before surgery **Exclusion criteria** 1. Pregnancy or breastfeeding 2. Allergy to dexketoprofen or any other NSAIDs 3. Systemic diseases such as diabetes, uncontrolled hypertension or gastric ulcer 4. Suspicion or evidence of narcotics or illicit drugs use
Interventions	**Group 1 (30 participants):** 25 mg PO dexketoprofen trometamol 30 minutes before the surgery and placebo capsule immediately after the procedure **Group 2 (30 participants):** placebo capsule 30 minutes before the surgical intervention and 25 mg of PO dexketoprofen trometamol immediately after surgery
Outcomes	1. Postoperative pain (0-100 mm VAS/NRS first 8 hours after surgery) 2. Time to analgesic request (minutes) 3. Adverse events (first 7 days after surgery but no details reported)
Notes	Funding: not reported Declarations of interest: none declared Authors contacted: yes Other: pain score data 100 mm VAS as opposed to NRS due to impossible values. Authors contacted as not enough information reported to include time-to-event data. Pain score from one hour included to allow oral post-incision intervention to work. Included in pre-emptive as not all participants received postoperative NSAIDs

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random numbers. Quote: "randomized using software for simple random numbers"
Allocation concealment (selection bias)	Low risk	Blinded. Quote: "all randomization processes were performed by a separate collaborator".
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Study used double-dummy placebo. Quote: "blinding was maintained by using over-encapsulated dexketoprofen trometamol tablets in white gelatin capsules. The placebo used was an identical empty white gelatin capsule. Neither the patient, the surgeon, nor the person in charge of the administration of drugs to each group was aware of the identity of the drugs assigned".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	As above
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants analysed

Esparza-Villalpando 2016 *(Continued)*

Selective reporting (reporting bias)	High risk	NCT02380001. Registration reports measuring pain for 72 hours and trial only reports data for 8 hours
Other bias	High risk	More participants in pre-emptive group had more complicated surgery which is likely to be more painful

Flath 1987

Study characteristics	
Methods	Study design: parallel-group randomized controlled trial Sample size: 28 Country: USA Setting: dental medical school Dates conducted: not reported Postoperative opioid used and delivery: none Pain score collection: patient self-report Concurrent postoperative analgesics: not reported
Participants	**Inclusion criteria** 1. Age 20-80 years 2. Non-surgical endodontic therapy **Exclusion criteria** 1. Root canal therapy complicated by sclerotic or bayonet-shaped canals 2. ASA 3, 4 or 5 3. Long-term steroid or immunosuppressant therapy 4. Pregnancy 5. Recent administration of analgesics
Interventions	**Group C (13 participants):** 100 mg flurbiprofen 30 minutes before procedure and placebo 3 hours after surgery **Group B (15 participants):** placebo 30 minutes before procedure and 100 mg flurbiprofen 3 hours after surgery
Outcomes	1. Postoperative pain (0-100 mm VAS and categorical rating scale at 3, 7 and 24 hours) 2. Adverse events (gastrointestinal, central nervous and other during follow-up)
Notes	Funding: 'The Upjohn Company provided no financial support for this study' Declarations of interest: not reported Authors contacted: no Other: pain score data extracted from graph. Three-hour data not included as this was when postoperative administration occurred. SD estimated. Pain score data only included symptomatic preoperative patients.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random draw of envelopes. Quote: "By random draw"

Flath 1987 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	No details regarding the envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-dummy placebo. Quote: "Placebos and the flurbiprofen (The Upjohn Co Kalamazoo, MI) were compounded into identical blue tablets".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Likely blinded as patient self-report and blinded intervention
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only four dropouts, unlikely to cause bias. Quote: "...of the 120 patients enrolled in the study, 116 completed all phases".
Selective reporting (reporting bias)	Unclear risk	No protocol
Other bias	Low risk	Similar baseline characteristics. No industry funding

Fleckenstein 2016

Study characteristics	
Methods	Study design: parallel-group randomized controlled trial Sample size: 45 Country: Germany Setting: secondary care Dates conducted: February 2006 to December 2011 Postoperative opioid used and delivery: morphine PCA Pain score collection: not reported Concurrent postoperative analgesics: none reported
Participants	**Inclusion criteria** 1. Aged ≥ 18 years old 2. Abdominal or thoracic surgery 3. ASA 1 or 2 **Exclusion criteria** 1. Severe cardiac, pulmonary, renal or neurologic diseases 2. Type 1 diabetes 3. Diseases influencing the peripheral nervous system (e.g. polyneuropathy, chronic pain syndromes) 4. Regional anaesthesia 5. Use of analgesics 6. Pregnancy or lactation 7. Uncontrolled hypertension 8. Contraindications listed in the product information of etoricoxib
Interventions	**Group 1 (unclear number of participants):** PO etoricoxib 120 mg on morning of surgery then PO etoricoxib 120 mg/day for 3 days and postoperative placebo

Fleckenstein 2016 *(Continued)*

	Group 3 (unclear number of participants): placebo on morning of surgery then PO etoricoxib 120 mg/day etorocoxib for 3 days
Outcomes	1. Morphine consumption (mg consumed at 1, 2, 4 hours and day 1-3) 2. Postoperative pain (on 0-10 cm VAS and DGSS pain questionnaire during the first 48 hours) 3. Quantitative sensory testing (various parameters at 48 hours)
Notes	Funding: MSD Sharp and Dome (industry) Declarations of interest: none declared Authors contacted: yes Other: standard deviation from post-incision group estimated from preventive group. Data extracted from graph. Pain score data not reported. Participant numbers unclear but estimated from total number of participants receiving etoricoxib. Some information extracted from published protocol

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated
Allocation concealment (selection bias)	Low risk	Pharmacy-controlled. Quote: "sequentially numbered envelopes containing two boxes of study medication for pre- and postoperative use performed by pharmacy"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-dummy placebo used. The pills were similar in appearance.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded. Quote: "analysis of all records is performed by blinded evaluators".
Incomplete outcome data (attrition bias) All outcomes	High risk	Patients lost to follow-up and some for high pain. Quote: "six out of the eight dropouts (75%) because of increased pain were part of the placebo group".
Selective reporting (reporting bias)	High risk	NCT00716833 and published protocol. Pain data not fully reported
Other bias	Unclear risk	No separate data to assess. Industry funding but stated not involved in study

Fletcher 1995

Study characteristics

Methods	Study design: parallel-group randomized controlled trial Sample size: 40 Country: France Setting: secondary care Dates conducted: not reported Postoperative opioid used and delivery: IV bolus then PCA morphine

Fletcher 1995 *(Continued)*

	Pain score collection: blinded investigator Concurrent postoperative analgesics: none reported
Participants	**Inclusion criteria** 1. ASA 1 or 2 2. Elective total hip replacement **Exclusion criteria** 1. Contraindications to NSAIDs 2. Aged younger than 18 years or older than 85 years 3. ASA > 3 4. Any type of surgery other than THR 5. Regional anaesthesia 6. Any condition precluding the limitation of intraoperative fentanyl administration 7. Contraindications to the self-administration of opioids 8. Past history of drug abuse 9. Severe respiratory insufficiency 10. Long duration of surgery (more than 4 hours) 11. Cumulative intraoperative dose of fentanyl higher than 4 mcg/kg 12. A second operation within 48 hours 13. Severe respiratory depression after surgery or administration of naloxone 14. Difficulty in using the PCA device 15. Use of analgesic drugs other than morphine
Interventions	**Group PRE (20 participants):** 60 mg IV ketorolac before induction and then 2 mL IV normal saline at the end of surgery **Group POST (20 participants):** 2 mL IV normal saline before induction and then 60 mg IV ketorolac at the end of surgery
Outcomes	1. Morphine consumption (mg consumed every 12 hours for 48 hours) 2. Postoperative pain at rest and on movement (0-10 cm VAS in the recovery room and at 1, 2, 3, 4, 5, 6 hours and every 6 hours for 48 hours) 3. Adverse events (nausea and vomiting, pruritus, urinary retention, blood loss, number of transfusions, sedation, respiratory depression during study follow-up)
Notes	Funding: not reported Declarations of interest: not reported Authors contacted: no Other: some pain score and morphine consumption data extracted from graph

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number table. Quote: "a random-number table was used to generate a randomized schedule specifying the group to which each patient would be assigned upon entry into the trial".
Allocation concealment (selection bias)	Unclear risk	No mention

Fletcher 1995 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-dummy placebo. Identical in appearance. Quote: "The pre-operative KET group (PRE; n = 20) received 60 mg of KET and then 2 ml of NS".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded. Quote: "all patients and personnel involved in patient management and data collection were unaware of the group to which the patient had been assigned".
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants analysed
Selective reporting (reporting bias)	High risk	Some adverse events not reported
Other bias	High risk	More females in POST group (Gerbershagen 2014)

Gabbott 1997

Study characteristics	
Methods	Study design: parallel-group randomized controlled trial Sample size: 65 Country: UK Setting: secondary care hospital Dates conducted: not reported Postoperative opioid used and delivery: PCA morphine Pain score collection: trained nurse Concurrent postoperative analgesics: none reported
Participants	**Inclusion criteria** 1. ASA 1 or 2 2. Female 3. Elective total abdominal hysterectomy with or without salpingo-oophorectomy for non-malignant disease **Exclusion criteria** 1. > 100 kg weight 2. > 60 years old 3. Renal impairment 4. Peptic ulceration 5. Asthma 6. Coagulopathy or anticoagulants 7. Allergy to NSAIDs 8. Drug or alcohol abuse 9. Current NSAID use 10. Lithium
Interventions	**Group D (34 participants):** IM ketorolac 30 mg 45-90 minutes preoperatively and placebo at incision **Group B (31 participants):** IM ketorolac 30 mg at incision and placebo 45-90 minutes preoperatively

Gabbott 1997 *(Continued)*

Outcomes	1. Morphine consumption (mg consumed at 1, 2, 4, 8 and 12 hours) 2. Postoperative pain (VRS of nil, mild, moderate, severe and asleep at 1, 2, 4, 8 and 12 hours) 3. Nausea (nil, mild, moderate, severe and asleep at 1, 2, 4, 8 and 12 hours) 4. Sedation (nil, mild, moderate, severe and asleep at 1, 2, 4, 8 and 12 hours) 5. Respiratory rate (at 1, 2, 4, 8 and 12 hours)
Notes	Funding: not reported Declarations of interest: not reported Authors contacted: yes Other: unable to use any data due to different time points, lack of reporting and inability to convert the scales used

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unclear whether a truly random process. Quote: "Randomization was achieved by allocating each patient the next numbered pair of study ampoules".
Allocation concealment (selection bias)	Unclear risk	Pharmacy-controlled but in view of above unclear. Quote: "The code determining the contents of each ampoule was kept by the pharmacy department and not released to the investigators until after the study was terminated".
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-dummy placebo. Quote: "All ampoules were identical and packaged in pairs labelled 'pre-operative' and 'intra-operative'. Each boxed pair was sequentially coded allowing the study to be carried out in a double-blind fashion".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Likely blinded from above
Incomplete outcome data (attrition bias) All outcomes	Low risk	Large number of dropouts, although these individuals had been randomized and thus intention-to-treat was not followed but the intervention was assigned double-blinded; the total dropout rate was only 14%, and there were similar numbers of dropouts between the groups (ranging from 10-23%). Quote: "One hundred and sixty patients agreed to take part in the study. Of these, 23 were withdrawn before induction of anaesthesia. These patients were either not given the study drug or more than 90 min had elapsed between the preoperative injection and the time of arrival in the anaesthetic room".
Selective reporting (reporting bias)	High risk	Some outcomes not reported or not fully reported
Other bias	Low risk	Similar baseline characteristics. Unclear role for Selecta UK in trial conduct

Gelir 2016

Study characteristics

Methods	Study design: parallel-group randomized controlled trial

Gelir 2016 *(Continued)*

	Sample size: 50 Country: Turkey Setting: secondary care Dates conducted: not reported Postoperative opioid used and delivery: IV morphine infusion Pain score collection: blinded anaesthetist Concurrent postoperative analgesics: none reported
Participants	**Inclusion criteria** 1. ASA 1 or 2 2. Aged 18-60 years old 3. Elective abdominal hysterectomy **Exclusion criteria** 1. Renal, hepatic, pulmonary or cardiovascular disorders 2. Increased intracranial pressure 3. Epilepsy 4. Alcohol and opioid dependence 5. Chronic analgesics 6. Allergies
Interventions	**Group I (25 participants):** IV infusion of 50 mg dexketoprofen in 100 mL saline solution 30 minutes before surgery and 100 mL of IV saline solution 15 minutes after the incision **Group II (25 participants):** 100 mL of IV saline solution 30 minutes before the operation and 50 mg of dexketoprofen in 100 mL of saline solution 15 minutes after incision
Outcomes	1. Postoperative pain (0-100 mm VAS at 1, 4, 8, 12 and 24 hours) 2. Morphine consumption (mg consumed at 1, 4, 8, 12 and 24 hours) 3. Time to analgesic request (minutes) 4. Adverse events (nausea, vomiting, increase in oral secretions, nightmares, diplopia, hallucinations and agitation during study follow-up)
Notes	Funding: not reported Declarations of interest: none declared Authors contacted: no Other: Nausea and vomiting not included as reported separately

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Closed envelope method but unclear if random. Quote: "the patients were randomized into two groups using the closed envelope method".
Allocation concealment (selection bias)	Unclear risk	Closed envelope method. Unclear if opaque and/or sealed
Blinding of participants and personnel (performance bias) All outcomes	Low risk	All drugs were prepared by the investigators before the operations but double-dummy. The drugs were administered by an anaesthetist who was blinded to the patient grouping. Quote: "Group I (n 25) received an intravenous (IV) infusion of 50 mg dexketoprofen in 100 ml saline solution 30 minutes before the operation...the patients in Group I received 100 ml of IV saline solution 15 minutes after the incision was made".

Gelir 2016 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Postoperative evaluations were performed by the same blinded doctor.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants analysed
Selective reporting (reporting bias)	High risk	Not all adverse events reported
Other bias	Low risk	Similar baseline characteristics and no conflicts of interest. Quote: "No significant difference was found between the groups in terms of demographic data, the duration of anesthesia, the duration of the surgical procedure or ketamine consumption".

Giuliani 2015

Study characteristics	
Methods	Study design: parallel-group randomized controlled trial Sample size: 87 Country: Italy Setting: secondary care hospital Dates conducted: February 2009 to May 2011 Postoperative opioid used and delivery: none (paracetamol) Pain score collection: medical students Concurrent postoperative analgesics: paracetamol
Participants	**Inclusion criteria** 1. > 18 years old 2. Trigger finger release, carpal tunnel release, DeQuervain tenosynovitis operation, surgical correction of minor bone injuries or pathologies under local anaesthesia **Exclusion criteria** 1. Allergy to NSAIDs 2. Gastric or duodenal ulcers
Interventions	**Group A (43 participants):** PO Ibuprofen 400 mg 30 minutes before the operation, placebo after the procedure and Ibuprofen 400 mg every 6 hours thereafter for a total duration of 18 hours **Group B (44 participants):** placebo 30 minutes before the operation, PO Ibuprofen 400 mg at the end of the procedure and every 6 hours thereafter for a total duration of 18 hours
Outcomes	1. Postoperative pain (0-100 mm VAS at preoperative, 30 minutes before the operation, early postoperative at the end of the procedure and at 6, 12 and 18 hours) 2. Paracetamol consumption (during study follow-up) 3. Adverse events (not specified, at study follow-up) 4. Patient satisfaction (0-10 scale at end of follow-up)
Notes	Funding: no mention Declarations of interest: "All the authors declare that there is no potential conflict of interest referring to this article". Authors contacted: yes (data received from authors)

Giuliani 2015 *(Continued)*

	Other: unpublished data used

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated. Quote: "AB, the pharmacist, prepared the randomization sequence using Microsoft Excel".
Allocation concealment (selection bias)	Low risk	Pharmacy-controlled. Quote: "AB, the pharmacist, prepared the randomization sequence using Microsoft Excel".
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-dummy placebo. Quote: "AB prepared placebo and treatment ibuprofen capsules, enclosed them in consecutively numbered sealed envelopes in the specific sequence that each group required. AB then stored envelopes in consecutively numbered sealed boxes, each representing the therapy of one individual patient. No reference to treatment group was present on either envelopes or boxes".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Likely blinded from above
Incomplete outcome data (attrition bias) All outcomes	High risk	High attrition. Quote: "Thirteen were lost during follow-up due to patient failure to complete VAS records".
Selective reporting (reporting bias)	Unclear risk	No protocol
Other bias	Low risk	Similar baseline characteristics. Quote: "After randomization, groups were similar regarding age, sex and type of surgery, no statistically significant difference was found for these variables".

Gramke 2006

Study characteristics

Methods	Study design: parallel-group randomized controlled trial Sample size: 52 Country: unclear Setting: secondary care Dates conducted: not reported Postoperative opioid used and delivery: tramadol PCA Pain score collection: blinded investigator or nurse Concurrent postoperative analgesics: none reported
Participants	**Inclusion criteria** 1. ASA 1 or 2 2. Laparoscopic treatment of bilateral inguinal hernia 3. General anaesthesia 4. Anticipated hospitalization of at least 48 hours **Exclusion criteria**

Gramke 2006 *(Continued)*

1. Aged < 18 or > 65 years old
2. Allergy to NSAIDs
3. Gastric ulcer
4. Renal failure
5. Migraine
6. Postoperative nausea and vomiting

Interventions	**Group PRE (25 participants):** 40 mg SL piroxicam 2 hours before surgery and placebo 10 minutes post-operatively. Also received a dose of 40 mg piroxicam the morning after surgery **Group POST (27 participants):** placebo 2 hours before surgery and 40 mg SL piroxicam 10 minutes postoperatively. Also received a dose of 40 mg piroxicam the morning after surgery
Outcomes	1. Postoperative pain at rest (0-10 cm VAS in recovery and at 6, 20 and 30 hours postoperatively) 2. Tramadol consumption (mg consumed in recovery and at 6, 20 and 30 hours postoperatively) 3. Nausea and vomiting (yes/no at follow-up)
Notes	Funding: not reported Declarations of interest: not reported Authors contacted: yes Other: data estimated from median and IQR. Data from 20 hours included in 24-hour data. Nausea data added as stated in methods: the outcome was nausea and vomiting.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unclear details. Quote: "randomization was performed by sealed numbered envelopes".
Allocation concealment (selection bias)	Unclear risk	Unclear if opaque. Quote: "randomization was performed by sealed numbered envelopes".
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-dummy placebo used. Quote: "40 mg SL piroxicam 2 hours before surgery and placebo 10 minutes postoperatively"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded. Quote: "the scoring was performed by a blinded investigator or blinded nursing staff".
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants analysed
Selective reporting (reporting bias)	Unclear risk	No protocol or trial registration
Other bias	Low risk	Similar baseline characteristics

Grifka 2008

Study characteristics

Grifka 2008 *(Continued)*

Methods	Study design: parallel-group randomized controlled trial Sample size: 89 Country: unclear Setting: secondary care Dates conducted: not reported Postoperative opioid used and delivery: PO oxycodone Pain score collection: blinded investigator Concurrent postoperative analgesics: paracetamol
Participants	**Inclusion criteria** 1. Male or female outpatients 2. Aged at least 18 years 3. Minor ambulatory arthroscopic knee surgery **Exclusion criteria** 1. Allergy to narcotics, NSAIDs or COX-2 inhibitors 2. Drug or alcohol abuse 3. Peptic ulcer 4. Gastroesophageal reflux disease 5. Inflammatory bowel disease 6. Cardiovascular, hepatobiliary, pancreatic and renal disorders 7. Anticoagulants and antiplatelets (except low-dose aspirin) 8. Pregnant or breastfeeding
Interventions	**Group Preemptive (45 participants):** 400 mg PO lumiracoxib one hour before the start of surgery and a placebo tablet 15 minutes after surgery **Group Postoperative (44 participants):** placebo tablet one hour before surgery and 400 mg PO lumiracoxib given 15 minutes after surgery
Outcomes	1. Postoperative pain at rest and movement (on 0-100 mm VAS at 1, 2, 3, 4 and 24 hours) 2. Number of patients requiring rescue medication (paracetamol and oxycodone use in 24 hours) 3. Time to first rescue medication (hours) 4. Global evaluation of response to treatment (four-point Likert scale) 5. Adverse events (incidence during follow-up of cardiac disorders, angina, abdominal pain, vomiting and headache)
Notes	Funding: not reported Declarations of interest: not reported but some authors from pharmaceutical company Authors contacted: yes Other: data estimated from median and SD estimated from other studies. Analgesic consumption not added as included paracetamol. Although time to analgesic reported as time-to-event, not enough information to calculate summary statistics. Cardiac adverse events not included as not clearly defined. Not enough reported information to include satisfaction

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No mention

Grifka 2008 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	No mention
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-dummy placebo used. Quote: "...patients in the first group received a single dose of lumiracoxib 400 mg 1 hour before surgery and a placebo tablet 15 min after surgery (Pre-emptive group)".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded. Quote: "patients, investigators, persons performing the assessments, data analysts and clinical team members were blinded to the identity of the treatment".
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat analysis
Selective reporting (reporting bias)	Unclear risk	No protocol or trial registration
Other bias	High risk	More females in pre-emptive group (Gerbershagen 2014). Industry involvement but unclear on role

Gunter 2012

Study characteristics	
Methods	Study design: parallel-group randomized controlled trial Sample size: 80 Country: Germany Setting: secondary care Dates conducted: May 2004 to August 2007 Postoperative opioid used and delivery: IV piritramide Pain score collection: not reported Concurrent postoperative analgesics: none reported
Participants	**Inclusion criteria** 1. Aged between 18 and 70 years old 2. ASA 1 to 3 3. Minor trauma surgery 4. General anaesthesia 5. Good understanding of the German language **Exclusion criteria** 1. Chronic or acute analgesic use 2. Severe preoperative pain 3. Substance abuse 4. Heart failure NYHA 3 or 4 5. Hypersensitivity to parecoxib or any of the excipients in the powder 6. Sulfonamide allergy 7. Gastrointestinal ulcer or bleeding in last year 8. Moderate and severe hepatic dysfunction (Child-Pugh score > 7) 9. Renal insufficiency (creatinine clearance < 30 mL/min)

Gunter 2012 *(Continued)*

	10.Asthma or rhinitis 11.Chronic nasal swelling 12.Angio-oedema or urticaria in response to NSAIDs 13.Inflammatory bowel disease 14.Pregnancy and breastfeeding 15.Emergency intervention 16.Severe cognitive impairment
Interventions	**Group 1 (40 participants):** 40 mg IV parecoxib 30 minutes before surgery and 12 and 24 hours after surgery. Placebo 30 minutes before end of surgery **Group 2 (40 participants):** 40 mg IV parecoxib 30 minutes before the end surgery and 12 and 24 hours after surgery. Placebo 30 minutes before surgery
Outcomes	1. Postoperative pain at rest and movement (0-10 NRS in recovery room and 10, 20 minutes then 1, 2, 4, 6, 10, 22 and 24 hours after surgery) 2. Piritramide consumption (mg consumed in recovery room and 10, 20 minutes then 1, 2, 4, 6, 10, 22 and 24 hours after surgery) 3. Time to analgesic request (minutes) 4. Adverse events (incidence of nausea, vomiting, sedation, headache and pruritus at follow-up)
Notes	Funding: not reported Declarations of interest: not reported Authors contacted: no Other: data estimated from median and IQR from graphs. Time to analgesic request not reported as time-to-event

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated. Quote: "computerized random number generator"
Allocation concealment (selection bias)	Unclear risk	No mention
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-dummy placebo, identical
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No mention
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Ten participants excluded, more in pre-emptive group although unclear if these were or were not included in the analysis
Selective reporting (reporting bias)	Unclear risk	No protocol or trial registration
Other bias	High risk	More females in pre-emptive group and more knee arthroscopies in post-incision group (Gerbershagen 2014)

Guran 2010

Study characteristics	
Methods	Study design: parallel-group randomized controlled trial Sample size: 82 Country: Romania Setting: secondary care Dates conducted: not reported Postoperative opioid used and delivery: IV pethidine Pain score collection: not reported Concurrent postoperative analgesics: paracetamol, tramadol and metamizole
Participants	**Inclusion criteria** 1. Aged 18 and 80 years old 2. ASA 1-3 3. Elective laparoscopic cholecystectomy **Exclusion criteria** 1. Hypersensitivity or intolerance to NSAIDs 2. Upper gastrointestinal haemorrhage or ulcerative pathology 3. Moderate cardiac, renal or hepatic impairment
Interventions	**Group A (39 participants):** IV 50 mg of dexketoprofen with normal saline up to 5 mL 30 minutes before induction and injection with 5 mL of IV saline at the time of suturing the skin **Group B (43 participants):** IV 50 mg of dexketoprofen with normal saline up to 5 mL at the time of suturing the skin and 5 mL of IV saline 30 minutes before surgery
Outcomes	1. Postoperative pain (0-10 cm VAS every 2 hours for 24 hours) 2. Pethidine consumption (mg consumed at 24 hours) 3. Adverse events (nausea and vomiting, sedation and gastrointestinal side effects at 24 hours)
Notes	Funding: not reported Declarations of interest: not reported Authors contacted: yes (response received but no further data available) Other: SD from pain score data estimated. Data extracted from graph. Nausea and vomiting not included as unclear to which group the data referred

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number list. Quote: "random number list"
Allocation concealment (selection bias)	Unclear risk	No mention
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-dummy placebo used. Quote: "the contents of the two syringes were given to a member of the team not involved in that anesthetic or in immediate postoperative follow-up".

Guran 2010 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No mention
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropouts unlikely to cause bias as similar number and reasons for exclusions. Quote: "three patients in group A and 2 were excluded from the group B due to technical difficulties in laparoscopy and one in each group for diagnosis of acute gallbladder".
Selective reporting (reporting bias)	Unclear risk	No protocol or trial registration
Other bias	Low risk	Similar baseline characteristics

Inanoglu 2007

Study characteristics	
Methods	Study design: parallel-group randomized controlled trial Sample size: 44 Country: Turkey Setting: secondary care Dates conducted: not reported Postoperative opioid used and delivery: PO tramadol Pain score collection: self-report Concurrent postoperative analgesics: PO paracetamol
Participants	**Inclusion criteria** 1. ASA 1 or 2 2. Male 3. Elective unilateral varicocelectomy using local anaesthesia **Exclusion criteria** 1. Aged < 18 years or > 65 years old 2. History of allergy to any NSAID 3. Renal impairment 4. Asthma 5. Coagulopathy 6. Peptic ulcer disease
Interventions	**Group 1 (22 participants):** 8 mg IV lornoxicam in 100 mL of normal saline over 10 minutes in the preoperative room 30 minutes before skin incision and 100 mL of normal saline over 10 minutes immediately after wound closure **Group 2 (22 participants):** 100 mL of normal saline over 10 minutes in the preoperative room 30 minutes before skin incision and 8 mg IV lornoxicam in 100 mL of normal saline over 10 minutes immediately after wound closure
Outcomes	1. Postoperative pain (0-10 cm VAS every hour for 8 hours and then at 12, 16, 20, and 24 hours) 2. Time to analgesic request (hours) 3. Number requiring paracetamol and tramadol (% during 24 hours) 4. Global satisfaction (0-5 scale during the postoperative period)

Inanoglu 2007 *(Continued)*

Notes	Funding: not reported Declarations of interest: not reported Authors contacted: yes Other: patient satisfaction not included as unclear what values represented. Time to analgesia not time-to-event

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated. Quote: "computer-generated table of random numbers"
Allocation concealment (selection bias)	Unclear risk	No mention
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-dummy placebo used. Quote: "...group 1 received 8 mg of lornoxicam diluted in 100 mL of normal saline as an intravenous infusion over a period of 10 minutes in the pre-operative room. This infusion was completed 30 minutes before skin incision. One hundred milliliters of plain normal saline was infused over 10 minutes immediately after wound closure in this group".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded. Quote: "...investigators participating in the pain assessments and patients were blinded as to the type of medication administered".
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients analysed
Selective reporting (reporting bias)	Unclear risk	No protocol or trial registration
Other bias	Low risk	Similar baseline characteristics

Kaczmarzyk 2010

Study characteristics

Methods	Study design: parallel-group randomized controlled trial Sample size: 64 Country: Poland Setting: secondary care hospital Dates conducted: not reported Postoperative opioid used and delivery: no opioid used Pain score collection: self-report Concurrent postoperative analgesics: paracetamol PRN
Participants	**Inclusion criteria** 1. Healthy individuals 2. Surgical extraction of the lower wisdom teeth **Exclusion criteria**

Kaczmarzyk 2010 *(Continued)*

1. Age under 18 or over 60 years
2. Pregnancy
3. Allergy to ketoprofen, aspirin or any other NSAID
4. Lactose intolerance
5. Gastrointestinal disease
6. Inflammation in the area of the tooth to be extracted
7. Any antibiotic or analgesic intake within the previous 7 days

Interventions	**Group Pre (34 participants):** 100 mg ketoprofen PO 60 minutes preoperatively, followed by 100 mg placebo PO 60 minutes postoperatively **Group Post (30 participants):** 100 mg placebo PO 60 minutes preoperatively, followed by 100 mg ketoprofen PO 60 minutes postoperatively
Outcomes	1. Postoperative pain (0-100 mm VAS every hour for 12 hours postoperatively) 2. Paracetamol consumption (number of doses consumed) 3. Time to first and second analgesic request (minutes)
Notes	Funding: "Grant of the Jagiellonian University (K/ZDS/00519)" Declarations of interest: none declared Authors contacted: no Other: pain data extracted from graphs and SD estimated. Pain score from 2 hours to allow postoperative dosing time to take effect

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number table. Quote: "Each envelope contained the group assignment for one patient, which was determined in advance by a random number table".
Allocation concealment (selection bias)	Low risk	Sealed and opaque envelopes. Quote: "One hundred opaque, sequentially numbered envelopes were used for the concealed allocation of patients to trial groups".
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-dummy placebo. Quote: "The patients, the statistician and the surgeon performing the qualification, operative procedure and follow-up examination were all blinded with regard to which patients had received which form of treatment...Identical, nonmarked capsules with 100 mg ketoprofen or 100 mg placebo were prepared and coded in a professional pharmaceutical laboratory".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Likely blinded from above as self-report
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only two dropouts from post group, unlikely to cause bias. Quote: "one hundred patients entered the trial, of whom 4 did not check-in for the follow-up examination. In all, complete data sets from 96 patients were statistically analysed".
Selective reporting (reporting bias)	Unclear risk	No protocol
Other bias	Low risk	Similar baseline characteristics

Karaman 2008

Study characteristics	
Methods	Study design: parallel-group randomized controlled trial Sample size: 40 Country: Turkey Setting: secondary care Dates conducted: not reported Postoperative opioid used and delivery: tramadol PCA Pain score collection: blinded anaesthesia resident Concurrent postoperative analgesics: lornoxicam if pain uncontrolled with opioid
Participants	**Inclusion criteria** 1. Major abdominal surgery (laparotomy) 2. Treated postoperatively in the intensive care unit **Exclusion criteria** 1. Preoperative use of analgesics 2. Allergy to NSAIDs 3. History of peptic ulcer disease 4. Coagulopathy 5. Renal disease
Interventions	**Group PRE (20 participants):** 8 mg IV lornoxicam 20 minutes before incision and IV saline after skin closure **Group POST (20 participants):** IV saline 20 minutes before incision and 8 mg IV lornoxicam after skin closure
Outcomes	1. Postoperative pain at rest and movement (0-10 cm VAS at 1, 2, 4, 12 and 24 hours) 2. Tramadol consumption (mg at 1, 2, 4, 12 and 24 hours) 3. Adverse events (nausea, vomiting, dizziness, drowsiness, sedation, anxiety, dyspepsia and indigestion during follow-up) 4. Patient satisfaction (incidence on 4-point scale)
Notes	Funding: none Declarations of interest: none declared Authors contacted: no Other: included as pre-emptive as not all patients received postoperative lornoxicam. Patient satisfaction not included as not reported as continuous. Nausea and vomiting taken from anti-emetic rescue as this was given when nausea and vomiting occurred

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No details. Quote: "sixty participants were randomly assigned to three groups".
Allocation concealment (selection bias)	Unclear risk	No mention

Karaman 2008 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-dummy placebo. None of the patients and managing anaesthetists were aware of the randomization code. Quote: "Patients in Group PRE received lornoxicam (Nycomed GmbH, Austria) IV 8 mg 20min before incision and saline IV after skin closure".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded. Quote: "...all measurements were recorded by the same anaesthesia resident who was blinded to the study drugs administered".
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants analysed
Selective reporting (reporting bias)	Unclear risk	ISRCTN: 2006/34 but unable to find on trial registry
Other bias	Low risk	Similar baseline characteristics and no conflicts of interest

Lee 2008

Study characteristics	
Methods	Study design: parallel-group randomized controlled trial Sample size: 40 Country: Hong Kong Setting: secondary care Dates conducted: not reported Postoperative opioid used and delivery: IV morphine then PCA Pain score collection: blinded nurse Concurrent postoperative analgesics: none reported
Participants	**Inclusion criteria** 1. Open colorectal surgery **Exclusion criteria** 1. Aged < 18 or > 70 years old 2. Allergy to coxibs, sulphonamides or NSAIDS 3. Not able to use patient-controlled analgesia 4. Received analgesics, NSAIDs or corticosteroids within the preceding 24 hours of the study
Interventions	**Group PS (20 participants):** 40 mg IV parecoxib before induction of anaesthesia and IV normal saline at skin suture **Group SP (20 participants):** IV normal saline before induction of anaesthesia and 40 mg IV parecoxib at skin suture
Outcomes	1. Postoperative pain at rest and cough (0-10 NRS up to 48 hours) 2. Time to analgesic request (minutes) 3. Morphine consumption (mg consumed up to 48 hours) 4. Adverse events (nausea, vomiting, dizziness and pruritus up to 48 hours and myocardial infarction, thrombosis and stroke up to 3 months after surgery)

Lee 2008 *(Continued)*

Notes	Funding: not reported Declarations of interest: not reported Authors contacted: yes (response received but no further data available) Other: unable to include morphine consumption data as unclear at what time points it was measured. Time to analgesic request not reported. Pain data converted from median and extracted from graph with SD estimated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated. Quote: "computer-generated codes"
Allocation concealment (selection bias)	Low risk	Numbered and opaque envelopes. Quote: "maintained in sequentially numbered, opaque envelopes"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-dummy placebo used. Quote: "...parecoxib was dissolved to form a clear, colourless solution and an equivalent volume of normal saline was used as the placebo".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded. Quote: "the patients, investigators and clinicians who collected the data were blinded to the assigned treatment".
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants analysed
Selective reporting (reporting bias)	High risk	No protocol but primary outcome not reported (time to analgesic request)
Other bias	High risk	More females in PS group (Gerbershagen 2014)

Likar 1997

Study characteristics

Methods	Study design: parallel-group randomized controlled trial Sample size: 48 Country: Austria Setting: secondary care hospital Dates conducted: not reported Postoperative opioid used and delivery: PCA piritramide Pain score collection: not reported Concurrent postoperative analgesics: none reported
Participants	**Inclusion criteria** 1. ASA 1 or 2 2. Female 3. Ages between 18 and 70 years 4. Weight 60-90 kg

Likar 1997 *(Continued)*

	5. Gynaecology laparotomy or laparoscopy **Exclusion criteria** 1. Cardiovascular disease 2. Respiratory disease 3. CNS disease 4. Renal dysfunction 5. Liver dysfunction 6. Peptic ulcer 7. Chronic opioid or benzodiazepines 8. Pregnancy
Interventions	**Group Ketoprofen Pre-op (26 participants):** 20 minutes before surgery ketoprofen 2 mg/kg IV and at the end of the operation IV placebo **Group Ketoprofen Post-op (22 participants):** placebo IV before surgery and ketoprofen 2 mg/kg IV at the end of the operation (last suture)
Outcomes	1. Postoperative pain on rest and cough (0-10 cm VAS before the first analgesic intake, after 15 and 30 minutes then 1, 2, 3, 6, 9, 12, 18 and 24 hours postoperatively) 2. Piritramide consumption (mg consumed after 15 and 30 minutes then 1, 2, 3, 6, 9, 12, 18 and 24 hours postoperatively) 3. Time to analgesic request (minutes) 4. Side effects (urinary retention, pruritus, nausea, vomiting, dizziness, headache and coughing during follow-up) 5. Sedation (1-5 scale)
Notes	Funding: not reported Declarations of interest: not reported Authors contacted: no Other: translated from German. Data extracted from graphs. Nausea and vomiting not included as not composite. No data for sedation. Piritramide converted to morphine by x 0.75. Early pain score from 30 minutes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details. Quote: "The patients were divided into 2 groups".
Allocation concealment (selection bias)	Unclear risk	No details. Quote: "The list on which the group allocation and patient name noted was always locked and only after completion of the study was revealed".
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-dummy placebo. Quote: "...the first group received ketoprofen 2 mg/kg body weight IV 20 minutes before the beginning of surgery and placebo IV at the end of surgery".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The infusions were from a person of the nursing staff who are not involved in the anesthesia and not involved in the postoperative monitoring".

Likar 1997 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants analysed
Selective reporting (reporting bias)	Unclear risk	No protocol
Other bias	Low risk	Similar baseline characteristics

Likar 1998

Study characteristics	
Methods	Study design: parallel-group randomized controlled trial Sample size: 50 Country: Austria Setting: secondary care hospital Dates conducted: not reported Postoperative opioid used and delivery: PCA piritramide Pain score collection: not reported Concurrent postoperative analgesics: none reported
Participants	**Inclusion criteria** 1. ASA 1 or 2 2. Female 3. Ages between 18 and 70 years 4. Weight 60-90 kg 5. Gynaecology laparotomy or laparoscopy **Exclusion criteria** 1. Cardiovascular disease 2. Respiratory disease 3. CNS disease 4. Renal dysfunction 5. Liver dysfunction 6. Peptic ulcer 7. Chronic opioid or benzodiazepines 8. Pregnancy
Interventions	**Group I (25 participants):** ketoprofen 100 mg IV 20 minutes before incision then saline placebo at last skin suture then ketoprofen 12 mg/hour during surgery and for 48 hours afterwards **Group II (25 participants):** placebo IV 20 minutes before incision and during surgery then ketoprofen 100 mg IV at last skin suture then ketoprofen 12 mg/hour for 48 hours afterwards
Outcomes	1. Postoperative pain (0-100 mm VAS at 15 minutes, 30 minutes, 1, 2, 3, 6, 9, 12, 18, 24 and 48 hours postoperatively) 2. Piritramide consumption (mg consumed at 15 minutes, 30 minutes, 1, 2, 3, 6, 9, 12, 18, 24 and 48 hours postoperatively) 3. Time to analgesic request (minutes) 4. Side effects (urinary retention, pruritus, nausea, vomiting, dizziness and headache during follow-up)

Likar 1998 *(Continued)*

Notes	Funding: not reported Declarations of interest: not reported Authors contacted: no Other: translated from German. Data extracted from graphs. SD estimated for analgesic consumption and pain score data. Nausea and vomiting not included as not composite. Piritramide converted to morphine by x 0.75. Early pain score from 30 minutes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details. Quote: "drawing of numbers"
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-dummy placebo used. Quote: "...ketoprofen 100 mg IV 20 minutes before incision then saline placebo at last skin suture"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No mention
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropouts unlikely to cause bias. Quote: "1 patient was excluded as surgery lasted 20 minutes, 3 patients were missed because of missing documentation values, 1 patient had to go to intensive care and 1 patient had to withdraw due to compliance issues"
Selective reporting (reporting bias)	Unclear risk	No protocol
Other bias	Low risk	Similar baseline characteristics

Lu 2015

Study characteristics

Methods	Study design: parallel-group randomized controlled trial Sample size: 113 Country: China Setting: secondary care Dates conducted: January 2011 to June 2013 Postoperative opioid used and delivery: none reported Pain score collection: not reported Concurrent postoperative analgesics: none reported
Participants	**Inclusion criteria** 1. Lung cancer with radical resection 2. ASA 1-3

Lu 2015 *(Continued)*

	3. Non-small cell lung cancer at staging IIIb-IV **Exclusion criteria** 1. History of chronic pain or chronic analgesic use
Interventions	**Group Research (56 participants):** 2 mL of 40 mg IV parecoxib 30 minutes before surgery and 2 mL IV saline after surgery **Group Control (57 participants):** 2 mL IV saline 30 minutes before surgery and 2 mL of 40mg IV parecoxib after surgery
Outcomes	1. Postoperative pain (0-10 cm VAS at 1, 2, 4, 8, 12, 24 and 48 hours after surgery) 2. Restlessness (0-4 scale during recovery period)
Notes	Funding: Health Medicine and Science Technology development plan, Shan Dong Probince, China. Project number: 2013WS0076 Declarations of interest: none declared Authors contacted: no Other: N/A

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details. Quote: "...were randomly divided into the research group and the control group"
Allocation concealment (selection bias)	Unclear risk	No mention
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-dummy placebo used. Quote: "patients in the research group were treated with 2 ml parecoxib (40 mg parecoxib dissolved in 2 ml saline) IV 30 min before operation, and 2 ml saline IV after operation".
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No mention
Incomplete outcome data (attrition bias) All outcomes	Low risk	Two excluded from pre-emptive group for hospital transfer. Unlikely to cause bias
Selective reporting (reporting bias)	Unclear risk	No protocol or trial registration
Other bias	Low risk	Similar baseline characteristics

Martinez 2007

Study characteristics

Methods	Study design: parallel-group randomized controlled trial Sample size: 41

Martinez 2007 *(Continued)*

	Country: France Setting: secondary care Dates conducted: not reported Postoperative opioid used and delivery: morphine PCA Pain score collection: blinded nurse Concurrent postoperative analgesics: none reported
Participants	**Inclusion criteria** 1. Total hip arthroplasty 2. General anaesthesia **Exclusion criteria** 1. Contraindications to parecoxib (including cardiovascular pathology and renal insufficiency) 2. Previous hip surgery 3. Hip trauma 4. Preoperative use of opioid or NSAID within 48 hours before surgery 5. Patients were withdrawn from the study if they withdrew consent during the follow-up period, developed a complication that required intervention within 24 hours after surgery or required prolonged (> 60 minutes) mechanical ventilation after surgery.
Interventions	**Group Pre (22 participants):** 40 mg IV parecoxib at induction, placebo at wound closure and 40 mg IV parecoxib at 12 hours **Group Post (19 participants):** placebo at induction, 40 mg IV parecoxib at wound closure and 40 mg IV parecoxib 12 hours after surgery
Outcomes	1. Postoperative pain at rest and movement (0-100 mm VAS 4 hourly for 24 hours) 2. Morphine consumption (mg consumed during 24 hours after surgery) 3. Time to analgesic request (minutes) 4. Morphine side effects (incidence of sedation, urinary retention and nausea or vomiting during 24 hours) 5. Intraoperative bleeding (mL and incidence of transfusion at day 5 after surgery)
Notes	Funding: NIH Grant GM 061655 (Bethesda, MD), the Gheens Foundation (Louisville, KY), the Joseph Drown Foundation (Los Angeles, CA) and the Commonwealth of Kentucky Research Challenge Trust Fund (Louisville, KY). No financial support of Pfizer Declarations of interest: not reported Authors contacted: no Other: pain score data for 24 hours extracted from graph and SD estimated. Time to analgesic request not time-to-event

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated. Quote: "computer-generated codes"
Allocation concealment (selection bias)	Low risk	Quote: "the randomization instructions were stored in sequentially numbered opaque envelopes opened the day of surgery before induction of anesthesia".

Martinez 2007 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-dummy placebo used. Quote: "...all patients received three IV injections: one with anesthesia induction, a second at wound closure, and a third 12 hours after induction".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	Fourteen exclusions. Quote: "Eleven patients were eliminated from the study: two patients withdrew consent, one required prolonged postoperative mechanical ventilation, two were inadvertently given paracetamol (one of the exclusion criterion), four because of inadequate order of treatment attribution (third injection made instead the second), one had a surgical complication that required intervention, and one because the patient's data were lost...Two additional patients were eliminated from the study after morphine titration in the PACU".
Selective reporting (reporting bias)	Unclear risk	No protocol or trial registration
Other bias	Low risk	Similar baseline characteristics and no drug company involvement

Mishra 2012

Study characteristics	
Methods	Study design: parallel-group randomized controlled trial Sample size: 25 Country: India Setting: secondary care hospital Dates conducted: January 2010 to January 2011 Postoperative opioid used and delivery: none (ibuprofen) Pain score collection: not reported Concurrent postoperative analgesics: none reported
Participants	**Inclusion criteria** 1. Elective dental extraction **Exclusion criteria** (none reported)
Interventions	**Group Ketorolac Preoperatively (12 participants):** PO 20 mg ketorolac 30 minutes preoperatively **Group Ketorolac Postoperatively (13 participants):** PO 20 mg ketorolac 30 minutes after surgery
Outcomes	1. Postoperative pain (VRS 1-7 scale at 30 minutes and 2, 4 and 6 hours after the procedure) 2. Ibuprofen consumption (mg consumed at 6 hours) 3. Time to analgesic request (minutes) 4. Adverse events (sleepiness, dizziness, weakness/tiredness, nausea and vomiting, paraesthesia and serious adverse events at 6 hours)
Notes	Funding: none Declarations of interest: "none declared" Authors contacted: yes

Mishra 2012 *(Continued)*

	Other: unable to include pain as 1-7 scale which was specific to study. SD estimated for time to analgesia. Adverse events not reported separately for ketorolac groups

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated. Quote: "Computer generated random numbers"
Allocation concealment (selection bias)	Unclear risk	No mention
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unclear if double-dummy placebo given. Quote: "Placebo was glucose powder filled in empty capsule... Both the investigator and patient were blind…Each drug was coded and packed into identical appearing packets".
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No mention
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants analysed
Selective reporting (reporting bias)	Unclear risk	No protocol
Other bias	Low risk	Similar baseline characteristics and no industry funding. Quote: "All the six patients groups were similar in terms of gender distribution, average age, the amount of local anaesthetic administered, the antibiotic coverage given, the position of the molar extracted and the duration of the procedure".

Mojsa 2017

Study characteristics

Methods	Study design: parallel-group randomized controlled trial Sample size: 60 Country: Poland Setting: secondary care hospital Dates conducted: not reported Postoperative opioid used and delivery: none Pain score collection: surgeon Concurrent postoperative analgesics: none reported
Participants	**Inclusion criteria** 1. Surgical extraction of a partially or totally impacted lower third molar (Pell and Gregory classification IIB or IIIB), with no associated inflammation of the tissue 2. Aged 18–50 years old 3. General good health **Exclusion criteria**

Mojsa 2017 *(Continued)*

	1. Allergy to paracetamol, lornoxicam, aspirin or any other NSAID 2. Lactose intolerance 3. Pregnancy or breastfeeding 4. Any analgesic intake in the 24 hours immediately prior to the surgery
Interventions	**Group A (30 participants):** PO lornoxicam 60 mg 60 minutes before surgery and placebo 60 minutes after surgery **Group B (30 participants):** placebo 60 minutes before surgery and PO lornoxicam 60 mg 60 minutes after surgery
Outcomes	1. Postoperative pain (sum of the grading of the level of pain at 1, 2, 4, 6, 8, 12 and 24 hours after surgery) 2. Paracetamol consumption (mg consumed at 24 hours) 3. Adverse events (not specified which at 24 hours) 4. Time to analgesic request (hours)
Notes	Funding: "no funding to declare" Declarations of interest: "none declared" Authors contacted: yes (data received from authors for VAS pain scores) Other: time to analgesia time-to-event but not enough information to extract data. Early pain score from 2 hours to allow post-incision dose to take effect

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random numbers. Quote: "random number generator"
Allocation concealment (selection bias)	Low risk	Opaque envelopes. Quote: "To ensure allocation concealment, 90 identical non-transparent sequentially numbered envelopes were used".
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-dummy placebo used. Quote: "Identical unmarked capsules containing either 16 mg of lornoxicam or the same weight of placebo were administered".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Likely blinded from above
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants analysed. Quote: "No data were missing, and all patients included in the present study attended all study visits".
Selective reporting (reporting bias)	Unclear risk	No protocol
Other bias	Low risk	Similar baseline characteristics and no industry funding. Quote: "There was no difference between the three study groups in terms of age (P = 0.325) or sex distribution (P = 0.526), surgical difficulty of the procedure (P = 0.721) or duration of surgery (P = 0.919)".

Moonla 2018

Study characteristics	
Methods	Study design: parallel-group randomized controlled trial Sample size: 84 Country: Thailand Setting: secondary care hospital Dates conducted: February 2016 to May 2017 Postoperative opioid used and delivery: PCA morphine Pain score collection: not reported Concurrent postoperative analgesics: none
Participants	**Inclusion criteria** 1. Aged 21–88 years old 2. Not pregnant or lactating 3. Fully conscious and able to agree with the study protocol 4. Major spinal surgery (expected to be a long surgery) involving > 2 spinal levels or using spinal fixation devices 5. Attended by a neurosurgeon with > 3 years experience in spinal surgery 6. ASA 1-3 **Exclusion criteria** 1. < 50 kg 2. Receiving any analgesic drug within 24 hours prior to surgery 3. Liver impairment 4. Renal impairment or signs of fluid retention 5. Fluconazole within 1 week prior to surgery 6. Hypersensitivity to parecoxib, sulfonamides, or other NSAIDs, including compounds contained in parecoxib 7. Contraindication to parecoxib administration 8. Contraindication to lorazepam use, anesthesia medications, and morphine
Interventions	**Group Pre (42 participants):** 40 mg parecoxib before skin incision and at 12 and 24 hours after the first dose **Group Post (42 participants):** 40 mg parecoxib at wound closure and at 12 and 24 hours after the first dose
Outcomes	1. Postoperative pain (0-10 cm VAS every 2 hours for the first 8 hours after surgery and then every 4 hours for the next 16 hours thereafter) 2. Morphine consumption (mg in 24 hours) 3. Time to analgesia (not reported) 4. Adverse events (nausea and vomiting, abdominal pain, flatulence, limb oedema, dizziness, drowsiness, and oliguria at 24 hours)
Notes	Funding: none reported Declarations of interest: "No potential conflict of interest relevant to this article was reported". Authors contacted: no Other: data taken from graphs and SD calculated from SEM

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Moonla 2018 *(Continued)*

Random sequence generation (selection bias)	Low risk	Block randomization. Quote: "...block randomization sampling method"
Allocation concealment (selection bias)	Unclear risk	No mention
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-dummy placebo. Quote: "This study was a double-blind trial. Each group received six doses of intravenous solution. All solutions were colorless, and each solution was given in a 2 mL volume, prepared by a nurse anesthetist who was not involved in the assessment and patient care before, during, and after operation".
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No mention
Incomplete outcome data (attrition bias) All outcomes	High risk	Large number of dropouts. Quote: "Because of incomplete data, 17 of 144 patients were excluded from the study; nine patients withdrew consent, five had surgical complications that required intervention, and three required prolonged postoperative mechanical ventilation".
Selective reporting (reporting bias)	Unclear risk	No protocol
Other bias	Low risk	Similar groups

Munteanu 2016

Study characteristics	
Methods	Study design: parallel-group randomized controlled trial Sample size: 110 Country: Romania Setting: secondary care Dates conducted: January to September 2014 Postoperative opioid used and delivery: IV and SC morphine Pain score collection: blinded staff Concurrent postoperative analgesics: IV paracetamol
Participants	**Inclusion criteria** 1. ASA 1-2 2. Aged 20 to 85 years old 3. BMI 20 to 25 4. Haematocrit > 30% 5. Primary total knee arthroplasty 6. Spinal anaesthesia 7. Informed consent given **Exclusion criteria** 1. Severe hepatic or renal dysfunction 2. Asthma

Munteanu 2016 *(Continued)*

	3. Congestive heart failure (NYHA 2 to 4) 4. Neuropathies 5. Bleeding disorders 6. Pre-existing peptic ulcer or dyspepsia 7. History of gastrointestinal bleeding 8. Inability to cooperate 9. Substance abuse 10. Sensitivity to etoricoxib, paracetamol or morphine 11. Chronic treatment with antidepressants, sedatives or corticosteroids 12. Long-acting NSAIDs administered in the last 4 days preoperatively 13. Cerebrovascular or peripheral arterial disease 14. Inadequately controlled arterial hypertension
Interventions	**Group ETORICOX-PREOP (55 participants):** etoricoxib 120 mg PO 1 hour before surgery, one placebo pill upon arrival in the postoperative care unit (PACU) and a second etoricoxib dose after 24 hours **Group ETORICOX-POSTOP (55 participants):** one placebo pill 1 hour before surgery, etoricoxib 120 mg PO at the end of surgery, immediately after arrival in the PACU, and a second etoricoxib dose after 24 hours
Outcomes	1. Morphine consumption (mg consumed at 24 and 48 hours) 2. Time to analgesic request (minutes) 3. Adverse events (sedation, nausea, vomiting, gastric discomfort, itching, urinary retention after removal of the catheter, respiratory depression, hypotension and tachycardia at 48 hours)
Notes	Funding: no funding Declarations of interest: the first author is also the chair of the ethics committee that approved the study. Authors contacted: yes (response received but no further pain score data available) Other: included in pre-emptive as second dose at 24 hours. Authors contacted for pain score data and some adverse events. Nausea and vomiting not included as reported separately

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated. Quote: "computer-generated random number list"
Allocation concealment (selection bias)	Unclear risk	Unclear if opaque. Quote: "the assigned allocation group was written on a note placed inside a numbered envelope (one number corresponding to every patient enrolled); the envelope was then sealed".
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-dummy placebo. Quote: "to maintain the blinding conditions, medical staff had no knowledge of the randomisation of the patients or the contents of the pills...one placebo pill 1 h before surgery, etoricoxib 120 mg orally at the end of surgery, immediately after arrival in the PACU and a second etoricoxib dose after 24 h".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded. Quote: "...to maintain the blinding conditions, medical staff had no knowledge of the randomisation of the patients or the contents of the pills".
Incomplete outcome data (attrition bias)	Low risk	Intention-to-treat analysis

Munteanu 2016 *(Continued)*
All outcomes

Selective reporting (reporting bias)	Low risk	NCT02534610. All prespecified outcomes reported
Other bias	Low risk	Similar baseline characteristics and no conflicts of interest

Murphy 1993

Study characteristics	
Methods	Study design: parallel-group randomized controlled trial Sample size: 50 Country: Australia Setting: secondary care Dates conducted: not reported Postoperative opioid used and delivery: IV infusion and boluses of papaveretum Pain score collection: nurses Concurrent postoperative analgesics: none reported
Participants	**Inclusion criteria** 1. Elective thoracotomy **Exclusion criteria** 1. History of peptic ulceration
Interventions	**Group Preoperative (22 participants):** indomethacin PR 200 mg commencing on the night before surgery and 100 mg BD **Group Postoperative (28 participants):** same indomethacin regimen after completion of surgery
Outcomes	1. Postoperative pain at rest and during physiotherapy (0-10 cm VAS three times daily) 2. Papaveretum consumption (mg consumed at 2, 4, 6, 12, 18, 24, 30, 36, 42 and 48 hours)
Notes	Funding: not reported Declarations of interest: not reported Authors contacted: no Other: pain score data not fully reported, 14:00-15:00 day one after surgery used for late acute pain Extracted from graph

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No details. Quote: "the patients were allocated randomly to one of two groups".
Allocation concealment (selection bias)	Unclear risk	No mention

Murphy 1993 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	No double-dummy placebo used. Quote: "One group received indomethacin suppositories 200 mg commencing on the night before surgery and 100 mg twice daily thereafter. The second group commenced the same indomethacin regimen after completion of surgery".
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No mention
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants analysed
Selective reporting (reporting bias)	High risk	Pain score data not fully reported
Other bias	Low risk	Similar baseline characteristics

Nakayama 2001

Study characteristics	
Methods	Study design: parallel-group randomized controlled trial Sample size: 30 Country: Japan Setting: secondary care hospital Dates conducted: not reported Postoperative opioid used and delivery: none Pain score collection: blinded author Concurrent postoperative analgesics: PRN diclofenac
Participants	**Inclusion criteria** 1. Female 2. ASA 1 3. 40 to 60 years old 4. Elective abdominal hysterectomy (vertical lower abdominal incision) because of myoma of the uterus **Exclusion criteria** 1. Chronic pain
Interventions	**Group PRE (15 participants):** 1 mg/kg flurbiprofen IV 30 minutes before surgery and placebo at the end of surgery **Group POST (15 participants):** 1 mg/kg flurbiprofen IV at the end of surgery and placebo 30 minutes before surgery
Outcomes	1. Postoperative pain (0-10 cm VAS on rest and cough at first request of analgesia, 15, 24, 48 and 72 hours postoperatively) 2. Diclofenac consumption (number consumed at 24 hours) 3. Adverse events (nausea and vomiting and from intervention during follow-up) 4. Time to analgesia (minutes)
Notes	Funding: not reported

Nakayama 2001 *(Continued)*

Declarations of interest: not reported
Authors contacted: yes
Other: data for pain extracted from graph although unable to for early pain as unclear from graph

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details. Quote: "via sealed envelope assignment"
Allocation concealment (selection bias)	Unclear risk	Insufficient details. Quote: "via sealed envelope assignment"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-dummy placebo. Quote: "The PRE group received 1 mg/kg flurbiprofen IV 30 min before surgery and a placebo at the end of surgery…Both placebo and the flurbiprofen solution looked the same".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded. Quote: "...one of the authors (MN), who was blinded to group allocation"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants analysed
Selective reporting (reporting bias)	Unclear risk	No protocol
Other bias	Low risk	Similar baseline characteristics

Nezafati 2017

Study characteristics

Methods	Study design: parallel-group randomized controlled trial Sample size: 40 Country: Iran Setting: secondary care hospital Dates conducted: March 2016 to January 2017 Postoperative opioid used and delivery: IV pethidine and morphine Pain score collection: blinded nurses Concurrent postoperative analgesics: none reported
Participants	**Inclusion criteria** 1. Unilateral fractures in the body, angle or the symphysis of the mandible for ORIF 2. Aged 20-60 years old 3. ASA 1-2 **Exclusion criteria** 1. Surgical operations lasting for more than two hours 2. Drugs of abuse 3. Psychiatric patients

Nezafati 2017 *(Continued)*

	4. Allergy to study medications 5. Systemic conditions 6. Seizures 7. More than one incision
Interventions	**Group 1 (10 participants):** 30 mg ketorolac IV before induction **Group 2 (10 participants):** 60 mg ketorolac IV before induction **Group 3 (10 participants):** 30 mg ketorolac IV end of surgery **Group 4 (10 participants):** 60 mg ketorolac IV end of surgery
Outcomes	1. Postoperative pain (0-10 cm VAS at baseline and at 2, 4, 6, 12 and 24 hours postoperatively) 2. Pethidine and morphine consumption (mg consumed at 24 hours) 3. Time to analgesia (minutes)
Notes	Funding: "None" Declarations of interest: "None" Authors contacted: yes Other: Group 1/2 and 3/4 combined for analysis. Analgesic consumption not included as morphine and pethidine and unclear how dose in mg was calculated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated. Quote: "The subjects were assigned into five study groups with the use of the Randlist (Version 1.2) by an operator blinded to the aims of the study (simple randomization method)".
Allocation concealment (selection bias)	Unclear risk	No details on envelope. Quote: "...was placed in a closed envelope"
Blinding of participants and personnel (performance bias) All outcomes	High risk	No double-dummy placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded. Quote: "...the nurses who recorded pain scores, the dose of the analgesic agents administered and the time of the first administration of the analgesic agent were blinded to the study".
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants analysed. Quote: "All the subjects completed the study and none was excluded from the study".
Selective reporting (reporting bias)	Unclear risk	No protocol
Other bias	Low risk	Similar baseline characteristics. No industry funding

Norris 2001

Study characteristics

Norris 2001 *(Continued)*

Methods	Study design: parallel-group randomized controlled trial Sample size: 78 Country: Canada Setting: secondary care Dates conducted: not reported Postoperative opioid used and delivery: IV fentanyl then codeine Pain score collection: blinded research assistant Concurrent postoperative analgesics: PO diclofenac on discharge and paracetamol/codeine
Participants	**Inclusion criteria** 1. ASA 1 and 2 2. Ambulatory unilateral knee arthroscopies and intra-articular surgery **Exclusion criteria** 1. Aged greater than 65 or less than 18 years old 2. Active gastrointestinal ulcerative disease 3. History of adverse reaction to NSAIDs 4. History of drug abuse 5. Anticipated airway difficulty 6. Hiatus hernia 7. Morbid obesity 8. Analgesic use in the previous 8 hours
Interventions	**Group Preop (40 participants):** 50 mg of PO diclofenac 1 hour before surgery and a placebo 30 minutes postoperatively **Group Postop (38 participants):** placebo 1 hour before surgery and 50 mg of PO diclofenac 30 minutes postoperatively
Outcomes	1. Postoperative pain on rest, flexion, extension and weight bearing (0-100 mm VAS and 0-100 NRS every 30 minutes in PACU and on discharge) 2. Fentanyl consumption (mcg consumed in PACU) 3. Paracetamol and codeine consumption (on discharge) 4. Functional score (1 = able to stand with support, 2 = able to stand without support, 3 = walk with support, 4 = walk without support, 5 = stairs with support, 6 = stairs without support)
Notes	Funding: not reported Declarations of interest: not reported Authors contacted: no Other: early acute pain recorded from one hour to allow postoperative dosing to take effect

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number table. Quote: "...random numbers table"
Allocation concealment (selection bias)	Unclear risk	No mention

Norris 2001 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-dummy placebo. Quote: "diclofenac and placebo (lactose) were re-formulated into identical capsules by Toronto Western Hospital pharmacy department...the Preop group received 50 mg of potassium diclofenac PO 1 hour pre-operatively and a placebo 30 minutes postoperatively".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded. Quote: "...pre-operative and postoperative assessment was done by a research assistant who was blinded to group allocation".
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Six exclusions but unclear to which groups they belonged
Selective reporting (reporting bias)	Unclear risk	No protocol
Other bias	High risk	More females in Postop group (Gerbershagen 2014)

O'Hanlon 1996

Study characteristics	
Methods	Study design: parallel-group randomized controlled trial Sample size: 60 Country: Northern Ireland Setting: secondary care Dates conducted: not reported Postoperative opioid used and delivery: cyclimorph or co-codamol Pain score collection: self-report Concurrent postoperative analgesics: paracetamol PRN (as part of co-codamol)
Participants	**Inclusion criteria** 1. ASA 1 and 2 2. Diagnostic laparoscopy **Exclusion criteria** 1. Hypersensitivity to NSAIDs 2. Peptic ulcer disease 3. Asthma 4. Renal impairment 5. Concurrent NSAID medication
Interventions	**Group 1 (20 participants):** PO piroxicam 20 mg 2 hours before surgery and placebo at induction and one hour postoperatively **Group 2 (20 participants):** PO piroxicam 20 mg at induction and placebo 2 hours before surgery and one hour postoperatively **Group 3 (20 participants):** PO piroxicam 20 mg one hour postoperatively and placebo 2 hours before surgery and at induction
Outcomes	1. Time to analgesic request (minutes)

O'Hanlon 1996 *(Continued)*

	2. Postoperative pain (0-10 cm VAS on admission to the recovery ward, at 1, 2, 4, 8 and 24 hours) 3. Analgesic consumption (cyclimorph and paracetamol/codeine during postoperative period)
Notes	Funding: not reported Declarations of interest: not reported Authors contacted: no Other: pain score data extracted from graph. Group 1 and 2 combined for the pre-emptive group. Pain score at 2 hours included to allow postoperative dosing to take effect

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details. Quote: "...in a randomised double blind manner"
Allocation concealment (selection bias)	Unclear risk	No mention
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Triple-dummy placebo used. Quote: "...in a double blind manner, either 20 mg piroxicam or placebo in the "melt" form at the following times; two hours preoperatively, immediately before induction of anaesthesia or one hour postoperatively"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No mention
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients analysed
Selective reporting (reporting bias)	Unclear risk	No protocol
Other bias	Low risk	Similar baseline characteristics. Quote: "...patients in the three treatment groups were equally matched with respect to age, height and weight".

Ozer 2012

Study characteristics

Methods	Study design: parallel-group randomized controlled trial Sample size: 50 Country: Turkey Setting: secondary care hospital Dates conducted: not reported Postoperative opioid used and delivery: tramadol bolus then PCA Pain score collection: no mention Concurrent postoperative analgesics: none reported
Participants	**Inclusion criteria** 1. Septo-rhinoplasty 2. ASA 1 or 2

Ozer 2012 *(Continued)*

	Exclusion criteria 1. Known heart, kidney, liver and haematological diseases 2. Peptic ulcer and gastrointestinal bleeding 3. Allergy to NSAIDs 4. Chronic pain 5. Those who received analgesics within 24 hours of study
Interventions	**Group 50/0 (25 participants):** 100 mL saline containing 50 mg dexketoprofen as an infusion 30 minutes before the surgical incision and 100 mL saline 30 minutes before the end of the surgical procedure **Group 0/50 (25 participants):** 100 mL saline 30 minutes before the surgical incision and 100 mL saline containing 50 mg dexketoprofen as an infusion 30 minutes before the end of the surgical procedure
Outcomes	1. Postoperative pain (0-10 cm VAS at recovery, 1, 2, 3, 4, 5, 6, 7, 8, 12 and 24 hours) 2. Tramadol consumption (mg in recovery and at 24 hours) 3. Sedation (Ramsey Sedation Scale at recovery, 1, 2, 3, 4, 5, 6, 7, 8, 12 and 24 hours) 4. Nausea and vomiting (0-3 score at recovery, 1, 2, 3, 4, 5, 6, 7, 8, 12 and 24 hours) 5. Satisfaction (0-5 at 24 hours)
Notes	Funding: not reported Declarations of interest: not reported Authors contacted: no Other: could not use data for sedation (unable to dichotomise), nausea and vomiting (unable to dichotomise) and patient satisfaction (ordinal scale)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No mention. Quote: "Patients were randomly divided into four groups".
Allocation concealment (selection bias)	Unclear risk	No mention
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical placebo used and double-dummy. Quote: "...patients who received 100 ml saline containing 50 mg dexketoprofen as an infusion 30 minutes before the surgical incision and received 100 ml saline 30 minutes before the end of the surgical procedure"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The infusions of dexketoprofen and SP were prepared by a practitioner who was not involved in either application of anesthesia or postoperative evaluation".
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants appeared to have been analysed.
Selective reporting (reporting bias)	Unclear risk	No protocol or clinical trial registration
Other bias	High risk	More females in post-incision group (Gerbershagen 2014)

Ozyilmaz 2005

Study characteristics	
Methods	Study design: parallel-group randomized controlled trial Sample size: 40 Country: Turkey Setting: secondary care hospital Dates conducted: not reported Postoperative opioid used and delivery: PCA morphine Pain score collection: not reported Concurrent postoperative analgesics: none reported
Participants	**Inclusion criteria** 1. Lumbar microdiscectomy 2. ASA 1 or 2 3. Aged between 18-65 years old **Exclusion criteria** 1. Cardiovascular disease 2. Renal disease 3. Liver disease 4. Asthma 5. Chronic opioid or NSAID use 6. Difficulty communicating
Interventions	**Group I (20 participants):** IV lornoxicam 8 mg before surgery and saline placebo at closure **Group II (20 participants):** saline at induction and IV lornoxicam 8 mg before skin closure
Outcomes	1. Postoperative pain (0-10 cm VAS at 0, 15, 30, 45 minutes and 1, 2, 4, 6, 12 and 24 hours) 2. Morphine consumption (mg consumed at 0, 15, 30, 45 minutes and 1, 2, 4, 6, 12 and 24 hours) 3. Nausea or vomiting (yes/no at 24 hours)
Notes	Funding: not reported Declarations of interest: not reported Authors contacted: yes Other: pain score extracted from graph. Unable to include nausea and vomiting as not composite. Translated from Turkish. No pain at 24 hours so could not include. SD estimated for pain

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No details. Quote: "...this study was carried out in a prospective, randomized, double-blind fashion".
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-dummy placebo used. Quote: "Group-II (n=20, intraoperative group) patients received IV 2 ml saline solution before surgery and 8 mg IV lornoxicam before skin closure".

Ozyilmaz 2005 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No mention
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants analysed
Selective reporting (reporting bias)	Unclear risk	No protocol
Other bias	Low risk	Similar baseline characteristics

Pandazi 2010

Study characteristics	
Methods	Study design: parallel-group randomized controlled trial Sample size: 40 Country: Greece Setting: secondary care hospital Dates conducted: not reported Postoperative opioid used and delivery: morphine PCA Pain score collection: blinded anaesthetist Concurrent postoperative analgesics: none reported
Participants	**Inclusion criteria** 1. Elective surgery for colorectal cancer 2. ASA 1 or 2 **Exclusion criteria** 1. Allergy to NSAIDs 2. Peptic ulcer 3. Coronary artery disease 4. Severe cardiac insufficiency 5. Renal insufficiency 6. COPD 7. IBD 8. Use of analgesic medication the week before surgery
Interventions	**Group PRE (20 participants):** 40 mg IV parecoxib 30 minutes before surgery and 100 mL saline 30 minutes after incision. Then parecoxib 40 mg BD for three days **Group POST (20 participants):** 40 mg IV parecoxib 30 minutes after incision and 100 mL saline 30 minutes before surgery. Then parecoxib 40 mg BD for three days
Outcomes	1. Postoperative pain (0-10 VRS at 1, 6, 18 and 24 hours) 2. Morphine consumption (mg at 1, 6, 18 and 24 hours) 3. Nausea and vomiting (24 hours) 4. Cytokines (IL-6, IL-8, and TNF-alpha at baseline, intraoperative and 24 hours) 5. Pruritus and respiratory depression (24 hours)
Notes	Funding: not reported

Pandazi 2010 *(Continued)*

	Declarations of interest: not reported Authors contacted: no Other: pain scores reported as median so used as means and IQR/1.35 to convert to SD. No events for pruritus or respiratory depression

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated. Quote "Computer generated randomization list run by the hospital pharmacist"
Allocation concealment (selection bias)	Low risk	Pharmacy-controlled. Quote "Computer generated randomization list run by the hospital pharmacist"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-dummy placebo. Quote "A trained nurse administered an intravenous (IV) solution of 100 ml normal saline with parecoxib 40 mg to group PRE (preincisional) and an IV solution of 100 ml normal saline to group POST (post-incisional) 30 min before skin incision. The same nurse administered 100 ml normal saline with parecoxib 40 mg to group POST and 100 ml normal saline to group PRE 30 min after skin incision. The solutions were dispensed by the hospital pharmacist".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded. Quote "All participants in the study (nurse, surgeon, anesthesiologist, patients) were blinded to the perioperative intervention".
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only one participant excluded, unlikely to cause bias
Selective reporting (reporting bias)	Unclear risk	24807/20-12-06 trial registration but unable to locate protocol
Other bias	Low risk	Similar baseline characteristics

Parke 1995

Study characteristics

Methods	Study design: parallel-group randomized controlled trial Sample size: 77 Country: USA Setting: secondary care hospital Dates conducted: not reported Postoperative opioid used and delivery: morphine PCA Pain score collection: blinded investigator Concurrent postoperative analgesics: none reported
Participants	**Inclusion criteria** 1. Abdominal or vaginal hysterectomy 2. ASA 1 or 2 3. Aged 25-80 years old **Exclusion criteria**

Parke 1995 *(Continued)*

1. Upper gastrointestinal bleed
2. Renal disease
3. Intolerance to NSAIDS
4. Asthma
5. Psychiatric disease
6. Malignancy

Interventions	**Group Pre-emptive (37 participants):** 30 mg ketorolac 30 minutes before incision and saline placebo at skin closure (both 1 mL) **Group Postsurgical (40 participants):** saline placebo 30 minutes before incision and 30 mg ketorolac at skin closure (both 1 mL)
Outcomes	1. Postoperative pain (0-100 mm VAS at 12 and 24 hours) 2. Morphine consumption (mg at 24 hours)
Notes	Funding: not reported Declarations of interest: not reported Authors contacted: no Other: median and range converted to mean and SD for pain score data (Hozo 2005)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No mention. Quote "Patients were randomised..."
Allocation concealment (selection bias)	Unclear risk	No mention. Quote "Patients were randomised..."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical placebo used and both 1 mL. Quote "...placebo injection at skin closure"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded. Quote "...by an investigator who was unaware of the group to which the patient belonged"
Incomplete outcome data (attrition bias) All outcomes	High risk	High number of dropouts, more in intervention group including two who were discharged early and therefore likely to have lower pain. Quote "...were discharged before 24 hour follow up"
Selective reporting (reporting bias)	Unclear risk	No protocol or clinical trial registration
Other bias	High risk	More vaginal hysterectomies in post-incision group which on regression analysis were associated with pain as an outcome

Peduto 1995

Study characteristics

Methods	Study design: parallel-group randomized controlled trial Sample size: 30

Peduto 1995 *(Continued)*

	Country: Italy Setting: secondary care hospital Dates conducted: not reported Postoperative opioid used and delivery: none Pain score collection: blinded independent observer Concurrent postoperative analgesics: none
Participants	**Inclusion criteria** 1. Elective septoplasty 2. ASA 1 or 2 3. Aged 18-45 years old **Exclusion criteria** 1. Long-term NSAIDs or other analgesics 2. Steroid treatment 3. Lithium 4. Aminoglycosides 5. Oral hypoglycaemics 6. Antihypertensives or diuretics 7. Peptic ulcer 8. Bleeding 9. G6PD deficiency 10.Liver or renal disease 11.Asthma/COPD
Interventions	**Group I (15 participants):** IV ketorolac 4 mg/kg 10 minutes before induction and saline placebo 5 minutes after incision **Group II (15 participants):** IV ketorolac 4 mg/kg 5 minutes after incision and placebo 10 minutes before induction
Outcomes	1. Postoperative pain (0-10 cm VAS and 11-point scale at 60, 90, 120, 150 and 180 minutes postoperatively) 2. Blood pressure and heart rate (mmHg and beats per minute at 60, 90, 120, 150 and 180 minutes postoperatively) 3. Adverse events (composite of skin reactions, nausea, vomiting, shivering, headache and bleeding during follow-up)
Notes	Funding: not reported Declarations of interest: not reported Authors contacted: no Other: pain data extracted from graph and SD estimated. Side effects not included as composite

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details. Quote: "Patients were randomly divided into two groups".
Allocation concealment (selection bias)	Unclear risk	No details. Quote: "Patients were randomly divided into two groups".

Peduto 1995 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-dummy placebo. Quote: "...in the other...30 min before surgery, placebo (physiological solution of volume equal to 0.4 mg / kg of ketorolac) 10 min before intervention"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded. Quote: "An independent observer, in the dark of the type of treatment performed"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No mention
Selective reporting (reporting bias)	Unclear risk	No protocol
Other bias	Low risk	Similar baseline characteristics. Quote: "No differences were found significant between the two groups as far as concerns anthropometric data (weight, height age, sex, age) and the duration of the intervention (average 37 min, with a minimum of 23 min and a maximum of 51 min)".

Priya 2002

Study characteristics	
Methods	Study design: parallel-group randomized controlled trial Sample size: 50 Country: India Setting: secondary care hospital Dates conducted: not reported Postoperative opioid used and delivery: IV tramadol Pain score collection: blinded investigator Concurrent postoperative analgesics: none reported
Participants	**Inclusion criteria** 1. ASA 1 or 2 2. Elective breast surgery such as lumpectomy, simple mastectomy and modified radical mastectomy **Exclusion criteria** 1. Less than 18 years or more than 65 years of age 2. Allergy to any NSAID 3. Renal disease 4. Asthma 5. Coagulopathy 6. Peptic ulcer disease
Interventions	**Group I (25 participants):** 100 mg IV ketoprofen 30 minutes before incision and saline immediately after incision **Group II (25 participants):** 100 mg IV ketoprofen immediately after incision and saline placebo 30 minutes before incision
Outcomes	1. Postoperative pain (0-10 cm VAS at 1, 1.5, 2, 4, 6, 8, 10, 12, 14, 16, 18 and 20 hours postoperatively)

Priya 2002 *(Continued)*

	2. Time to analgesia (hours) 3. Number of analgesics (number during follow-up) 4. PONV (1-5 scale during follow-up, number with a score of 5 (nausea and vomiting) included in analysis)
Notes	Funding: "None" Declarations of interest: "None" Authors contacted: no Other: time to analgesia reported as time-to-event but not enough information to extract data

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated. Quote: "...computer-generated table of random numbers"
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-dummy placebo. Quote: "This infusion was completed 30 minutes before the surgical incision was taken. 100 ml plain normal saline was infused over 15 minutes immediately after surgical incision in this group".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded. Quote: "...were recorded by an independent, blinded observer"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants completed study.
Selective reporting (reporting bias)	Unclear risk	No protocol
Other bias	High risk	Participants excluded from pain scores once received analgesia

Riest 2006

Study characteristics

Methods	Study design: parallel-group randomized controlled trial Sample size: 360 Country: Germany Setting: secondary care hospital Dates conducted: not reported Postoperative opioid used and delivery: morphine PCA Pain score collection: not reported Concurrent postoperative analgesics: none reported
Participants	**Inclusion criteria** 1. Spinal, breast and orthopaedic surgery 2. Aged 18-88 years old 3. General anaesthesia

Riest 2006 *(Continued)*

	Exclusion criteria 1. Mental or physical inability to handle a PCA 2. ASA > 3 3. Opioid abuse 4. Renal disease
Interventions	**Group Perioperative (180 participants):** rofecoxib 50 mg preoperatively and on postoperative days 1–3 **Group Postoperative (180 participants):** placebo preoperatively and rofecoxib on postoperative days 1–3
Outcomes	1. Postoperative pain (0-4 scale at 12, 24, 48 and 72 hours postoperatively) 2. Morphine consumption (mg at 12, 24, 48 and 72 hours postoperatively) 3. Opioid adverse events (0-4 scale at 12, 24, 48 and 72 hours postoperatively) 4. Patient satisfaction (0-4 scale at 12, 24, 48 and 72 hours postoperatively)
Notes	Funding: "This work was supported financially by MSD, Germany. MSD did not participate in either generations of hypothesis, data collection, analysis or writing" up the manuscript. Declarations of interest: as above Authors contacted: no Other: unable to include pain, opioid adverse events and patient satisfaction due to 0-4 scale. Although multiple participant exclusions, data table for morphine consumption stated data from 540 patients.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated. Quote: "Randomization of study medications was performed by the hospital's pharmacy using a computer generated random list".
Allocation concealment (selection bias)	Low risk	Pharmacy-controlled. Quote: "Randomization of study medications was performed by the hospital's pharmacy using a computer generated random list".
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinded. Quote: "To ensure blinding the study drugs were delivered as coated tablets in blister packages not allowing identification of content".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Likely blinded from above information
Incomplete outcome data (attrition bias) All outcomes	High risk	90 patients excluded before outcome assessment. Quote: "We secondarily excluded 90 of the 630 patients before assessment of the primary criteria for to the following reasons: cancellation of surgery after the first dose of the study medication, administration of NSAIDs, steroids or opioids other than morphine during the study period, patients' desire to be excluded from the study before assessment of the main outcome criteria (24 h after skin closure), patients' discharge before assessment of main criteria, and sedation for mechanical ventilation at time of assessment of the main criteria".

Riest 2006 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	No protocol
Other bias	Unclear risk	No baseline characteristics. Industry funded but stated no involvement

Riest 2008

Study characteristics	
Methods	Study design: parallel-group randomized controlled trial Sample size: 160 Country: Germany Setting: secondary care hospital Dates conducted: not reported Postoperative opioid used and delivery: morphine PCA Pain score collection: trained nurse Concurrent postoperative analgesics: none reported
Participants	**Inclusion criteria** 1. Discectomy 2. Aged 18-88 years old **Exclusion criteria** 1. Mental or physical inability to handle a PCA 2. ASA > 3 3. Preoperative opioids 4. Administration of steroids or NSAIDs within 24 hours before skin incision 5. Allergy against sulphonamides or NSAIDs 6. Severe liver dysfunction 7. Congestive heart failure 8. History of myocardial infarction 9. Stroke 10. Pulmonary embolism 11. Gastrointestinal bleeding 12. Refusal 13. Pregnancy and/or lactation
Interventions	**Group Perioperative (80 participants):** 40 mg IV parecoxib 45 minutes before surgery and 12 and 24 hours after surgery **Group Postoperative (80 participants):** placebo 45 minutes before surgery and 12 and 24 hours after surgery
Outcomes	1. Postoperative pain (average pain score over 24 hours using 0-10 VRS and BPI) 2. Morphine consumption (mg at 25 hours) 3. Opioid adverse events (using SDS at 25 hours) 4. Adverse events (myocardial infarction, stroke, pulmonary embolism, deep vein thrombosis or gastrointestinal bleeding during follow-up)
Notes	Funding: "Investigator initiated trial funded by Pfizer, Germany. Pfizer did not participate in generation of the study design or interpretation of results". Declarations of interest: as above

Riest 2008 *(Continued)*

	Authors contacted: no Other: unable to include opioid adverse events as not individually reported. Pain not included as average used

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated. Quote: "...randomization with a computer-generated random list"
Allocation concealment (selection bias)	Unclear risk	No mention
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-dummy placebo used
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No mention
Incomplete outcome data (attrition bias) All outcomes	High risk	Many patients excluded but unclear to which groups they belonged. Quote: "43 patients were excluded before assessment of the primary criteria for the following reasons..."
Selective reporting (reporting bias)	Unclear risk	No protocol or trial registration
Other bias	Unclear risk	No baseline characteristics table. Industry funded but stated no involvement in study

Rogers 1995

Study characteristics

Methods	Study design: parallel-group randomized controlled trial Sample size: 58 Country: UK Setting: secondary care hospital Dates conducted: not reported Postoperative opioid used and delivery: diamorphine PCA Pain score collection: not collected Concurrent postoperative analgesics: none reported
Participants	**Inclusion criteria** 1. Abdominal hysterectomy by transverse lower abdominal incision **Exclusion criteria** 1. ASA 3 or 4 2. < 45 kg or > 90 kg in weight 3. Malignancy 4. Endometriosis 5. Alcohol or drug addiction

Rogers 1995 *(Continued)*

	6. Chronic analgesic use 7. Contraindication to ketorolac
Interventions	**Group Ketorolac before operation (30 participants):** 10 mg IV ketorolac between induction and skin incision and saline placebo between closure of skin and recovery **Group Ketorolac after operation (28 participants):** saline placebo between induction and skin incision and 10 mg IV ketorolac between closure of skin and recovery
Outcomes	1. Diamorphine consumption (mg at 2, 4 and 12 hours) 2. Opioid adverse events (nausea, vomiting, anti-emetic use and pruritus at 12 hours) 3. Intraoperative blood loss (in a standard way by weighing swabs and measuring the volume of suction loss intraoperatively)
Notes	Funding: no mention Declarations of interest: no mention Authors contacted: no Other: anti-emetic used for nausea and vomiting. No events for pruritus so data not entered

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated. Quote: "...computer-generated random numbers in blocks of 12"
Allocation concealment (selection bias)	Low risk	Pharmacy-controlled. Quote: "The hospital pharmacy prepared.."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-dummy placebo used. Quote: "...containing either 0.9% normal saline 51 ml alone or 0.9% normal saline 50 ml with ketorolac 10 mg (1 ml). They were labelled with a code held by the pharmacy until the end of the study. Each patient was given one infusion between induction of anaesthesia and skin incision, and another between skin closure and arrival in the recovery ward".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Likely blinded from above
Incomplete outcome data (attrition bias) All outcomes	High risk	Thirteen participants excluded. Quote: "...13 patients were later withdrawn; seven because a different operative procedure was performed, three because endometriosis was diagnosed at operation and three because of administrative errors in the conduct of the study".
Selective reporting (reporting bias)	Unclear risk	No protocol
Other bias	Low risk	Similar baseline characteristics

Salonen 2001

Study characteristics

Methods	Study design: parallel-group randomized controlled trial

Salonen 2001 *(Continued)*

	Sample size: 81 Country: Finland Setting: secondary care hospital Dates conducted: not reported Postoperative opioid used and delivery: IM and IV oxycodone Pain score collection: nursing staff Concurrent postoperative analgesics: none reported
Participants	**Inclusion criteria** 1. ASA 1 2. Adults 3. Elective tonsillectomy or adeno-tonsillectomy **Exclusion criteria** 1. History of severe adverse reactions to NSAIDs 2. Asthma 3. Renal disease 4. Liver disease 5. Bleeding disorders
Interventions	**Group PRE (41 participants):** IV ketoprofen 5 minutes after induction (0.5 mg/kg) and saline in PACU then 3 mg/kg over 24 hours **Group POST (40 participants):** IV ketoprofen in PACU (0.5 mg/kg) and saline 5 minutes after induction then 3 mg/kg over 24 hours
Outcomes	1. Oxycodone consumption (number of doses at 0-4 hours and 5-24 hours) 2. Postoperative pain (0-100 mm VAS at rest and on swallowing at 1, 2, 3, 4 and 24 hours) 3. Adverse events (at study follow-up including nausea, vomiting, headache, pruritus, sedation, reoperation or electrocautery for bleeding)
Notes	Funding: no mention Declarations of interest: no mention Authors contacted: no Other: oxycodone converted to morphine and 70 kg weight. Pain score data extracted from graphs. Sedation not included as no events. Nausea and vomiting calculated from vomiting and nausea without vomiting numbers. SD estimated for opioid consumption

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated. Quote: "The allocation was computer generated".
Allocation concealment (selection bias)	Unclear risk	Unclear if envelopes opaque. Quote: "...sealed envelope method was used to ensure blinding".
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-dummy placebo. Quote: "In the PRE ketoprofen group, patients were given ketoprofen...intravenously, mixed with 10 ml of normal saline and injected over 5 min after induction of anaesthesia but before surgical incision, and placebo (10 ml normal saline) injected over 5 min in the postanaesthesia care unit (PACU) followed by a continuous IV ketoprofen infusion of 3 mg/kg over

Salonen 2001 *(Continued)*

		24 h. The drug syringes were prepared by a nurse not otherwise involved in the study, ensuring blinding".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Likely blinded from above
Incomplete outcome data (attrition bias) All outcomes	Low risk	No participants excluded. Quote: "No patients were withdrawn from the study".
Selective reporting (reporting bias)	Unclear risk	No protocol
Other bias	Low risk	Similar baseline characteristics

Sandin 1993

Study characteristics	
Methods	Study design: parallel-group randomized controlled trial Sample size: 42 Country: Sweden Setting: secondary care hospital Dates conducted: not reported Postoperative opioid used and delivery: dextropropoxyphene (with paracetamol) Pain score collection: no details Concurrent postoperative analgesics: none reported postoperatively, preoperative epidural block
Participants	**Inclusion criteria** 1. Knee arthroscopy 2. ASA 1 **No exclusion criteria reported**
Interventions	**Group PRE (20 participants):** 75 mg IM diclofenac one hour before tourniquet inflation and saline 30 minutes after start of surgery **Group POST (22 participants):** 75 mg IM diclofenac 30 minutes after start of surgery and one hour before tourniquet inflation
Outcomes	1. Dextropropoxyphene (with paracetamol) (number of tablets consumed before and after 6 hours) 2. Postoperative pain (0-100 mm VAS at < 6 hours and morning after surgery)
Notes	Funding: no mention Declarations of interest: "CIBA-GEIGY AB is gratefully acknowledged for supplying the trial medicine" (unclear role in trial) Authors contacted: no Other: Pain scores extracted from graph. 24-hour data from pain scores the next morning. Mean taken from median and IQR/1.35 used to estimate SD. Analgesic use not used as combination therapy

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Sandin 1993 *(Continued)*

Random sequence generation (selection bias)	Low risk	Computer-generated. Quote: "Randomisation was according to a computer-manufactured list".
Allocation concealment (selection bias)	Unclear risk	No mention
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-dummy placebo. Quote: "All patients were given two intramuscular injections in the contralateral thigh".
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No mention
Incomplete outcome data (attrition bias) All outcomes	High risk	One excluded but from non-intervention group for severe pain. Quote: "One patient in group 0 was excluded from the study after the 5-h assessment due to severe pain".
Selective reporting (reporting bias)	Unclear risk	No protocol
Other bias	Low risk	Similar baseline characteristics

Shuying 2014

Study characteristics	
Methods	Study design: parallel-group randomized controlled trial Sample size: 75 Country: China Setting: secondary care hospital Dates conducted: not reported Postoperative opioid used and delivery: IV sufentanil and IM tramadol Pain score collection: blinded anaesthetist Concurrent postoperative analgesics: none reported
Participants	**Inclusion criteria** 1. Age > 18 years old 2. ASA 1 and 2 3. Laparoscopic cholecystectomy **Exclusion criteria** 1. Age < 18 years old 2. Bleeding history 3. Gastrointestinal ulcer 4. Renal or liver disease 5. Severe cardiovascular disease 6. Severe hypertension 7. Allergy to NSAIDs or sulphonamides 8. Open conversion 9. Drain used postoperatively

Shuying 2014 *(Continued)*

Interventions	**Group A (37 participants):** IV 40 mg parecoxib injected 30-45 minutes before anaesthesia induction and 4 mL saline injected when gallbladder removed **Group B (38 participants):** IV 40 mg parecoxib injected when gallbladder removed and 4 mL saline injected 30-45 minutes before anaesthesia induction
Outcomes	1. Postoperative recovery (time to modified Aldrete score of > 9 and modified PADSS > 9) 2. Adverse events (nausea, vomiting, backache, dizziness, sedation, agitation (Ramsey sedation scale) and urinary retention at 24 hours) 3. Analgesic consumption (number of patients requiring analgesia during 24 hours follow-up) 4. Postoperative pain (0-10 cm VAS at 0, 0.5, 1, 2, 4, 6, 12, 24 hours)
Notes	Funding: no funding Declarations of interest: no declarations Authors contacted: no Other: Pain scores extracted from graph. Analgesic consumption calculated from number requiring analgesia, tramadol and sufentanil similar conversion rate to morphine (5 mg). Unable to use Ramsey scores for sedation so taken from somnolence numbers

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated. Quote: "...computer-randomized number"
Allocation concealment (selection bias)	Low risk	Third party performed. Quote: "...which generated by professional statisticians"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-dummy placebo. Quote: "...40 mg parecoxib injected 30-45 min before anesthesia induction and 4 ml saline injected when gallbladder was removed"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded. Quote: "An anesthesiologist who gave the dugs implemented the blinding protocol and another anesthesiologist who didn't know the regimen evaluated the postoperative indexes".
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear to which groups exclusions belonged. Quote: "...7 patients were excluded eventually. The excluding reasons are described as follows: drain tube was installed after surgery in 6 patients; the LC was switched to open cholecystectomy in 1 patient".
Selective reporting (reporting bias)	Low risk	ChiCTR-PRRC-12002540. Main outcomes reported
Other bias	Low risk	Similar baseline characteristics

Sun 2008

Study characteristics

Sun 2008 *(Continued)*

Methods	Study design: parallel-group randomized controlled trial Sample size: 76 Country: USA Setting: secondary care hospital Dates conducted: not reported Postoperative opioid used and delivery: IV fentanyl or oral hydrocodone and acetaminophen in PACU and IV morphine PCA if admitted or oral hydrocodone and acetaminophen if discharged Pain score collection: blinded researcher Concurrent postoperative analgesics: none reported postoperatively in addition to above
Participants	**Inclusion criteria** 1. Age 18-75 years old 2. ASA 1-3 3. Major plastic surgery procedures (breast augmentation or abdominoplasty with or without liposuction involving the abdomen, buttocks and lower extremities) **Exclusion criteria** 1. Allergy or contraindication to NSAIDs 2. Chronic NSAID therapy 3. Received any analgesic medication within a 12-hour period before the operation 4. Pregnant or breastfeeding 5. Alcohol or drug abuse 6. Bleeding disorder 7. Unstable neurological, cardiovascular, renal, hepatic or gastrointestinal diseases 8. Unwilling to complete the follow-up evaluations
Interventions	**Group Perioperative (39 participants):** 2 celecoxib 200 mg capsules 30–90 minutes before surgery and 2 placebo capsules 1 hour after surgery and celecoxib 200 mg twice daily postoperatively **Group Postoperative (37 participants):** 2 celecoxib 200 mg capsules 1 hour after surgery and 2 placebo capsules 30–90 minutes before surgery and celecoxib 200 mg twice daily postoperatively
Outcomes	1. Postoperative pain (0-10 VRS at 0.5, 1, 2, 3, 4, 24, 48 and 72 hours) 2. Opioid consumption (mg morphine in PACU and at 24, 48 and 72 hours) 3. Patient satisfaction (unclear scale and time point) 4. Return of bowel function (in days) 5. Time to analgesia (minutes) 6. PACU stay (minutes) 7. Nausea and vomiting (in PACU, yes/no and requirement for anti-emetic) 8. Resume normal diet (days) 9. Resume normal activity (days) 10. Quality of recovery (0-18 VRS at 24, 48 and 72 hours) 11. Cardiovascular and wound complications (yes/no at 7 and 30 days)
Notes	Funding: non-industry Declarations of interest: not reported Authors contacted: no Other: myocardial infarction not included as no events. Patient satisfaction not included as unclear scale used. Pain score data extracted from graph and 2 hours used for early pain as postoperative intervention given at one hour. Morphine consumption calculated as PACU plus 24 hours and extracted from graph with SD estimated. No outcomes reported as time-to-event. Time to bowel movement mean from median and IQR/1.35 to estimate SD

Sun 2008 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated. Quote: "...computer generated random number schedule"
Allocation concealment (selection bias)	Low risk	Pharmacy-controlled. Quote: "The study medication was prepared by a hospital pharmacist in identical-appearing capsules according to a computer generated random number schedule".
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-dummy placebo. Quote: "The patients, nurses, surgeons, and anesthesiologists directly involved in the patients' care were blinded as to the content of the oral study medication capsules".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded. Quote: "A trained interviewer who was also blinded to the study medication contacted each patient at 24, 48, and 72 postoperatively to inquire about their maximum VRS pain score".
Incomplete outcome data (attrition bias) All outcomes	Low risk	Four participants excluded. Reasons unlikely to cause bias
Selective reporting (reporting bias)	Unclear risk	No protocol
Other bias	Low risk	Similar baseline characteristics. Non-industry funding

Trampitsch 2003

Study characteristics

Methods	Study design: parallel-group randomized controlled trial Sample size: 44 Country: Austria Setting: secondary care hospital Dates conducted: not reported Postoperative opioid used and delivery: PCA morphine Pain score collection: staff not involved in the anaesthetic Concurrent postoperative analgesics: none reported
Participants	**Inclusion criteria** 1. Age 19-70 years old 2. ASA 1 or 2 3. Body weight between 60 and 90 kg 4. Gynaecology laparoscopy **Exclusion criteria** 1. Cardiovascular disease 2. Respiratory disease 3. Neurological disease 4. Liver or renal impairment

Trampitsch 2003 *(Continued)*

	5. Gastrointestinal disease 6. Chronic opioids or benzodiazepines 7. Pregnancy
Interventions	**Group I (22 participants):** 8 mg IV lornoxicam 20 minutes before skin incision and saline placebo at the end of surgery then 8 mg every 8 hours postoperatively **Group II (22 participants):** saline placebo 20 minutes before skin incision and 8 mg IV lornoxicam at the end of surgery then 8 mg every 8 hours postoperatively
Outcomes	1. Postoperative pain (0-100 mm VAS at 15, 30 minutes and 1, 2, 3, 6, 9, 12, 18, 24 hours) 2. Morphine consumption (mg consumed at 15, 30 minutes and 1, 2, 3, 6, 9, 12, 18, 24 hours) 3. Opioid adverse events (sedation (0-5 scale), urinary retention, pruritus, nausea, vomiting, dizziness and headache during study follow-up) 4. Time to analgesic request (minutes) 5. Blood loss (mL lost in 24 hours)
Notes	Funding: not reported Declarations of interest: not reported Authors contacted: no Other: nausea and vomiting reported separately so not included. Other adverse events not fully reported. Values in text appeared to be SEM when compared to SD in graph. Pain scores taken from graphs

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not fully reported. Quote: "...randomized by means of the envelope method"
Allocation concealment (selection bias)	Unclear risk	Unclear envelope safeguards. Quote: "...randomized by means of the envelope method"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-dummy placebo used. Quote: "at the end of surgery, before the last suture, the patients received 100 ml NaCl (placebo)".
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear as staff were not involved in anaesthetic but unclear if blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants analysed
Selective reporting (reporting bias)	High risk	Not all outcomes reported
Other bias	Low risk	Similar baseline characteristics

Vanlersberghe 1996

Study characteristics

Vanlersberghe 1996 *(Continued)*

Methods	Study design: parallel-group randomized controlled trial Sample size: 60 Country: Belgium Setting: secondary care hospital Dates conducted: not reported Postoperative opioid used and delivery: morphine bolus in PACU Pain score collection: not reported Concurrent postoperative analgesics: none reported
Participants	**Inclusion criteria** 1. Age 18-60 years old 2. ASA 1 or 2 3. Minor orthopaedic surgery (< 2 hours) **Exclusion criteria** 1. Renal disease 2. Hepatic disease 3. Haematological disease 4. Asthma 5. Gastrointestinal bleeding and peptic ulcer 6. Allergy to NSAIDs 7. Psychological disease 8. Drug and alcohol abuse 9. Chronic analgesics 10. Pregnancy
Interventions	**Group K (30 participants):** 30 mg IV ketorolac 30 minutes before surgery and placebo in PACU **Group P (30 participants):** placebo 30 minutes before surgery and in PACU 30 mg IV ketorolac
Outcomes	1. Postoperative pain (0-100 mm VAS at 0, 15, 30, 45 minutes and every hour for 6 hours) 2. Morphine consumption (mg consumed at 6 hours) 3. Nausea and vomiting (during follow-up) 4. Time to analgesic request (minutes)
Notes	Funding: not reported Declarations of interest: not reported Authors contacted: no Other: pain score data taken from 45 minutes to allow post-incision dose time to be effective. Data estimated from median and IQR/1.35

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details. Quote: "...allocated randomly"
Allocation concealment (selection bias)	Unclear risk	No details. Quote: "...allocated randomly"
Blinding of participants and personnel (performance bias)	Low risk	Double-dummy placebo used. Quote: "...30 mg ketorolac 30 mins before surgery followed by a single placebo injection"

Vanlersberghe 1996 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No mention
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants analysed
Selective reporting (reporting bias)	Unclear risk	No protocol
Other bias	High risk	More females in K group. Quote: "A larger proportion of male patients were present in group P" (Gerbershagen 2014).

Vijayendra 1998

Study characteristics	
Methods	Study design: parallel-group randomized controlled trial Sample size: 40 Country: India Setting: secondary care hospital Dates conducted: not reported Postoperative opioid used and delivery: not reported Pain score collection: not reported Concurrent postoperative analgesics: none reported
Participants	**Inclusion criteria** 1. ASA 1 or 2 2. Male or female 3. Removal of orthopaedic implant < 90 minutes **Exclusion criteria** 1. Renal disease 2. Hepatic disease 3. Bleeding disorders 4. Peptic ulcer disease 5. Sensitivity to NSAIDs 6. Anticoagulants
Interventions	**Group I (20 participants):** IV 60 mg ketorolac just before induction and saline placebo at the end of surgery **Group II (20 participants):** IV 60 mg ketorolac at the end of surgery and saline placebo before induction
Outcomes	1. Postoperative pain (0-10 cm VAS at 0, 1, 2, 4, 6, 12 and 24 hours) 2. Morphine consumption (mg consumed at 24 hours) 3. Bleeding time (minutes at 2, 4, 6 hours) 4. Time to analgesic request (minutes)

Vijayendra 1998 *(Continued)*

Notes	Funding: not reported Declarations of interest: not reported Authors contacted: no Other: pain score data taken from graph and SD estimated from other studies. Early acute postoperative pain taken from one hour to allow post-incision dose to be effective

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No mention. Quote: "...the patients were divided".
Allocation concealment (selection bias)	Unclear risk	No mention. Quote: "...the patients were divided".
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-dummy placebo used. Quote: "Group I received 60 mg ketorolac...and 5cc of normal saline at the end of surgery".
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No mention
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants analysed
Selective reporting (reporting bias)	Unclear risk	No protocol
Other bias	Low risk	Similar baseline characteristics. Quote: "The two groups were comparable..."

Vogol 1992

Study characteristics

Methods	Study design: parallel-group randomized controlled trial Sample size: 36 Country: USA Setting: secondary care hospital Dates conducted: not reported Postoperative opioid used and delivery: not reported Pain score collection: patient self-scoring Concurrent postoperative analgesics: none reported
Participants	**Inclusion criteria** 1. Elective periodontal flap and osseous recontouring of at least 3 teeth 2. Aged > 18 years old 3. Co-operative 4. Good health **Exclusion criteria**

Vogol 1992 *(Continued)*

1. Uncontrolled systemic disease
2. Drug abuse
3. Contraindication to NSAIDs
4. Pregnancy and lactation
5. Sedatives
6. Antidepressants
7. Analgesic use

Interventions	**Group I-pretreatment (19 participants):** 600 mg ibuprofen 5-10 mins before LA and placebo after suturing **Group I-post-treatment (17 participants):** placebo 5-10 mins before LA and 600 mg ibuprofen after suturing
Outcomes	1. Postoperative pain (1-4 ordinal scale every hour until 8 hours) 2. Patient satisfaction (1-5 scale at 8 hours) 3. Time to analgesic request (hours) 4. Adverse events (nonspecific during follow-up)
Notes	Funding: not reported Declarations of interest: not reported Authors contacted: no Other: unable to include pain and patient satisfaction due to ordinal scales

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No mention. Quote: "Subjects were randomly distributed..."
Allocation concealment (selection bias)	Unclear risk	No mention. Quote: "Subjects were randomly distributed..."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-dummy placebo used. Quote: "...600 mg ibuprofen immediately presurgically and placebo immediately after surgery"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No mention
Incomplete outcome data (attrition bias) All outcomes	High risk	Seven participants excluded. Quote: "...7 were excluded from the efficacy analysis".
Selective reporting (reporting bias)	Unclear risk	No protocol
Other bias	Low risk	Similar baseline characteristics. Quote: "There were no statistically significant differences..."

Wang 2010

Study characteristics	
Methods	Study design: parallel-group randomized controlled trial Sample size: 40 Country: China Setting: secondary care hospital Dates conducted: not reported Postoperative opioid used and delivery: PCA butorphanol Pain score collection: not reported Concurrent postoperative analgesics: none reported
Participants	**Inclusion criteria** 1. Elective laparoscopic colorectal surgery 2. ASA 1 or 2 3. Age 30-64 years **Exclusion criteria** 1. Liver and renal disease 2. Contraindication to NSAIDs 3. Chronic pain 4. Alcohol and drug abuse
Interventions	**Group A (20 participants):** IV parecoxib 40 mg at anaesthesia induction **Group B (20 participants):** IV parecoxib 40 mg 30 minutes before end of surgery
Outcomes	1. Postoperative pain (0-100 mm VAS at 2, 4, 6, 8, 12 and 24 hours) 2. Butorphanol consumption (mg consumed at 12 and 24 hours) 3. Global evaluation of analgesia (no details) 4. Adverse events (during follow-up, not reported)
Notes	Funding: Fund Project Institute Guangdong Medical Research Fund (A2009025) Declarations of interest: not reported Authors contacted: no Other: butorphanol converted to morphine using conversion factor of 2.5

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details. Quote: "The patients were randomly divided..."
Allocation concealment (selection bias)	Unclear risk	No details. Quote: "The patients were randomly divided..."
Blinding of participants and personnel (performance bias) All outcomes	High risk	No double-dummy placebo
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No mention

Wang 2010 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Table stated n = 20 but unclear if each group
Selective reporting (reporting bias)	High risk	Adverse events not fully reported
Other bias	Unclear risk	Not enough information on participant characteristics. Non-industry funding

Wnek 2004

Study characteristics	
Methods	Study design: parallel-group randomized controlled trial Sample size: 60 Country: Poland Setting: secondary care hospital Dates conducted: not reported Postoperative opioid used and delivery: NCA ketoprofen Pain score collection: blinded doctor Concurrent postoperative analgesics: none reported
Participants	**Inclusion criteria** 1. Elective neurosurgery (herniated lumbar disc) **Exclusion criteria** 1. Liver and renal disease 2. Cardiovascular disease 3. Psychiatric disease 4. Analgesics consumed within 24 hours of surgery 5. Unable to rate pain
Interventions	**Group PRE (30 participants):** IV 100 mg of ketoprofen in 100 mL of normal saline 60 minutes before the induction of general anaesthesia and directly after the operation, the patients received IV 100 mL of normal saline **Group POST (30 participants):** IV 100 mL of normal saline 60 minutes before the induction of general anaesthesia and directly after the operation the patients received IV 100 mg of ketoprofen in 100 mL of normal saline
Outcomes	1. Postoperative pain (0-100 mm VAS at activation of NCA, 4, 8 and 12 hours following the operation, at 8 am, 12 pm, 4 pm and 8 pm the following day) 2. Ketoprofen consumption (mg consumed at 1-4, 4-8, 8-12 and 12-36 hours) 3. Time to analgesic request (minutes) 4. PGE2 concentration (1 hour before, before drug, 8 hours postoperatively and 12 hours postoperatively)
Notes	Funding: grant 501/KL/463/L from The Collegium Medicum, Jagiellonian University, Kraków, Poland Declarations of interest: not reported Authors contacted: no

Wnek 2004 *(Continued)*

	Other: classed as preventive as used NCA of ketoprofen. Data extracted from graphs. SD estimated for pain

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details. Quote: "Patients were randomly allocated into two groups..."
Allocation concealment (selection bias)	Unclear risk	No mention
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-dummy placebo used. Quote: "...100 mg of ketoprofen in 100 ml of 0.9% NaCl IV 60 min before the induction of general anesthesia, and directly after the operation, the patients received IV 100 ml of 0.9% NaCl".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded. Quote: "Pain intensity was evaluated by a physician who was unaware about the division into study groups".
Incomplete outcome data (attrition bias) All outcomes	Low risk	One excluded, unlikely to cause bias. Quote: "One patient was excluded from the study on account of laminectomy, which is one of the reasons for postoperative opioid administration caused by insufficient ketoprofen analgesia".
Selective reporting (reporting bias)	Unclear risk	No protocol
Other bias	Low risk	Similar baseline characteristics. Non-industry funding

Yagar 2011

Study characteristics

Methods	Study design: parallel-group randomized controlled trial Sample size: 41 Country: Turkey Setting: secondary care hospital Dates conducted: not reported Postoperative opioid used and delivery: IV fentanyl Pain score collection: blinded anaesthetist Concurrent postoperative analgesics: none reported
Participants	**Inclusion criteria** 1. ASA 1 and 2 2. Elective laparoscopic cholecystectomy **Exclusion criteria** 1. Inability to cooperate 2. Psychiatric disorders 3. Contraindications to study drugs

Yagar 2011 *(Continued)*

	4. Been using drugs acting on central nervous system or NSAIDs
Interventions	**Group I (21 participants):** IV 40 mg tenoxicam 30 minutes before anaesthesia **Group II (20 participants):** IV 40 mg tenoxicam at the end of surgery
Outcomes	1. Postoperative pain (0-10 NRS immediately after arrival to the PACU and continued at 30-minute intervals during the first 6 hours of PACU stay) 2. Fentanyl consumption (mcg consumed and number of patients requiring at 6 hours) 3. Time to analgesic request (minutes) 4. Adverse events (nausea, vomiting, dizziness and urinary retention during follow-up at 6 hours)
Notes	Funding: not reported Declarations of interest: not reported Authors contacted: no Other: pain score extracted from graph and SD estimated as unclear from graph

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details. Quote: "...randomly divided into two groups"
Allocation concealment (selection bias)	Unclear risk	No details. Quote: "...randomly divided into two groups"
Blinding of participants and personnel (performance bias) All outcomes	High risk	No double-dummy placebo used
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded. Quote: "Pain was scored by an anesthesiologist blinded to the drug allocation".
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants analysed
Selective reporting (reporting bias)	High risk	Adverse events not fully reported
Other bias	High risk	More women in Group II (Gerbershagen 2014)

Yamashita 2006

Study characteristics

Methods	Study design: parallel-group randomized controlled trial Sample size: 24 Country: Japan Setting: secondary care hospital Dates conducted: not reported Postoperative opioid used and delivery: morphine PCA

Yamashita 2006 *(Continued)*

	Pain score collection: blinded anaesthetist and nurse Concurrent postoperative analgesics: none reported
Participants	**Inclusion criteria** 1. ASA 1 and 2 2. Spinal fusion surgery **Exclusion criteria** 1. Patients aged < 30 or > 75 years old 2. Allergy to any NSAIDs or opioids 3. Coagulopathy 4. Renal disease 5. Peptic ulcer disease 6. NSAIDs and steroids were discontinued 24 hours and 1 week prior to surgery, respectively.
Interventions	**Group A (12 participants):** IV 1 mg/kg flurbiprofen axetil 30 minutes before surgery **Group B (12 participants):** IV 1 mg/kg flurbiprofen axetil after surgery
Outcomes	1. Postoperative pain (0-100 mm VAS at 0, 1, 2, 6, 12 and 24 hours after surgery) 2. Morphine consumption (mg consumed at 0-6 and 6-24 hours after surgery) 3. Adverse events (no details or time points)
Notes	Funding: not reported Declarations of interest: not reported Authors contacted: no Other: data extracted from graphs. Mean estimated from median. For pain data, early pain from 6 hours as unclear when postoperative dosing occurred. SD estimated from IQR for pain. For morphine consumption, 0-6 and 6-24 hour time points added. SD estimated from other studies

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details. Quote: "The subjects were randomly assigned into one of three groups...".
Allocation concealment (selection bias)	Unclear risk	No details. Quote: "The subjects were randomly assigned into one of three groups...".
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unclear whether double-dummy placebo and how blinded. Quote: "The study was performed by three investigators in a double-blinded manner as follows: Each solution was prepared in a syringe by the first investigator, who was responsible for subject grouping. The second investigator, who did not know the type of test solution, performed the intravenous injection. The third investigator, who was blinded to the type of test solution, evaluated postoperative morphine consumption by measuring the weight of the pump using a precision electronic balance".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded as above. Blinded nurse for pain score data. Quote: "The third investigator, who was blinded to the type of test solution, evaluated postoperative morphine consumption...".
Incomplete outcome data (attrition bias)	Low risk	All participants analysed

Yamashita 2006 *(Continued)*

All outcomes

Selective reporting (reporting bias)	Unclear risk	No protocol
Other bias	High risk	Longer duration of surgery in Group A

Yan 2004

Study characteristics

Methods	Study design: parallel-group randomized controlled trial Sample size: 30 Country: China Setting: secondary care hospital Dates conducted: not reported Postoperative opioid used and delivery: not reported Pain score collection: not reported Concurrent postoperative analgesics: none reported
Participants	**Inclusion criteria** 1. ASA 1 and 2 2. Abdominal hysterectomy for myoma 3. Female 4. Aged 36-60 years old 5. Epidural anaesthesia **Exclusion criteria** (none reported)
Interventions	**Group Preoperative (15 participants):** IV 8 mg lornoxicam before incision **Group Intraoperative (15 participants):** IV 8 mg lornoxicam 30 minutes before end of surgery
Outcomes	1. Postoperative pain (0-10 cm VAS at 6 hours after surgery) 2. Adverse events (nausea, vomiting, dizziness and urinary retention at 6 hours)
Notes	Funding: not reported Declarations of interest: not reported Authors contacted: no Other: no adverse events in study so not added to the analysis

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Drawing lots. Quote: "...the patients were randomized, by drawing lots...".
Allocation concealment (selection bias)	Unclear risk	No mention
Blinding of participants and personnel (performance bias)	High risk	No double-dummy placebo used

Yan 2004 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No mention
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No details
Selective reporting (reporting bias)	Unclear risk	No protocol
Other bias	Unclear risk	No baseline characteristics

Young 2006

Study characteristics	
Methods	Study design: parallel-group randomized controlled trial Sample size: 38 Country: USA Setting: secondary care hospital Dates conducted: not reported Postoperative opioid used and delivery: no opioid used Pain score collection: self-report Concurrent postoperative analgesics: none reported
Participants	**Inclusion criteria** 1. Bracket placement in the maxillary or mandibular arches (or both) 2. 18 years of age or older 3. No antibiotic prophylaxis needed 4. No chronic systemic diseases or clotting disorders 5. Not currently taking antibiotics or analgesics for any reason 6. Not lactose intolerant 7. Not pregnant 8. No contraindications for the use of valdecoxib **Exclusion criteria** 1. Patients with existing brackets on any teeth 2. No bands or separators were placed the day of initial bonding.
Interventions	**Group Preemptive (17 participants):** valdecoxib 40 mg at least 30 minutes before initial archwire placement, placebo two hours after procedure and valdecoxib for 48 hours after surgery **Group Postoperative (21 participants):** placebo at least 30 minutes before initial archwire placement, valdecoxib 40 mg two hours after procedure and valdecoxib for 48 hours after surgery
Outcomes	1. Postoperative pain (0-10 cm VAS at rest, chewing and biting at baseline, 2, 6, 24 and 48 hours after surgery)

Young 2006 *(Continued)*

	2. Ibuprofen consumption (amount consumed)
Notes	Funding: not reported Declarations of interest: not reported Authors contacted: no Other: data extracted from graphs. Mean estimated from median. Change scores used. SD estimated from other studies. Pain taken from 6 hours to allow post-incision dosing to take effect

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number tables. Quote: "...using a random numbers table"
Allocation concealment (selection bias)	Unclear risk	No mention
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-dummy placebo used. Quote: "The preemptive valdecoxib group received a 40 mg valdecoxib loading dose before initial archwire placement and placebo two hours later. The postoperative valdecoxib group received a placebo at least 30 minutes before initial archwire placement and 40 mg valdecoxib two hours later".
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No mention
Incomplete outcome data (attrition bias) All outcomes	High risk	20% of participants did not complete study. Quote: "Thus, 56 (80%) completed surveys were included in the statistical analysis".
Selective reporting (reporting bias)	Unclear risk	No protocol
Other bias	High risk	Different baseline pain levels

Yuan 2019

Study characteristics

Methods	Study design: parallel-group randomized controlled trial Sample size: 204 Country: China Setting: secondary care hospital Dates conducted: January 2017 to December 2018 Postoperative opioid used and delivery: IV pethidine Pain score collection: not reported Concurrent postoperative analgesics: none reported
Participants	**Inclusion criteria** 1. Arthroscopic knee surgery for ligament reconstruction, meniscectomy, synovectomy, intra-articular fractures reduction or other knee joint diseases 2. Aged 18–65 years old

Yuan 2019 *(Continued)*

	3. Able to complete the pain visual analog scale and patient global assessment **Exclusion criteria** 1. Contraindications to the surgery or drug 2. Received analgesics within 1 week before the enrolment 3. Coagulopathy or thromboembolic disease 4. Intra-articular hyaluronic acid injections within 9 months or corticosteroid within 3 months before the enrolment 5. History of neurologic disease, knee surgery, chronic pain, and/or consumption of daily analgesics 6. Pregnancy or breastfeeding
Interventions	**Group EA (102 participants):** meloxicam 15 mg oral 1 hour before surgery and 7.5 mg oral at 24 hours after surgery **Group PA (102 participants):** meloxicam 15 mg oral at 4 hours after surgery and 7.5 mg oral at 24 hours after surgery
Outcomes	1. Postoperative pain (0-10 cm VAS from 24 hours before surgery to 48 hours after at rest and flexion) 2. Adverse events (nausea, vomiting, constipation, drowsiness and dizziness at 48 hours) 3. Pethidine consumption (mg at 48 hours)
Notes	Funding: not reported Declarations of interest: "The authors declare that they have no competing interest". Authors contacted: no Other: Early pain not included as not measured once post-incision dose had taken effect within 6 hours. Nausea and vomiting not reported separately so not included

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated. Quote: "A blocked randomization method was used in this study, and the randomization sequence was created using SAS 9.0".
Allocation concealment (selection bias)	Low risk	Third party randomization. Quote: "...by an independent analyst"
Blinding of participants and personnel (performance bias) All outcomes	High risk	No placebo described
Blinding of outcome assessment (detection bias) All outcomes	High risk	No placebo described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat analysis. Quote: "The analysis in our study was performed according to the intention to treat (ITT) protocol".
Selective reporting (reporting bias)	Unclear risk	No protocol
Other bias	Low risk	Similar groups. Quote: "No difference was found regarding age and gender among the three groups, and BMI, surgery type, operative duration, pain VAS

Yuan 2019 *(Continued)*

	score at rest, pain VAS score at flexion as well as PGA score were also not different, (all $P > 0.05$)".

Yuswono 2014

Study characteristics	
Methods	Study design: parallel-group randomized controlled trial Sample size: 36 Country: Indonesia Setting: secondary care hospital Dates conducted: March to June 2013 Postoperative opioid used and delivery: IV tramadol Pain score collection: not reported Concurrent postoperative analgesics: none reported
Participants	**Inclusion criteria** 1. Gynaecological laparotomy 2. Female 3. 18-60 years old 4. ASA 1 or 2 5. General anaesthesia **Exclusion criteria** 1. Allergy to parecoxib 2. Anticoagulant drugs
Interventions	**Group I (18 participants):** IV parecoxib 40 mg 30 minutes before incision **Group II (18 participants):** IV parecoxib 40 mg at skin closure
Outcomes	1. Postoperative pain (0-10 NRS every 30 minutes in recovery)
Notes	Funding: not reported Declarations of interest: not reported Authors contacted: no Other: unable to use pain score data as reported ordinally

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No mention
Allocation concealment (selection bias)	Unclear risk	No mention
Blinding of participants and personnel (performance bias) All outcomes	High risk	No double-dummy placebo. Quote: "Parecoxib 40 mg were given to the two groups, pre-operative (group I) and post-operative (group II)".

Yuswono 2014 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No mention
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No details
Selective reporting (reporting bias)	Unclear risk	No protocol
Other bias	Low risk	Similar baseline characteristics

Zhang 2011

Study characteristics	
Methods	Study design: parallel-group randomized controlled trial Sample size: 59 Country: China Setting: secondary care hospital Dates conducted: not reported Postoperative opioid used and delivery: IV tramadol Pain score collection: blinded nurse Concurrent postoperative analgesics: none reported
Participants	**Inclusion criteria** 1. ASA 1 or 2 2. Elective thyroid surgery 3. Aged 30-60 years old **Exclusion criteria** 1. Received NSAIDs, opioid or drugs with known analgesic properties in the 24 hours before surgery 2. Previous allergic reaction to local anaesthetics, opioids or NSAIDs 3. Contraindications for the use of NSAIDs such as: gastrointestinal ulcer, coagulation disorders, renal dysfunction, heart failure and ischaemic heart disease 4. Unable to comprehend the concept of the VAS
Interventions	**Group C (30 participants):** IV flurbiprofen axetil 50 mg 15 minutes before the cervical plexus block and a placebo at the end of the surgery **Group B (29 participants):** placebo 15 minutes before cervical plexus block and flurbiprofen axetil 50 mg at the end of surgery
Outcomes	1. Postoperative pain (0-10 cm VAS at rest at 1, 2, 4, 6, 8, 12 and 24 hours after surgery) 2. Tramadol consumption (% requiring this at 24 hours) 3. Time to analgesic request (minutes) 4. Adverse events (vomiting during follow-up) 5. Patient satisfaction (4-point scale at 24 hours)
Notes	Funding: "This work was supported by the grants from the outstanding youth science foundation (No. JC2007716), the Science and Technique foundation (No. GC06C410) and the important research project of education bureau of Heilongjiang Province of China (NO. 1152hz33)".

Zhang 2011 *(Continued)*

	Declarations of interest: "no conflicts of interest declared" Authors contacted: no Other: pain score data extracted from graphs and SD estimated as unclear what error bars represented. Tramadol mg consumed not reported. Time to analgesic request not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated. Quote: "...computerized random number generator"
Allocation concealment (selection bias)	Low risk	Sealed, opaque envelopes. Quote: "...sealed in numbered, opaque envelopes"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-dummy placebo. Quote: "The envelopes contained two 5 ml syringes, labeled pre and post, with the contents blinded to anesthesiology, surgeons, operating room staff, recovery room staff, and the patient until the study was completed".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded. Quote: "One ward nurse, who was blinded to group allocation.."
Incomplete outcome data (attrition bias) All outcomes	Low risk	One dropout unlikely to cause bias. Quote: "One patient from the group B did not have her scheduled surgery; eighty-nine patients completed the study".
Selective reporting (reporting bias)	High risk	Time to analgesic request and tramadol consumption not reported
Other bias	Low risk	Similar baseline characteristics. No industry funding

Zhang 2017

Study characteristics

Methods	Study design: parallel-group randomized controlled trial Sample size: 56 Country: China Setting: secondary care hospital Dates conducted: February 2014 to April 2015 Postoperative opioid used and delivery: sufentanil PCA Pain score collection: blinded anaesthetist Concurrent postoperative analgesics: none reported
Participants	**Inclusion criteria** 1. ASA 1 or 2 2. Aged 20-60 years old 3. Laparoscopic ovarian cyst resection **Exclusion criteria** 1. Coronary heart disease 2. Asthma

Zhang 2017 *(Continued)*

3. Cardiac, renal or liver disease
4. Severe hypertension
5. Diabetes mellitus
6. Psychiatric disease
7. Obesity
8. Chronic pain
9. Alcohol or opioid abuse
10. Chronic opioid use
11. Analgesic consumed within 48 hours
12. Pregnancy
13. Allergy to NSAIDs
14. Gastrointestinal disease
15. Contraindication to PCA

Interventions	**Group F1 (28 participants):** IV flurbiprofen 1 mg/kg before induction **Group F2 (28 participants):** IV flurbiprofen 1 mg/kg before skin closure
Outcomes	1. Postoperative pain (0-10 NRS on rest and movement at 1, 3, 6, 12 and 24 hours) 2. Sufentanil consumption (mcg consumed at 1, 6, 12 and 24 hours) 3. Pain threshold (mechanical and hyperalgesia at baseline and 24 hours) 4. Adverse events (sedation, headache, dizziness, nausea, vomiting, respiratory depression, shivering and pruritus at 24 hours) 5. Sedation in PACU (Ramsey sedation scale at 5, 10, 15, 30 and 60 minutes) 6. Time to analgesic request (minutes)
Notes	Funding: National Natural Science Foundation of China Declarations of interest: no conflicts of interest declared Authors contacted: no Other: unable to use sedation data as average used. Pain score data extracted from graphs. Sufentanil converted to IV morphine as 1:0.5 from 24-hour PCA

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated. Quote: "...computer-generated random number"
Allocation concealment (selection bias)	Unclear risk	Sealed envelope but unclear in opaque. Quote: "...sealed envelope"
Blinding of participants and personnel (performance bias) All outcomes	High risk	No double-dummy placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded. Quote: "...were blinded to randomization"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Similar dropout rates and reasons

Zhang 2017 *(Continued)*

Selective reporting (reporting bias)	Low risk	NCT02043366. Main outcomes reported
Other bias	Low risk	Similar baseline characteristics

Zhou 2017

Study characteristics	
Methods	Study design: parallel-group randomized controlled trial Sample size: 122 Country: China Setting: secondary care hospital Dates conducted: January 2014 to February 2017 Postoperative opioid used and delivery: IV pethidine Pain score collection: not reported Concurrent postoperative analgesics: none reported
Participants	**Inclusion criteria** 1. Meniscal disease about to receive meniscectomy and partial meniscectomy by arthroscopy 2. Age > 18 and < 65 years 3. ASA 1 or 2 **Exclusion criteria** 1. Reconstructive procedures for concomitant knee injuries 2. Internal fixation of osteochondrosis dissecans 3. Analgesic use within 1 week before the enrolment 4. Intra-articular hyaluronic acid injections within 9 months or corticosteroid within 3 months before the enrolment 5. History of knee surgery 6. Coagulopathy or thromboembolic disease 7. History of chronic pain and/or consumption of daily analgesics 8. Gastrointestinal disease, perforation, ulceration, obstruction or bleeding 9. Severe renal or hepatic disease 10. Malignancy 11. Allergic to COX-2 selective inhibitors or pethidine 12. Lactation or pregnancy
Interventions	**Group PEA (62 participants):** Celecoxib 400 mg at 1 hour before the operation, and then 200 mg every 12 hours **Group POA (60 participants):** Celecoxib 400 mg at 4 hours after the operation, and then 200 mg every 12 hours
Outcomes	1. Postoperative pain (0-10 cm VAS on rest, flexion and global assessment at preoperation, 4, 8, 12, 24 and 36 hours postoperatively) 2. Pethidine consumption (mg consumed at either 24 or 36 hours) 3. Adverse events (nausea, vomiting, constipation, drowsiness, dizziness at 36 hours)
Notes	Funding: not reported Declarations of interest: "the authors of this work have nothing to disclose".

Zhou 2017 *(Continued)*

	Authors contacted: yes Other: unclear if pethidine consumption at 24 or 36 hours. Early pain not used as occurred at time of postoperative group dosing. SD estimated as unclear from graph. Sedation extracted from drowsiness on graph

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Block randomization. Quote: "...randomization code was generated by a statistician using blocked randomization method".
Allocation concealment (selection bias)	Unclear risk	Unclear from description. Quote: "The randomization documents were subsequently sent to the Department of Orthopedics in Dongyang People's Hospital kept by a doctor separately and a copy was kept in Shanghai Qeejen for back-up. When a patient was eligible for the study, a unique subject identification number was provided from the randomized module and the patient was assigned to the identified group".
Blinding of participants and personnel (performance bias) All outcomes	High risk	No double-dummy placebo
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No mention
Incomplete outcome data (attrition bias) All outcomes	High risk	More than 10% of patients dropped out, some for lack of intervention efficacy. Quote: "In the POA group, there were 9 withdrawn patients (5 protocol violations, 3 insufficient efficacy, and 1 patient decision), and the remaining 60 (87%) patients completed the study. In the PEA group, there were 7 withdrawn patients, in which 4 were protocol violations, 2 insufficient efficacy, and 1 patient decision and the remaining 62 (90%) patients fulfilled the study".
Selective reporting (reporting bias)	Unclear risk	No protocol
Other bias	High risk	More women in PEA group (Gerbershagen 2014)

Zhou 2019

Study characteristics

Methods	Study design: parallel-group randomized controlled trial Sample size: 120 Country: China Setting: secondary care hospital Dates conducted: June 2014 to March 2016 Postoperative opioid used and delivery: no mention Pain score collection: blinded researcher Concurrent postoperative analgesics: none
Participants	**Inclusion criteria** 1. Hip arthroplasty

Zhou 2019 *(Continued)*

2. ASA 1 or 2
3. Age > 70 years

Exclusion criteria

1. History of gastric ulcer and duodenal ulcer
2. Allergic reaction to flurbiprofen
3. Severe hepatic and renal functional disorders
4. Ischaemic heart disease
5. General and local infections

Interventions	**Group PRE (60 participants):** IV 50 mg flurbiprofen 15 minutes before surgery **Group INTRA (60 participants):** IV 50 mg flurbiprofen 30 minutes before the end of surgery
Outcomes	1. Postoperative pain (10 cm VAS 24 hours before surgery then 3, 12 and 24 hours after surgery) 2. Cognitive function (Mini-Mental State Examination 24 hours before surgery then 3, 12 and 24 hours after surgery) 3. Cytokines (TNF-α, IL-1β, IL-6 and COX-2 levels 24 hours before surgery then 3, 12 and 24 hours after surgery)
Notes	Funding: "No funding was received". Declarations of interest: "The authors declare that they have no competing interests". Authors contacted: no Other: N/A

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No mention
Allocation concealment (selection bias)	Unclear risk	No mention
Blinding of participants and personnel (performance bias) All outcomes	High risk	No double-dummy placebo. Quote: "The PRE group received 50 mg flurbiprofen (Taide Pharmaceutical Co., Beijing, China) intravenously 15 min before surgery".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded. Quote: "A physician who was blinded to the group assignment assessed spontaneous postsurgical pain intensity at rest using a 10-cm visual analog scale (VAS)".
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants analysed
Selective reporting (reporting bias)	Unclear risk	No protocol
Other bias	Low risk	Similar groups. Quote: "As shown in Table I, there were no significant differences in the three groups in terms of sex, age, weight, height, and operation time".

ASA: American Society of Anesthesiologists grade

BD: twice daily
BPI: brief pain inventory
CNS: central nervous system
COPD: chronic obstructive pulmonary disease
COX-2: cyclooxygenase-2
DGSS: German Society for the Study of Pain
G6PD: glucose-6-phosphate dehydrogenase
IBD: inflammatory bowel disease
IL: interleukin
IM: intramuscular
IQR: interquartile range
IV: intravenous
LA: local anaesthetic
mg: milligrams
mcg: micrograms
N/A: not applicable
NaCl: sodium chloride
NCA: nurse-controlled analgesia
NRS: numeric rating scale
NSAID: non-steroidal anti-inflammatory
NYHA: New York Heart Association
OD: once daily
ORIF: open reduction and internal fixation
PACU: post-anaesthesia care unit
PADSS: Post Anaesthetic Discharge Scoring System
PCA: patient controlled analgesia
PEA: patient controlled epidural analgesia
PGE2: prostaglandin E2
PO: oral
PONV: postoperative nausea and vomiting
PR: per rectum
PRN: as required
SC: subcutaneous
SD: standard deviation
SDS: opioid-related symptom distress scale
SEM: standard error of the mean
SL: sublingual
TDS: three times daily
THR: total hip replacement
TNF: tumour necrosis factor
VAS: visual analogue scale
VRS: verbal rating scale

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

Study	Reason for exclusion
Bridgman 1996	Cross-over trial
Castiglione 1997	Two doses in pre-emptive versus one in post-incision
Espinet 1996	NSAID in combination with epidural anaesthesia
Hill 1987	No post-incision group

Study	Reason for exclusion
Hou 2019	Pre-emptive group had higher dose
Jung 2003	Paediatric participants included
Jung 2005	Paediatric participants included
Lau 2009	Cross-over trial
Liu 1997	Same drug, different transdermal locations on the body (interventions not comparable)
Liu 2018	Different doses
Nelson 1993	Pre-emptive group had higher dose
Nordbladh 1991	Paediatric participants included
Ramirez 2009	Paediatric participants included
Rosaeg 2001	Three pre-emptive interventions studied
Sai 2001	No post-incision group
Settecase 2002	Different doses
Turaga 2008	Different doses
Wuolijoki 1987	Different routes of administration
Zhu 2020	Pre-emptive group had higher dose
Zor 2014	Cross-over trial

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

Aoki 2002

Methods	Study design: parallel-group randomized controlled trial Sample size: 40 Country: Japan Setting: secondary care hospital Dates conducted: not reported Postoperative opioid used and delivery: not reported Pain score collection: not reported Concurrent postoperative analgesics: not reported
Participants	**Inclusion criteria** 1. Minor ear, neck and nose surgery **Exclusion criteria** (not reported)
Interventions	**Group Second (20 participants):** 1 mg/kg flurbiprofen IV at the end of surgery **Group Third (20 participants):** 1 mg/kg IV flurbiprofen before the start of surgery

Aoki 2002 *(Continued)*

Outcomes	1. Number requiring analgesia (%) 2. Time without analgesics 3. Serum concentration of flurbiprofen 4. Postoperative pain
Notes	Funding: not reported Declarations of interest: not reported Authors contacted: yes Other: not included as unable to translate. Concluded "...administration of flurbiprofen before the start of surgery is more effective for peri-operative analgesia in minor ear, neck and nose surgery".

Bai 1998

Methods	Study design: parallel-group randomized controlled trial Sample size: 30 Country: South Korea Setting: unknown Dates conducted: unknown Postoperative opioid used and delivery: PCA morphine Pain score collection: unknown Concurrent postoperative analgesics: unknown
Participants	**Inclusion criteria** 1. Hip replacement **Exclusion criteria** (not reported)
Interventions	**Group 3 (15 participants):** IV ketorolac 30 mg before induction **Group 2 (15 participants):** IV ketorolac 30 mg at one hour after skin incision
Outcomes	1. Postoperative pain (VAS on rest and movement) 2. Analgesic requirement (mg of morphine consumed) 3. Side effects
Notes	Funding: unknown Declarations of interest: unknown Authors contacted: yes Other: unable to translate

Beg 2001

Methods	Study design: parallel-group randomized controlled trial Sample size: unknown Country: Bangledesh Setting: unknown Dates conducted: unknown Postoperative opioid used and delivery: unknown Pain score collection: unknown

Beg 2001 *(Continued)*

	Concurrent postoperative analgesics: unknown
Participants	**Inclusion criteria** (unknown) **Exclusion criteria** (unknown)
Interventions	**Group Preemptive** (unknown) **Group Post-incision** (unknown)
Outcomes	Unknown
Notes	Funding: unknown Declarations of interest: unknown Authors contacted: yes Other: no abstract available. Unable to obtain full text

Belzarena 1994

Methods	Study design: parallel-group randomized controlled trial Sample size: unknown Country: unknown Setting: unknown Dates conducted: unknown Postoperative opioid used and delivery: unknown Pain score collection: unknown Concurrent postoperative analgesics: unknown
Participants	**Inclusion criteria** (unknown) **Exclusion criteria** (unknown)
Interventions	**Group Preemptive** (unknown) **Group Post-incision** (unknown)
Outcomes	Unknown
Notes	Funding: unknown Declarations of interest: unknown Authors contacted: yes Other: no abstract available. Unable to obtain full text.

De Oliveira 1999

Methods	Study design: parallel-group randomized controlled trial Sample size: 24 Country: Brazil Setting: secondary care hospital Dates conducted: not reported Postoperative opioid used and delivery: not reported Pain score collection: not reported

De Oliveira 1999 *(Continued)*

	Concurrent postoperative analgesics: not reported
Participants	**Inclusion criteria** 1. Aged 18-65 years old 2. ASA 1 or 2 3. Hemorrhoidectomy **Exclusion criteria** (not reported)
Interventions	**Group I (unknown participants):** tenoxicam 20 mg IV 15 minutes before the beginning of anaesthesia **Group II (unknown participants):** tenoxicam 20 mg IV immediately after surgery
Outcomes	1. Postoperative pain (VAS at 10, 24, 48 and 72 hours postoperatively)
Notes	Funding: not reported Declarations of interest: not reported Authors contacted: yes Other: not included as unable to obtain full text. Found no difference between groups

Jia 2011

Methods	Study design: parallel-group randomized controlled trial Sample size: 40 Country: China Setting: not reported Dates conducted: not reported Postoperative opioid used and delivery: not reported Pain score collection: not reported Concurrent postoperative analgesics: not reported
Participants	**Inclusion criteria** 1. Arthroscopy of knee **Exclusion criteria** (not reported)
Interventions	**Group Before (20 participants):** IV parecoxib sodium 40 mg before surgery **Group After (20 participants):** IV parecoxib sodium 40 mg after surgery
Outcomes	1. Postoperative pain (0-10 cm VAS at 2, 6, 12 and 24 hours postoperatively) 2. Analgesic consumption (24 hours) 3. Adverse events
Notes	Funding: not reported Declarations of interest: not reported Authors contacted: yes Other: not included as unable to obtain full text. "Pre-operative application of parecoxib may be more effective".

Nicholson 2014

Methods	Study design: parallel-group randomized controlled trial Sample size: 36 Country: not reported Setting: not reported Dates conducted: March 2013 to September 2013 Postoperative opioid used and delivery: not reported Pain score collection: not reported Concurrent postoperative analgesics: not reported
Participants	**Inclusion criteria** 1. Uretoscopy **Exclusion criteria** 1. NSAID contraindications 2. Use of a ureteric access sheath 3. Previous enrolment
Interventions	**Group Pre (16 participants):** PR diclofenac 100 mg before surgery **Group Post (20 participants):** PR diclofenac 100 mg at the end of surgery
Outcomes	1. Postoperative pain (0-10 cm VAS and 4-point scale at 1 and 4 hours postoperatively 2. Number of patients requiring analgesia (%)
Notes	Funding: not reported Declarations of interest: not reported Authors contacted: yes Other: not included as unable to obtain full text. "Our study shows a trend towards improved post-operative analgesia and lower post-operative opioid requirement with administration of NSAID analgesia".

IV: intravenous
NSAID: non-steroidal anti-inflammatory drug
PCA: patient controlled analgesia
PR: per rectum
VAS: visual analogue scale

DATA AND ANALYSES

Comparison 1. Pre-emptive NSAIDS/COX-2 inhibitors versus post-incision NSAIDS/COX-2 inhibitors

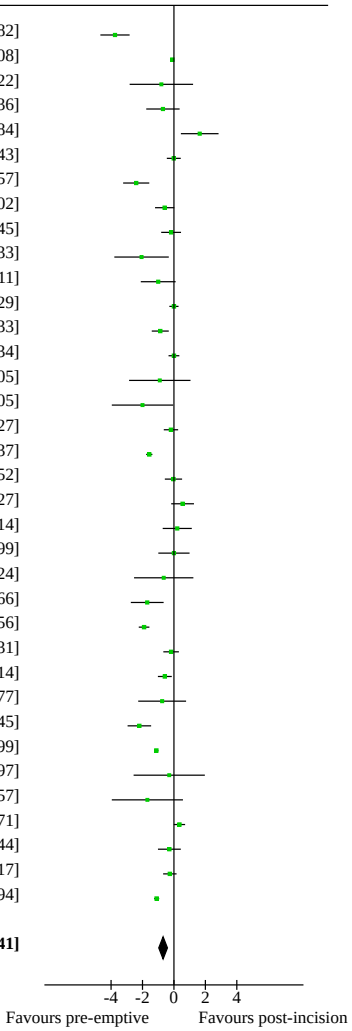
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Early acute postoperative pain (within 6 hours postoperatively)	36	2032	Mean Difference (IV, Random, 95% CI)	-0.69 [-0.97, -0.41]
1.2 Nausea and vomiting (short-term)	2	100	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.34, 2.94]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.3 Nausea and vomiting (long-term)	5	228	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.52, 1.38]
1.4 Late acute postoperative pain (24-48 hours postoperatively)	28	1645	Mean Difference (IV, Random, 95% CI)	-0.22 [-0.44, 0.00]
1.5 24-hour morphine consumption (mg)	16	854	Mean Difference (IV, Random, 95% CI)	-5.62 [-9.00, -2.24]
1.6 Time to first analgesic request (minutes)	18	975	Mean Difference (IV, Random, 95% CI)	17.04 [3.77, 30.31]
1.7 Pruritus (long-term)	4	254	Risk Ratio (M-H, Random, 95% CI)	0.40 [0.09, 1.76]
1.8 Sedation (long-term)	4	281	Risk Ratio (M-H, Random, 95% CI)	0.51 [0.16, 1.68]

Analysis 1.1. Comparison 1: Pre-emptive NSAIDS/COX-2 inhibitors versus post-incision NSAIDS/COX-2 inhibitors, Outcome 1: Early acute postoperative pain (within 6 hours postoperatively)

Study or Subgroup	Pre-emptive Mean	SD	Total	Post-incision Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Bajaj 2004	0	0.01	40	3.75	3	40	2.7%	-3.75 [-4.68 , -2.82]
Bao 2012	0.38	0.05	33	0.48	0.05	32	3.8%	-0.10 [-0.12 , -0.08]
Buggy 1994	4.5	2.74	20	5.3	3.7	20	1.3%	-0.80 [-2.82 , 1.22]
Bunemann 1994	3.2	2.81	59	3.9	3.04	58	2.4%	-0.70 [-1.76 , 0.36]
Cabell 2000	3.29	2.8	25	1.65	1.2	24	2.2%	1.64 [0.44 , 2.84]
Chen 2015	2.54	0.81	24	2.55	0.77	25	3.5%	-0.01 [-0.45 , 0.43]
Colbert 1998	2.2	1.82	37	4.6	1.9	40	2.8%	-2.40 [-3.23 , -1.57]
Demirbas 2019	0.98	1	25	1.57	1.2	25	3.2%	-0.59 [-1.20 , 0.02]
Esparza-Villalpando 2016	0.88	1.43	30	1.06	1.03	30	3.2%	-0.18 [-0.81 , 0.45]
Fletcher 1995	4.31	2.77	20	6.37	2.82	20	1.5%	-2.06 [-3.79 , -0.33]
Gelir 2016	6	2	25	7	2	25	2.4%	-1.00 [-2.11 , 0.11]
Grifka 2008	0.32	0.7	45	0.32	0.7	44	3.7%	0.00 [-0.29 , 0.29]
Inanoglu 2007	1.27	0.94	22	2.14	0.89	22	3.3%	-0.87 [-1.41 , -0.33]
Kaczmarzyk 2010	0.36	0.7	34	0.36	0.7	30	3.6%	0.00 [-0.34 , 0.34]
Karaman 2008	4.3	3.1	20	5.2	3.2	20	1.3%	-0.90 [-2.85 , 1.05]
Lee 2008	4	3.1	20	6	3.2	20	1.3%	-2.00 [-3.95 , -0.05]
Likar 1997	1.68	0.64	26	1.87	0.92	22	3.5%	-0.19 [-0.65 , 0.27]
Lu 2015	2.23	0.45	56	3.8	0.62	57	3.8%	-1.57 [-1.77 , -1.37]
Mojsa 2017	0.51	1.09	30	0.54	1.08	30	3.3%	-0.03 [-0.58 , 0.52]
Nezafati 2017	5.1	0.98	20	4.55	1.33	20	3.0%	0.55 [-0.17 , 1.27]
O'Hanlon 1996	2.79	1.88	40	2.58	1.64	20	2.7%	0.21 [-0.72 , 1.14]
Ozer 2012	4.16	2.21	25	4.16	1.24	25	2.6%	0.00 [-0.99 , 0.99]
Ozyilmaz 2005	4.7	2.2	20	5.35	3.7	20	1.4%	-0.65 [-2.54 , 1.24]
Peduto 1995	3.09	1.6	15	4.79	1.3	15	2.5%	-1.70 [-2.74 , -0.66]
Priya 2002	0.64	0.49	25	2.54	0.71	25	3.6%	-1.90 [-2.24 , -1.56]
Sandin 1993	0.72	1	20	0.9	0.55	22	3.4%	-0.18 [-0.67 , 0.31]
Shuying 2014	0.57	0.72	37	1.15	1.18	38	3.5%	-0.58 [-1.02 , -0.14]
Vanlersberghe 1996	3.25	3.63	30	4	2.22	30	1.8%	-0.75 [-2.27 , 0.77]
Vijayendra 1998	1.6	0.6	20	3.8	1.6	20	3.0%	-2.20 [-2.95 , -1.45]
Wang 2010	3	0.21	20	4.12	0.2	20	3.8%	-1.12 [-1.25 , -0.99]
Yagar 2011	5.18	3.7	21	5.48	3.7	20	1.1%	-0.30 [-2.57 , 1.97]
Yamashita 2006	3.42	1.59	12	5.11	3.67	12	1.1%	-1.69 [-3.95 , 0.57]
Yan 2004	1.53	0.56	15	1.18	0.44	15	3.6%	0.35 [-0.01 , 0.71]
Zhang 2011	2.59	1.9	30	2.88	0.7	29	3.0%	-0.29 [-1.02 , 0.44]
Zhang 2017	3.51	0.8	28	3.77	0.83	28	3.5%	-0.26 [-0.69 , 0.17]
Zhou 2019	3.2	0.4	60	4.3	0.5	60	3.8%	-1.10 [-1.26 , -0.94]
Total (95% CI)			**1029**			**1003**	**100.0%**	**-0.69 [-0.97 , -0.41]**

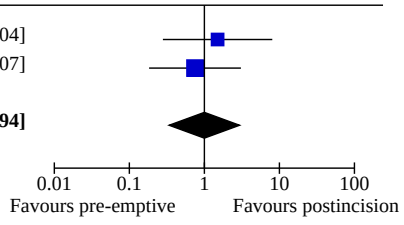
Heterogeneity: Tau² = 0.52; Chi² = 831.91, df = 35 (P < 0.00001); I² = 96%
Test for overall effect: Z = 4.90 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 1.2. Comparison 1: Pre-emptive NSAIDS/COX-2 inhibitors versus post-incision NSAIDS/COX-2 inhibitors, Outcome 2: Nausea and vomiting (short-term)

Study or Subgroup	Pre-emptive Events	Total	Post-incision Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Lee 2008	3	20	2	20	41.3%	1.50 [0.28 , 8.04]
Vanlersberghe 1996	3	30	4	30	58.7%	0.75 [0.18 , 3.07]
Total (95% CI)		**50**		**50**	**100.0%**	**1.00 [0.34 , 2.94]**
Total events:	6		6			

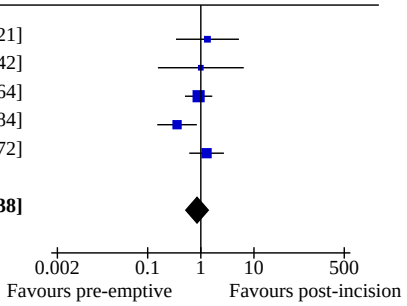
Heterogeneity: Tau² = 0.00; Chi² = 0.38, df = 1 (P = 0.54); I² = 0%
Test for overall effect: Z = 0.00 (P = 1.00)
Test for subgroup differences: Not applicable



Analysis 1.3. Comparison 1: Pre-emptive NSAIDS/COX-2 inhibitors versus post-incision NSAIDS/COX-2 inhibitors, Outcome 3: Nausea and vomiting (long-term)

Study or Subgroup	Pre-emptive Events	Pre-emptive Total	Post-incision Events	Post-incision Total	Weight	Risk Ratio M-H, Random, 95% CI
Fletcher 1995	4	20	3	20	10.8%	1.33 [0.34 , 5.21]
Karaman 2008	2	20	2	20	6.2%	1.00 [0.16 , 6.42]
Lee 2008	10	20	11	20	34.6%	0.91 [0.50 , 1.64]
Priya 2002	5	25	14	25	22.1%	0.36 [0.15 , 0.84]
Rogers 1995	11	30	8	28	26.3%	1.28 [0.61 , 2.72]
Total (95% CI)		**115**		**113**	**100.0%**	**0.85 [0.52 , 1.38]**
Total events:	32		38			

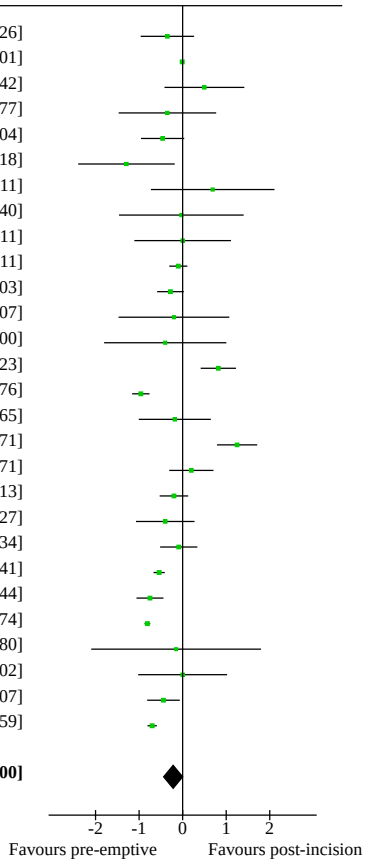
Heterogeneity: Tau² = 0.09; Chi² = 5.61, df = 4 (P = 0.23); I² = 29%
Test for overall effect: Z = 0.66 (P = 0.51)
Test for subgroup differences: Not applicable



Analysis 1.4. Comparison 1: Pre-emptive NSAIDS/COX-2 inhibitors versus post-incision NSAIDS/COX-2 inhibitors, Outcome 4: Late acute postoperative pain (24-48 hours postoperatively)

Study or Subgroup	Pre-emptive Mean	Pre-emptive SD	Pre-emptive Total	Post-incision Mean	Post-incision SD	Post-incision Total	Weight	Mean Difference IV, Random, 95% CI
Bajaj 2004	1.05	1.4	40	1.4	1.4	40	3.7%	-0.35 [-0.96 , 0.26]
Bao 2012	0.24	0.04	33	0.25	0.04	32	5.2%	-0.01 [-0.03 , 0.01]
Bunemann 1994	1.5	3.11	59	1	1.78	58	2.7%	0.50 [-0.42 , 1.42]
Cabell 2000	1.81	2	25	2.16	2	24	2.2%	-0.35 [-1.47 , 0.77]
Chen 2015	3.03	0.97	24	3.49	0.79	25	4.1%	-0.46 [-0.96 , 0.04]
Demirbas 2019	1.75	2	25	3.04	2	25	2.2%	-1.29 [-2.40 , -0.18]
Flath 1987	1.85	2	13	1.16	1.8	15	1.6%	0.69 [-0.73 , 2.11]
Fletcher 1995	3.06	2.1	20	3.09	2.5	20	1.6%	-0.03 [-1.46 , 1.40]
Gelir 2016	1	2	25	1	2	25	2.2%	0.00 [-1.11 , 1.11]
Grifka 2008	0.21	0.5	45	0.31	0.5	44	5.0%	-0.10 [-0.31 , 0.11]
Inanoglu 2007	0.86	0.56	22	1.14	0.47	22	4.7%	-0.28 [-0.59 , 0.03]
Karaman 2008	2	2	20	2.2	2.1	20	1.9%	-0.20 [-1.47 , 1.07]
Lee 2008	2.6	2	20	3	2.5	20	1.7%	-0.40 [-1.80 , 1.00]
Likar 1997	1.76	0.83	26	0.94	0.6	22	4.4%	0.82 [0.41 , 1.23]
Lu 2015	2.16	0.39	56	3.12	0.66	57	5.0%	-0.96 [-1.16 , -0.76]
Mojsa 2017	1.12	1.3	30	1.3	1.91	30	3.0%	-0.18 [-1.01 , 0.65]
Nezafati 2017	2.15	0.75	20	0.9	0.74	20	4.2%	1.25 [0.79 , 1.71]
O'Hanlon 1996	0.95	0.92	40	0.75	0.96	20	4.1%	0.20 [-0.31 , 0.71]
Ozer 2012	0.16	0.55	25	0.36	0.63	25	4.7%	-0.20 [-0.53 , 0.13]
Parke 1995	2.4	1.33	37	2.8	1.67	40	3.5%	-0.40 [-1.07 , 0.27]
Sandin 1993	0.38	0.81	20	0.47	0.57	22	4.3%	-0.09 [-0.52 , 0.34]
Shuying 2014	0.3	0.2	37	0.84	0.35	38	5.1%	-0.54 [-0.67 , -0.41]
Vijayendra 1998	0.6	0.5	20	1.35	0.5	20	4.7%	-0.75 [-1.06 , -0.44]
Wang 2010	0.72	0.11	20	1.53	0.1	20	5.2%	-0.81 [-0.88 , -0.74]
Yamashita 2006	2.88	1.81	12	3.03	2.93	12	1.0%	-0.15 [-2.10 , 1.80]
Zhang 2011	1.91	2	30	1.91	2	29	2.4%	0.00 [-1.02 , 1.02]
Zhang 2017	1.48	0.73	28	1.92	0.7	28	4.5%	-0.44 [-0.81 , -0.07]
Zhou 2019	1.8	0.3	60	2.5	0.3	60	5.1%	-0.70 [-0.81 , -0.59]
Total (95% CI)			**832**			**813**	**100.0%**	**-0.22 [-0.44 , 0.00]**

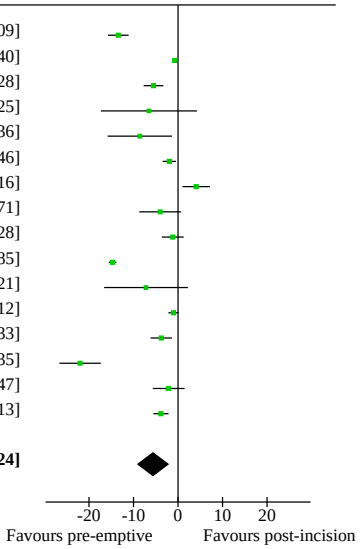
Heterogeneity: Tau² = 0.24; Chi² = 860.48, df = 27 (P < 0.00001); I² = 97%
Test for overall effect: Z = 1.96 (P = 0.05)
Test for subgroup differences: Not applicable



Analysis 1.5. Comparison 1: Pre-emptive NSAIDS/COX-2 inhibitors versus post-incision NSAIDS/COX-2 inhibitors, Outcome 5: 24-hour morphine consumption (mg)

Study or Subgroup	Pre-emptive Mean	SD	Total	Post-incision Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Bao 2012	25.72	4.08	33	39.14	5.39	32	6.7%	-13.42 [-15.75 , -11.09]
Chen 2015	34.08	0.72	24	34.83	0.51	25	6.9%	-0.75 [-1.10 , -0.40]
Coli 1993	4	4	25	9.5	4	25	6.7%	-5.50 [-7.72 , -3.28]
Fletcher 1995	31.12	16.9	20	37.66	17.89	20	4.1%	-6.54 [-17.33 , 4.25]
Gelir 2016	25.65	4	25	34.24	18	25	5.3%	-8.59 [-15.82 , -1.36]
Karaman 2008	21.41	2.45	20	23.36	2.37	20	6.8%	-1.95 [-3.44 , -0.46]
Likar 1997	26.67	5.07	26	22.59	5.72	22	6.5%	4.08 [1.00 , 7.16]
Munteanu 2016	30	11	55	34	14	55	6.1%	-4.00 [-8.71 , 0.71]
Ozer 2012	12.82	4.78	25	14	4.05	25	6.7%	-1.18 [-3.64 , 1.28]
Ozyilmaz 2005	7.6	0.76	20	22.3	1.78	20	6.9%	-14.70 [-15.55 , -13.85]
Parke 1995	45.6	14.4	37	52.8	26.4	40	4.5%	-7.20 [-16.61 , 2.21]
Shuying 2014	0.95	1.99	37	1.97	2.97	38	6.9%	-1.02 [-2.16 , 0.12]
Vijayendra 1998	3.5	4.32	20	7.25	3.43	20	6.7%	-3.75 [-6.17 , -1.33]
Wang 2010	100.75	7.75	20	122.75	7.25	20	6.1%	-22.00 [-26.65 , -17.35]
Yamashita 2006	11.69	4.8	12	13.79	4.1	12	6.4%	-2.10 [-5.67 , 1.47]
Zhang 2017	30.94	3.2	28	34.78	3.32	28	6.8%	-3.84 [-5.55 , -2.13]
Total (95% CI)			**427**			**427**	**100.0%**	**-5.62 [-9.00 , -2.24]**

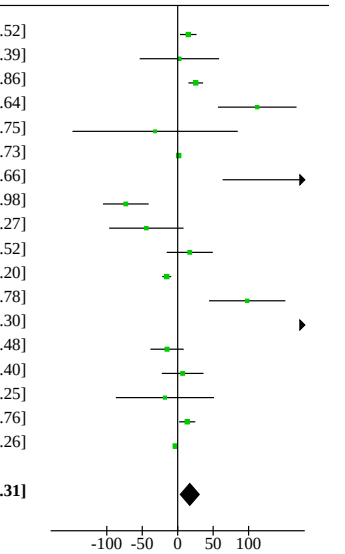
Heterogeneity: Tau² = 43.03; Chi² = 1075.47, df = 15 (P < 0.00001); I² = 99%
Test for overall effect: Z = 3.26 (P = 0.001)
Test for subgroup differences: Not applicable



Analysis 1.6. Comparison 1: Pre-emptive NSAIDS/COX-2 inhibitors versus post-incision NSAIDS/COX-2 inhibitors, Outcome 6: Time to first analgesic request (minutes)

Study or Subgroup	Pre-emptive Mean	SD	Total	Post-incision Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Buggy 1994	50.6	15.56	20	35.7	21.48	20	8.7%	14.90 [3.28 , 26.52]
Chen 2015	481.8	93.6	24	479.4	106.2	25	3.5%	2.40 [-53.59 , 58.39]
Colbert 1998	55.1	28	37	29.6	16.4	40	8.8%	25.50 [15.14 , 35.86]
Coli 1993	645.6	100	25	533.4	100	25	3.6%	112.20 [56.76 , 167.64]
Esparza-Villalpando 2016	396	227.54	30	427.83	233.17	30	1.1%	-31.83 [-148.41 , 84.75]
Gelir 2016	35.6	6	25	34.2	6	25	9.3%	1.40 [-1.93 , 4.73]
Inanoglu 2007	1440	0.01	22	1146	552	22	0.3%	294.00 [63.34 , 524.66]
Kaczmarzyk 2010	336.75	60.82	34	409.93	69.51	30	6.0%	-73.18 [-105.38 , -40.98]
Likar 1997	48.8	39.8	26	93	120.1	22	3.8%	-44.20 [-96.67 , 8.27]
Munteanu 2016	337	85	55	320	89	55	6.0%	17.00 [-15.52 , 49.52]
Nezafati 2017	57.65	8.94	20	73.15	11.26	20	9.1%	-15.50 [-21.80 , -9.20]
O'Hanlon 1996	128	165.9	40	30	36	20	3.7%	98.00 [44.22 , 151.78]
Priya 2002	928.2	172.2	25	253.2	153	25	1.8%	675.00 [584.70 , 765.30]
Vanlersberghe 1996	35	18.52	30	50	62.96	30	7.2%	-15.00 [-38.48 , 8.48]
Vijayendra 1998	51	30	20	44	60	20	6.4%	7.00 [-22.40 , 36.40]
Vogol 1992	414	116.4	19	432	95.4	17	2.6%	-18.00 [-87.25 , 51.25]
Yagar 2011	55	19.4	21	41.6	17.7	20	8.7%	13.40 [2.04 , 24.76]
Zhang 2017	26.96	5.78	28	30.36	6.19	28	9.3%	-3.40 [-6.54 , -0.26]
Total (95% CI)			**501**			**474**	**100.0%**	**17.04 [3.77 , 30.31]**

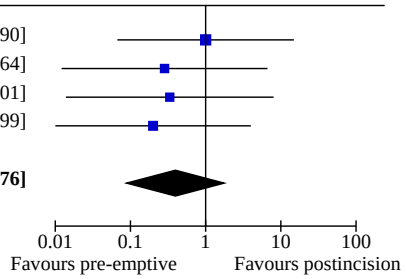
Heterogeneity: Tau² = 491.18; Chi² = 338.62, df = 17 (P < 0.00001); I² = 95%
Test for overall effect: Z = 2.52 (P = 0.01)
Test for subgroup differences: Not applicable



Analysis 1.7. Comparison 1: Pre-emptive NSAIDS/COX-2 inhibitors versus post-incision NSAIDS/COX-2 inhibitors, Outcome 7: Pruritus (long-term)

Study or Subgroup	Pre-emptive Events	Pre-emptive Total	Post-incision Events	Post-incision Total	Weight	Risk Ratio M-H, Random, 95% CI
Lee 2008	1	20	1	20	30.6%	1.00 [0.07 , 14.90]
Likar 1997	0	26	1	22	22.5%	0.28 [0.01 , 6.64]
Munteanu 2016	0	55	1	55	22.1%	0.33 [0.01 , 8.01]
Zhang 2017	0	28	2	28	24.9%	0.20 [0.01 , 3.99]
Total (95% CI)		**129**		**125**	**100.0%**	**0.40 [0.09 , 1.76]**
Total events:	1		5			

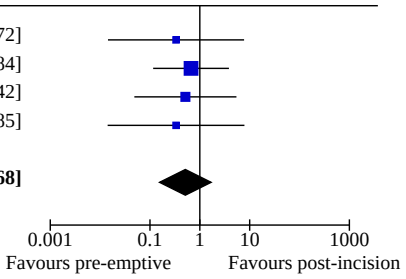
Heterogeneity: Tau² = 0.00; Chi² = 0.71, df = 3 (P = 0.87); I² = 0%
Test for overall effect: Z = 1.22 (P = 0.22)
Test for subgroup differences: Not applicable



Analysis 1.8. Comparison 1: Pre-emptive NSAIDS/COX-2 inhibitors versus post-incision NSAIDS/COX-2 inhibitors, Outcome 8: Sedation (long-term)

Study or Subgroup	Pre-emptive Events	Pre-emptive Total	Post-incision Events	Post-incision Total	Weight	Risk Ratio M-H, Random, 95% CI
Fletcher 1995	0	20	1	20	14.3%	0.33 [0.01 , 7.72]
Munteanu 2016	2	55	3	55	46.1%	0.67 [0.12 , 3.84]
Shuying 2014	1	37	2	38	25.4%	0.51 [0.05 , 5.42]
Zhang 2017	0	28	1	28	14.2%	0.33 [0.01 , 7.85]
Total (95% CI)		**140**		**141**	**100.0%**	**0.51 [0.16 , 1.68]**
Total events:	3		7			

Heterogeneity: Tau² = 0.00; Chi² = 0.23, df = 3 (P = 0.97); I² = 0%
Test for overall effect: Z = 1.10 (P = 0.27)
Test for subgroup differences: Not applicable



Comparison 2. Preventive NSAIDS/COX-2 inhibitors versus post-incision NSAIDS/COX-2 inhibitors

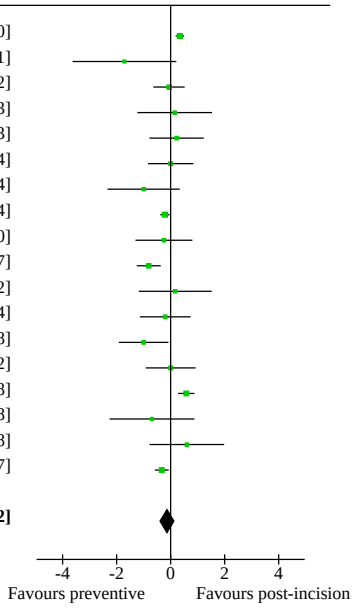
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Early acute postoperative pain (within 6 hours postoperatively)	18	1140	Mean Difference (IV, Random, 95% CI)	-0.14 [-0.39, 0.12]
2.2 Re-operation for bleeding	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.3 Nausea and vomiting (short-term)	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.4 Nausea and vomiting (long-term)	8	456	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.65, 1.22]
2.5 Late acute postoperative pain (24-48 hours postoperatively)	21	1441	Mean Difference (IV, Random, 95% CI)	-0.33 [-0.59, -0.07]
2.6 24-hour morphine consumption (mg)	16	1323	Mean Difference (IV, Random, 95% CI)	-1.93 [-3.55, -0.32]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.7 Time to first analgesic request (minutes)	8	410	Mean Difference (IV, Random, 95% CI)	8.51 [-31.24, 48.27]
2.8 Pruritus (long-term)	3	211	Risk Ratio (M-H, Random, 95% CI)	0.56 [0.09, 3.35]
2.9 Sedation (long-term)	5	497	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.44, 1.63]
2.10 Patient satisfaction	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.11 Time to bowel movement (hours)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only

Analysis 2.1. Comparison 2: Preventive NSAIDS/COX-2 inhibitors versus post-incision NSAIDS/COX-2 inhibitors, Outcome 1: Early acute postoperative pain (within 6 hours postoperatively)

Study or Subgroup	Preventive Mean	Preventive SD	Preventive Total	Post-incision Mean	Post-incision SD	Post-incision Total	Weight	Mean Difference IV, Random, 95% CI
Abanto 2014	0.52	0.4	30	0.18	0.17	30	11.1%	0.34 [0.18 , 0.50]
Ashworth 2002	4.19	3.14	15	5.9	2.13	15	1.5%	-1.71 [-3.63 , 0.21]
Aznar-Arasa 2012	1.13	1.56	53	1.19	1.52	56	7.3%	-0.06 [-0.64 , 0.52]
Boccara 2005	2.5	2.45	24	2.35	2.43	24	2.7%	0.15 [-1.23 , 1.53]
Giuliani 2015	2.04	2.72	43	1.82	2	44	4.2%	0.22 [-0.79 , 1.23]
Gramke 2006	1	1.85	25	1	1.11	27	5.2%	0.00 [-0.84 , 0.84]
Gunter 2012	4	3.7	40	5	2.22	40	2.8%	-1.00 [-2.34 , 0.34]
Guran 2010	0.41	0.4	39	0.62	0.4	43	11.0%	-0.21 [-0.38 , -0.04]
Likar 1998	1.66	1.9	25	1.91	1.9	25	3.9%	-0.25 [-1.30 , 0.80]
Martinez 2007	5.61	0.75	22	6.42	0.7	19	8.6%	-0.81 [-1.25 , -0.37]
Moonla 2018	4.19	2.92	42	4.02	3.37	42	2.8%	0.17 [-1.18 , 1.52]
Norris 2001	3.4	1.9	40	3.6	2.3	38	4.5%	-0.20 [-1.14 , 0.74]
Pandazi 2010	4	1.48	20	5	1.48	20	4.7%	-1.00 [-1.92 , -0.08]
Salonen 2001	2.4	2.2	41	2.4	2.04	40	4.6%	0.00 [-0.92 , 0.92]
Sun 2008	3.71	0.74	39	3.13	0.6	37	10.0%	0.58 [0.28 , 0.88]
Trampitsch 2003	5.32	2.8	22	6.01	2.5	22	2.2%	-0.69 [-2.26 , 0.88]
Wnek 2004	4.11	3.1	30	3.51	2.3	30	2.7%	0.60 [-0.78 , 1.98]
Young 2006	0.28	0.4	21	0.61	0.4	17	10.4%	-0.33 [-0.59 , -0.07]
Total (95% CI)			**571**			**569**	**100.0%**	**-0.14 [-0.39 , 0.12]**

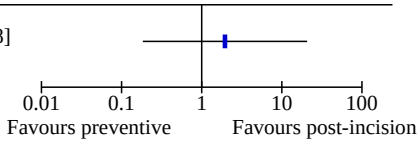
Heterogeneity: Tau² = 0.15; Chi² = 69.16, df = 17 (P < 0.00001); I² = 75%
Test for overall effect: Z = 1.05 (P = 0.30)
Test for subgroup differences: Not applicable



Analysis 2.2. Comparison 2: Preventive NSAIDS/COX-2 inhibitors versus post-incision NSAIDS/COX-2 inhibitors, Outcome 2: Re-operation for bleeding

Study or Subgroup	Preventive Events	Preventive Total	Post-incision Events	Post-incision Total	Risk Ratio M-H, Random, 95% CI
Salonen 2001	2	41	1	40	1.95 [0.18 , 20.68]

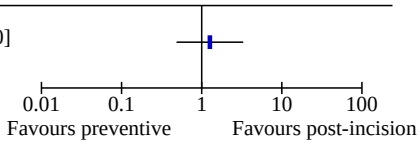
Test for subgroup differences: Not applicable



Analysis 2.3. Comparison 2: Preventive NSAIDS/COX-2 inhibitors versus post-incision NSAIDS/COX-2 inhibitors, Outcome 3: Nausea and vomiting (short-term)

Study or Subgroup	Preventive Events	Preventive Total	Post-incision Events	Post-incision Total	Risk Ratio M-H, Random, 95% CI
Sun 2008	8	39	6	37	1.26 [0.49 , 3.30]

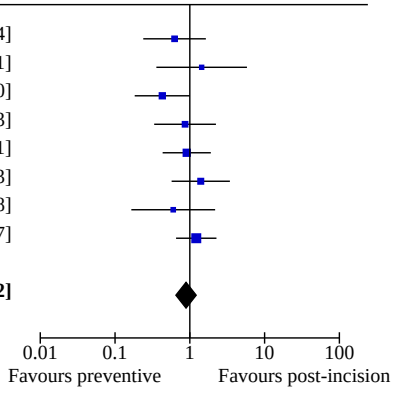
Test for subgroup differences: Not applicable



Analysis 2.4. Comparison 2: Preventive NSAIDS/COX-2 inhibitors versus post-incision NSAIDS/COX-2 inhibitors, Outcome 4: Nausea and vomiting (long-term)

Study or Subgroup	Preventive Events	Preventive Total	Post-incision Events	Post-incision Total	Weight	Risk Ratio M-H, Random, 95% CI
Boccara 2005	5	24	8	24	10.4%	0.63 [0.24 , 1.64]
Gramke 2006	4	25	3	27	5.0%	1.44 [0.36 , 5.81]
Gunter 2012	6	40	14	40	13.4%	0.43 [0.18 , 1.00]
Martinez 2007	6	22	6	19	10.7%	0.86 [0.33 , 2.23]
Moonla 2018	10	42	11	42	17.6%	0.91 [0.43 , 1.91]
Nakayama 2001	7	15	5	15	12.0%	1.40 [0.57 , 3.43]
Pandazi 2010	3	20	5	20	5.8%	0.60 [0.17 , 2.18]
Salonen 2001	15	41	12	40	25.0%	1.22 [0.65 , 2.27]
Total (95% CI)		**229**		**227**	**100.0%**	**0.89 [0.65 , 1.22]**
Total events:	56		64			

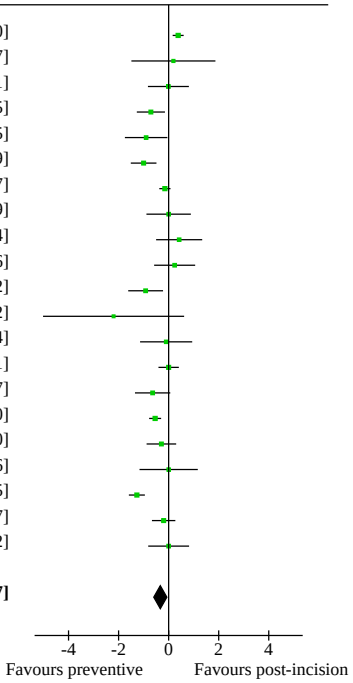
Heterogeneity: Tau² = 0.00; Chi² = 6.19, df = 7 (P = 0.52); I² = 0%
Test for overall effect: Z = 0.73 (P = 0.46)
Test for subgroup differences: Not applicable



Analysis 2.5. Comparison 2: Preventive NSAIDS/COX-2 inhibitors versus post-incision NSAIDS/COX-2 inhibitors, Outcome 5: Late acute postoperative pain (24-48 hours postoperatively)

	Preventive			Post-incision				Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Abanto 2014	0.78	0.49	30	0.4	0.37	30	7.0%	0.38 [0.16 , 0.60]	
Ashworth 2002	1.84	2.4	15	1.65	2.29	15	1.8%	0.19 [-1.49 , 1.87]	
Aznar-Arasa 2012	2.06	2.34	53	2.07	1.99	56	4.3%	-0.01 [-0.83 , 0.81]	
Boccara 2005	0.33	0.6	24	1.04	1.27	24	5.5%	-0.71 [-1.27 , -0.15]	
Gramke 2006	1.1	1.63	25	2	1.48	27	4.2%	-0.90 [-1.75 , -0.05]	
Gunter 2012	0	0.74	40	1	1.48	40	5.8%	-1.00 [-1.51 , -0.49]	
Guran 2010	0.27	0.6	39	0.42	0.4	43	7.0%	-0.15 [-0.37 , 0.07]	
Likar 1998	1.31	1.6	25	1.31	1.6	25	4.0%	0.00 [-0.89 , 0.89]	
Martinez 2007	1.55	1.5	22	1.13	1.5	19	3.9%	0.42 [-0.50 , 1.34]	
Moonla 2018	2.52	2.07	42	2.28	1.75	42	4.3%	0.24 [-0.58 , 1.06]	
Murphy 1993	0.35	0.53	22	1.27	1.78	28	4.8%	-0.92 [-1.62 , -0.22]	
Nakayama 2001	1.66	2.72	15	3.86	4.86	15	0.8%	-2.20 [-5.02 , 0.62]	
Norris 2001	4.5	1.8	29	4.6	2.3	31	3.4%	-0.10 [-1.14 , 0.94]	
Pandazi 2010	1	0.56	20	1	0.74	20	6.3%	0.00 [-0.41 , 0.41]	
Salonen 2001	1.07	1.22	41	1.71	1.93	40	4.8%	-0.64 [-1.35 , 0.07]	
Sun 2008	0.98	0.6	39	1.52	0.46	37	7.0%	-0.54 [-0.78 , -0.30]	
Trampitsch 2003	0.8	1	22	1.09	1	22	5.4%	-0.29 [-0.88 , 0.30]	
Wnek 2004	2.8	2.3	30	2.8	2.3	30	3.0%	0.00 [-1.16 , 1.16]	
Young 2006	0.29	0.5	21	1.56	0.5	17	6.7%	-1.27 [-1.59 , -0.95]	
Yuan 2019	3.1	1.8	102	3.3	1.6	102	6.0%	-0.20 [-0.67 , 0.27]	
Zhou 2017	2.64	2.3	62	2.64	2.3	60	4.3%	0.00 [-0.82 , 0.82]	
Total (95% CI)			**718**			**723**	**100.0%**	**-0.33 [-0.59 , -0.07]**	

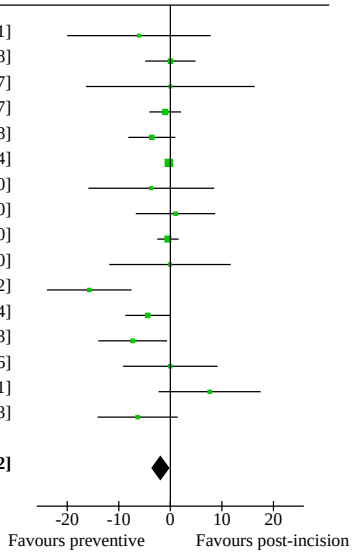
Heterogeneity: Tau² = 0.24; Chi² = 102.82, df = 20 (P < 0.00001); I² = 81%
Test for overall effect: Z = 2.51 (P = 0.01)
Test for subgroup differences: Not applicable



Analysis 2.6. Comparison 2: Preventive NSAIDS/COX-2 inhibitors versus post-incision NSAIDS/COX-2 inhibitors, Outcome 6: 24-hour morphine consumption (mg)

	Preventive			Post-incision				Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Ashworth 2002	19.7	21.2	15	25.8	17.5	15	1.3%	-6.10 [-20.01 , 7.81]	
Boccara 2005	17	7	24	17	10	24	7.3%	0.00 [-4.88 , 4.88]	
Fleckenstein 2016	21.25	28	22	21.25	28	23	0.9%	0.00 [-16.37 , 16.37]	
Gramke 2006	6	5.37	25	7	5.93	27	12.3%	-1.00 [-4.07 , 2.07]	
Gunter 2012	11.45	10.93	40	15.03	9.83	40	8.0%	-3.58 [-8.14 , 0.98]	
Guran 2010	0.76	0.14	39	1.08	0.21	43	22.0%	-0.32 [-0.40 , -0.24]	
Likar 1998	26.14	22	25	29.84	22	25	1.6%	-3.70 [-15.90 , 8.50]	
Martinez 2007	26	12	22	25	13	19	3.7%	1.00 [-6.70 , 8.70]	
Moonla 2018	5.21	4.41	42	5.68	5.25	42	16.1%	-0.47 [-2.54 , 1.60]	
Murphy 1993	42.23	20.23	22	42.31	22.15	28	1.7%	-0.08 [-11.86 , 11.70]	
Pandazi 2010	24.95	13.66	20	40.67	12.79	20	3.3%	-15.72 [-23.92 , -7.52]	
Riest 2006	22.5	19.8	180	26.9	22.3	180	8.5%	-4.40 [-8.76 , -0.04]	
Riest 2008	22.8	19.2	80	30.1	23.6	80	4.6%	-7.30 [-13.97 , -0.63]	
Salonen 2001	23.63	20	41	23.63	22	40	2.7%	0.00 [-9.16 , 9.16]	
Sun 2008	45.08	22	39	37.47	22	37	2.4%	7.61 [-2.29 , 17.51]	
Trampitsch 2003	25.15	11.07	22	31.5	14.96	22	3.6%	-6.35 [-14.13 , 1.43]	
Total (95% CI)			**658**			**665**	**100.0%**	**-1.93 [-3.55 , -0.32]**	

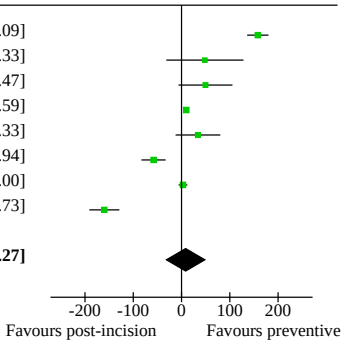
Heterogeneity: Tau² = 3.09; Chi² = 29.15, df = 15 (P = 0.02); I² = 49%
Test for overall effect: Z = 2.35 (P = 0.02)
Test for subgroup differences: Not applicable



Analysis 2.7. Comparison 2: Preventive NSAIDS/COX-2 inhibitors versus post-incision NSAIDS/COX-2 inhibitors, Outcome 7: Time to first analgesic request (minutes)

Study or Subgroup	Preventive Mean	Preventive SD	Preventive Total	Post-incision Mean	Post-incision SD	Post-incision Total	Weight	Mean Difference IV, Random, 95% CI
Boccara 2005	240	47	24	82	29	24	13.5%	158.00 [135.91 , 180.09]
Gunter 2012	51.55	257.84	40	3.15	6.5	40	9.0%	48.40 [-31.53 , 128.33]
Likar 1998	100.6	135	25	51	45.7	25	11.1%	49.60 [-6.27 , 105.47]
Martinez 2007	38	9	22	28.2	6.6	19	14.1%	9.80 [5.01 , 14.59]
Mishra 2012	407	60	12	373	58	13	11.9%	34.00 [-12.33 , 80.33]
Nakayama 2001	128	36	15	186	34	15	13.4%	-58.00 [-83.06 , -32.94]
Sun 2008	26	20	39	23	20	37	14.0%	3.00 [-6.00 , 12.00]
Wnek 2004	363.2	58	30	523.1	65	30	13.0%	-159.90 [-191.07 , -128.73]
Total (95% CI)			**207**			**203**	**100.0%**	**8.51 [-31.24 , 48.27]**

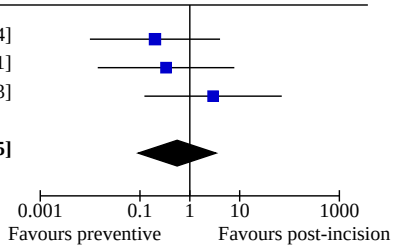
Heterogeneity: Tau² = 2909.34; Chi² = 320.81, df = 7 (P < 0.00001); I² = 98%
Test for overall effect: Z = 0.42 (P = 0.67)
Test for subgroup differences: Not applicable



Analysis 2.8. Comparison 2: Preventive NSAIDS/COX-2 inhibitors versus post-incision NSAIDS/COX-2 inhibitors, Outcome 8: Pruritus (long-term)

Study or Subgroup	Preventive Events	Preventive Total	Post-incision Events	Post-incision Total	Weight	Risk Ratio M-H, Random, 95% CI
Gunter 2012	0	40	2	40	35.6%	0.20 [0.01 , 4.04]
Likar 1998	0	25	1	25	32.4%	0.33 [0.01 , 7.81]
Salonen 2001	1	41	0	40	32.0%	2.93 [0.12 , 69.83]
Total (95% CI)		**106**		**105**	**100.0%**	**0.56 [0.09 , 3.35]**
Total events:	1		3			

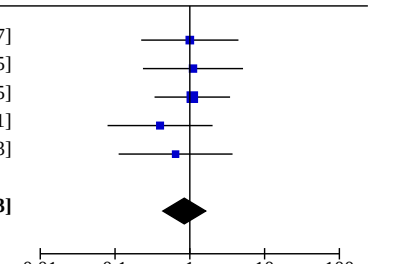
Heterogeneity: Tau² = 0.00; Chi² = 1.60, df = 2 (P = 0.45); I² = 0%
Test for overall effect: Z = 0.64 (P = 0.52)
Test for subgroup differences: Not applicable



Analysis 2.9. Comparison 2: Preventive NSAIDS/COX-2 inhibitors versus post-incision NSAIDS/COX-2 inhibitors, Outcome 9: Sedation (long-term)

Study or Subgroup	Preventive Events	Preventive Total	Post-incision Events	Post-incision Total	Weight	Risk Ratio M-H, Random, 95% CI
Boccara 2005	3	24	3	24	19.3%	1.00 [0.22 , 4.47]
Guran 2010	3	39	3	43	18.2%	1.10 [0.24 , 5.15]
Martinez 2007	5	22	4	19	32.0%	1.08 [0.34 , 3.45]
Yuan 2019	2	102	5	102	16.5%	0.40 [0.08 , 2.01]
Zhou 2017	2	62	3	60	14.0%	0.65 [0.11 , 3.73]
Total (95% CI)		**249**		**248**	**100.0%**	**0.84 [0.44 , 1.63]**
Total events:	15		18			

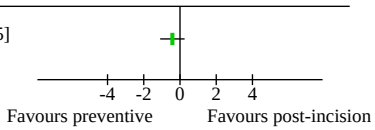
Heterogeneity: Tau² = 0.00; Chi² = 1.26, df = 4 (P = 0.87); I² = 0%
Test for overall effect: Z = 0.51 (P = 0.61)
Test for subgroup differences: Not applicable



Analysis 2.10. Comparison 2: Preventive NSAIDS/COX-2 inhibitors versus post-incision NSAIDS/COX-2 inhibitors, Outcome 10: Patient satisfaction

Study or Subgroup	Preventive Mean	SD	Total	Post-incision Mean	SD	Total	Mean Difference IV, Random, 95% CI
Giuliani 2015	9.04	1.74	35	9.46	1.08	37	-0.42 [-1.09 , 0.25]

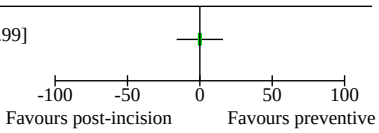
Test for subgroup differences: Not applicable



Analysis 2.11. Comparison 2: Preventive NSAIDS/COX-2 inhibitors versus post-incision NSAIDS/COX-2 inhibitors, Outcome 11: Time to bowel movement (hours)

Study or Subgroup	Preventive Mean	SD	Total	Post-incision Mean	SD	Total	Mean Difference IV, Random, 95% CI
Sun 2008	48	35.56	39	48	35.56	37	0.00 [-15.99 , 15.99]

Test for subgroup differences: Not applicable



APPENDICES

Appendix 1. Search strategies

MEDLINE

1 exp Anti-Inflammatory Agents, Non-Steroidal/ (196911)

2 (NSAID* or non-steroidal anti-inflammatory or non-steroidal antiinflammatory or cyclooxygenase enzyme* or cox or ibuprofen or ketoprofen or diclofenac or indomethacin or ketorolac or naproxen or celecoxib or parecoxib or valdecoxib).mp. (257855)

3 1 or 2 (376251)

4 exp Pain, Postoperative/ (40747)

5 exp postoperative complications/ (542898)

6 ((postoperat* or post operat* or postsurg* or post surg* or postan?esth* or post an?esth* or perioperat* or peri operat*) adj6 (pain* or recover* or analges*)).mp. (87317)

7 ((postoperat* or post operat* or postsurg* or post surg* or postan?esth* or post an?esth* or perioperat* or peri operat*) adj2 complication*).mp. (418222)

8 (((postoperat* or post operat* or postsurg* or post surg* or postan?esth* or post an?esth* or perioperat* or peri operat*) adj2 (care or period*)) and pain*).mp. (19394)

9 4 or 5 or 6 or 7 or 8 (632292)

10 Preanesthetic Medication/ (7948)

11 Premedication/ (12484)

12 (pre emptive or preemptive or preventive or preoperat* or pre operat* or preincision* or pre incision* or pre surg* or presurg* or perioperat* or peri operat* or intraoperat* or intra operat* or prophyla* or ((before or prior) adj3 (surg* or operat*))).mp. (951011)

13 10 or 11 or 12 (963150)

14 3 and 9 and 13 (5980)

15 ((randomized controlled trial or controlled clinical trial).pt. or randomi?ed.ab. or placebo.ab. or clinical trials as topic.sh. or randomly.ab. or trial.ti.) not (exp animals/ not humans.sh.) (1224369)

16 14 and 15 (2132)

17 (exp child/ or exp infant/) not exp adult/ (1661664)

18 16 not 17 (1989)

CENTRAL

#1 MeSH descriptor: [Anti-Inflammatory Agents, Non-Steroidal] explode all trees 7551

#2 (NSAID* or (non next steroidal next anti next inflammatory) or (non next steroidal next antiinflammatory) or (cyclooxygenase next enzyme*) or cox or ibuprofen or ketoprofen or diclofenac or indomethacin or ketorolac or naproxen or celecoxib or parecoxib or valdecoxib):ti,ab,kw 38187

#3 #1 or #2 40872

#4 MeSH descriptor: [Pain, Postoperative] explode all trees 14957

#5 MeSH descriptor: [Postoperative Complications] explode all trees 39006

#6 ((postoperat* or (post next operat*) or postsurg* or (post next surg*) or postan*esth* or (post next an*esth*) or perioperat* or (peri next operat*)) near (pain* or recover* or analges*)):ti,ab,kw 42979

#7 ((postoperat* or (post next operat*) or postsurg* or (post next surg*) or postan*esth* or (post next an*esth* or perioperat* or (peri next operat*))) near/2 complication*):ti,ab,kw 36606

#8 (((postoperat* or (post next operat*) or postsurg* or (post next surg*) or postan*esth* or (post next an*esth* or perioperat* or (peri next operat*))) near/2 (care or period*)) and pain*):ti,ab,kw 10812

#9 #4 or #5 or #6 or #7 or #8 78924

#10 MeSH descriptor: [Preanesthetic Medication] explode all trees 1715

#11 MeSH descriptor: [Premedication] explode all trees 4245

#12 ((pre next emptive) or preemptive or preventive or preoperat* or (pre next operat*) or preincision* or (pre next incision*) or (pre next surg*) or presurg* or perioperat* or (peri next operat*) or intraoperat* or (intra next operat*) or prophyla* or ((before or prior) near/3 (surg* or operat*))):ti,ab,kw 128393

#13 #10 or #11 or #12 130531

#14 #3 and #9 and #13 3186

#15 ((child* or infant* or pediatric* or paediatric*) not (adult* or elder* or aged or (old next age) or geriatric*)):ti,ab,kw 114324

#16 #14 not #15 3036

#17 #16 in Trials 3023

Embase

1 exp ANTI-INFLAMMATORY AGENTS, NON-STEROIDAL/

2 (NSAID* OR non-steroidal anti-inflammatory drug* OR cyclooxygenase enzyme* OR cox OR ibuprofen OR ketoprofen OR diclofenac or indomethacin OR ketorolac OR naproxen OR celecoxib OR parecoxib OR valdecoxib).ti,ab

3 1 OR 2

4 exp PAIN, POSTOPERATIVE/

5 ((postoperati* OR post-operati*) ADJ6 (pain* OR recover*)).ti,ab

6 4 OR 5

7 exp PREANESTHETICMEDICATION/ OR (pre-emptive OR preemptive OR preventive OR preoperati* OR pre-operat* OR preincision OR pre-incision OR perioperati* OR peri-operati* OR intraoperati* OR intra-operati* OR prophylactic* OR ((before OR prior) ADJ3 (surg* OR operat*)))

8 3 AND 6

9 7 AND 8 [Publication types Article OR Conference Abstract OR Conference Paper OR Conference Proceeding OR Journal] [Human age groups Adult 18 to 64 years OR Aged 65+ years] [Humans] [Clinical trials Clinical Trial OR Randomized Controlled Trial OR Controlled Clinical Trial OR Multicenter Study OR Phase 1 Clinical Trial OR Phase 2 Clinical Trial OR Phase 3 Clinical Trial OR Phase 4 Clinical Trial]

CINAHL

1 (NSAID* OR non-steroidal anti-inflammatory drug* OR cyclooxygenase enzyme* OR cox OR ibuprofen OR ketoprofen OR diclofenac or indomethacin OR ketorolac OR naproxen OR celecoxib OR parecoxib OR valdecoxib).ti,ab

2 (pain).ti,ab

3 ((postoperati* OR post-operati*) ADJ6 (pain* OR recover*)).ti,ab

4 (pre-emptive OR preemptive OR preventive OR preoperati* OR pre-operat* OR preincision OR pre-incision OR perioperati* OR peri-operati* OR intraoperati* OR intra-operati* OR prophylactic* OR ((before OR prior) ADJ3 (surg* OR operat*))).ti,ab

5 2 OR 3

6 1 AND 4 AND 5

AMED

1 (NSAID* OR non-steroidal anti-inflammatory drug* OR cyclooxygenase enzyme* OR cox OR ibuprofen OR ketoprofen OR diclofenac or indomethacin OR ketorolac OR naproxen OR celecoxib OR parecoxib OR valdecoxib).ti,ab

2 (pain).ti,ab

3 ((postoperati* OR post-operati*) ADJ6 (pain* OR recover*)).ti,ab

4 (pre-emptive OR preemptive OR preventive OR preoperati* OR pre-operat* OR preincision OR pre-incision OR perioperati* OR peri-operati* OR intraoperati* OR intra-operati* OR prophylactic* OR ((before OR prior) ADJ3 (surg* OR operat*))).ti,ab

5 2 OR 3

6 1 AND 4 AND 5

Appendix 2. Data Extraction Form

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)*

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 Characteristics	**Eligibility criteria** *(Insert eligibility criteria for each characteristic as defined in the protocol)*	Yes	No	Unclear	**Location in text** *(pg & /fig/ table)*
Type of study	Randomized Controlled Trial				

(Continued)

	Controlled Clinical Trial *(quasi-randomized trial)*
Participants	
Types of intervention	
Types of outcome measures	
INCLUDE	**EXCLUDE**
Reason for exclusion	
Notes:	

DO NOT PROCEED IF STUDY EXCLUDED FROM REVIEW

3. Population and setting

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

4. Methods

	Descriptions as stated in report/paper	**Location in text** *(pg & ¶/fig/table)*

(Continued)

Aim of study	
Design *(e.g. parallel-group, cross-over, 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**
	Low-risk	High-risk	Unclear		*(pg & ¶/fig/table)*
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)*					

(Continued)

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 *(or total pop. at start of study for NRCTs)*		
Clusters *(if applicable, no., type, no. people per cluster)*		
Baseline imbalances		
Withdrawals and exclusions *(if not provided below by outcome)*		
Age		
Sex		
Race/ethnicity		
Severity of illness		
Comorbidities		
Other treatment received *(additional to study intervention)*		
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 (pg & ¶/fig/table)
Outcome name		
Time points measured		
Time points reported		
Outcome definition *(with diagnostic criteria if relevant)*		
Person measuring/reporting		

(Continued)

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** *(pg & ¶/fig/table)*
Comparison					
Outcome					
Subgroup					
Time point *(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					

(Continued)

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							
Time point *(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						
Reanalysis possible?	Yes No Unclear						

(Continued)

Reanalysed results	
Notes:	

Other outcome

	Description as stated in report/paper				Location in text (pg & ¶/fig/table)
Comparison					
Outcome					
Subgroup					
Time point *(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:					

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:		

HISTORY

Protocol first published: Issue 3, 2018

CONTRIBUTIONS OF AUTHORS

Brett Doleman (BD), John P Williams (JPW), Jon Lund (JL), Jo Leonardi-Bee (JLB), Thomas Heinink (TH), Laura Carrick (LC), Hannah Boyd-Carson (HBC) and Rahil Mandalia (RM):

Conceiving the review: BD, JPW

Co-ordinating the review: BD, JPW, JL, JLB, TH, HBC, LC, RM

Undertaking manual searches: BD

Screening search results: BD

Organizing retrieval of papers: BD

Screening retrieved papers against inclusion criteria: BD, JPW, TH, JLB

Appraising quality of papers: BD, JPW, TH, JLB

Abstracting data from papers: BD, JPW, TH, RM, HBC, LC

Writing to authors of papers for additional information: BD

Providing additional data about papers: BD

Obtaining and screening data on unpublished studies: BD

Data management for the review: BD, JPW

Entering data into Review Manager 5 (RevMan 5): BD, JPW

RevMan statistical data: BD, JPW

Other statistical analysis not using RevMan 5: BD, RM

Interpretation of data: BD, JPW, JLB, HBC, RM, LC

Statistical inferences: BD, JPW, JLB

Writing the review: BD, JPW, HBC, RM, LC, JLB, JL

Securing funding for the review: N/A

Performing previous work that was the foundation of the present study: BD, JPW, JL, TH

Guarantor for the review (one author): BD

Person responsible for reading and checking review before submission: BD, JL, JPW, JLB, TH, LC, JLB, JL

DECLARATIONS OF INTEREST

Brett Doleman: has received a grant from Association of Anaesthetists of Great Britain and Ireland (AAGBI) for a randomized controlled trial of pre-emptive paracetamol (ongoing) and has previously undertaken a meta-analysis of pre-emptive paracetamol (Doleman 2015b).

John P Williams: has received a grant from AAGBI for a randomized controlled trial of pre-emptive paracetamol (ongoing) and has previously undertaken a meta-analysis of pre-emptive paracetamol (Doleman 2015b).

Jon Lund: has received a grant from AAGBI for a randomized controlled trial of pre-emptive paracetamol (ongoing) and has previously undertaken a meta-analysis of pre-emptive paracetamol (Doleman 2015b).

Jo Leonardi-Bee: no declarations of interest in relation to this review

Thomas Heinink: no declarations of interest

Hannah Boyd-Carson: no declarations of interest

Laura Carrick: no declarations of interest

Rahil Mandalia: no declarations of interest

SOURCES OF SUPPORT

Internal sources

- No sources of support provided

External sources

- No sources of support provided

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

1) Following editorial and peer review comments on the review protocol, we added sensitivity analysis by excluding studies with a low sample size (< 50 participants).

2) Nausea and vomiting was aggregated to reduce type 1 errors from multiple comparisons and following peer review feedback from our previous review on pre-emptive and preventive opioids (Doleman 2018b).

3) We have used an updated test for publication bias due to recently published research. This test uses inverse sample size instead of standard errors to assess small study effects. In extensive simulations it performs as well as traditional tests when no baseline risk is present and reduces type 1 errors when baseline risk is present in outcomes such as pain and morphine consumption (Doleman 2020).

4) To reduce type 1 errors in investigating heterogeneity, we did not perform meta-regression for type of NSAID as this replicated the subgroup analysis. We could not undertake meta-regression for dose of NSAID due to a lack of ability to convert doses between agents.

5) We did not include the earliest postoperative measurement for early acute postoperative pain and, instead, included the earliest time point when post-incision dosing was likely to be therapeutic. For example, if post-incision dosing occurred at two hours, we included a time point at three hours rather than one hour. This is because the latter scenario is comparing pre-emptive/preventive NSAIDs with no intervention which contradicts the objectives of the review (Doleman 2018b).

6) Sedation definition changed to include more studies for this outcome. This was previously defined on a continuous scale, although this was changed to number of events in the study.