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Single-dose intravenous ketorolac for acute postoperative pain in adults (Review)

McNicol ED, Ferguson MC, Schumann R

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[Intervention Review]

Single-dose intravenous ketorolac for acute postoperative pain in adults

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ABSTRACT

Background

Postoperative pain is common and may be severe. Postoperative administration of non-steroidal anti-inflammatory drugs (NSAIDs) reduces patient opioid requirements and, in turn, may reduce the incidence and severity of opioid-induced adverse events (AEs).

Objectives

To assess the analgesic efficacy and adverse effects of single-dose intravenous ketorolac, compared with placebo or an active comparator, for moderate to severe postoperative pain in adults.

Search methods

We searched the following databases without language restrictions: CENTRAL, MEDLINE, Embase and LILACS on 20 April 2020. We checked clinical trials registers and reference lists of retrieved articles for additional studies.

Selection criteria

Randomized double-blind trials that compared a single postoperative dose of intravenous ketorolac with placebo or another active treatment, for treating acute postoperative pain in adults following any surgery.

Data collection and analysis

We used standard methodological procedures expected by Cochrane.
Our primary outcome was the number of participants in each arm achieving at least 50% pain relief over a four- and six-hour period.
Our secondary outcomes were time to and number of participants using rescue medication; withdrawals due to lack of efficacy, adverse events (AEs), and for any other cause; and number of participants experiencing any AE, serious AEs (SAEs), and NSAID-related or opioid-related AEs.
For subgroup analysis, we planned to analyze different doses of parenteral ketorolac separately and to analyze results based on the type of surgery performed.
We assessed the certainty of evidence using GRADE.

Main results

We included 12 studies, involving 1905 participants undergoing various surgeries (pelvic/abdominal, dental, and orthopedic), with 17 to 83 participants receiving intravenous ketorolac in each study. Mean study population ages ranged from 22.5 years to 67.4 years. Most studies administered a dose of ketorolac of 30 mg; one study assessed 15 mg, and another administered 60 mg.

Most studies had an unclear risk of bias for some domains, particularly allocation concealment and blinding, and a high risk of bias due to small sample size. The overall certainty of evidence for each outcome ranged from very low to moderate. Reasons for downgrading certainty included serious study limitations, inconsistency and imprecision.

Ketorolac versus placebo

Very low-certainty evidence from eight studies (658 participants) suggests that ketorolac results in a large increase in the number of participants achieving at least 50% pain relief over four hours compared to placebo, but the evidence is very uncertain (risk ratio (RR) 2.81, 95% confidence interval (CI) 1.80 to 4.37). The number needed to treat for one additional participant to benefit (NNTB) was 2.4 (95% CI 1.8 to 3.7). Low-certainty evidence from 10 studies (914 participants) demonstrates that ketorolac may result in a large increase in the number of participants achieving at least 50% pain relief over six hours compared to placebo (RR 3.26, 95% CI 1.93 to 5.51). The NNTB was 2.5 (95% CI 1.9 to 3.7).

Among secondary outcomes, for time to rescue medication, moderate-certainty evidence comparing intravenous ketorolac versus placebo demonstrated a mean median of 271 minutes for ketorolac versus 104 minutes for placebo (6 studies, 633 participants). For the number of participants using rescue medication, very low-certainty evidence from five studies (417 participants) compared ketorolac with placebo. The RR was 0.60 (95% CI 0.36 to 1.00), that is, it did not demonstrate a difference between groups.

Ketorolac probably results in a slight increase in total adverse event rates compared with placebo (74% versus 65%; 8 studies, 810 participants; RR 1.09, 95% CI 1.00 to 1.19; number needed to treat for an additional harmful event (NNTH) 16.7, 95% CI 8.3 to infinite, moderate-certainty evidence). Serious AEs were rare. Low-certainty evidence from eight studies (703 participants) did not demonstrate a difference in rates between ketorolac and placebo (RR 0.62, 95% CI 0.13 to 3.03).

Ketorolac versus NSAIDs

Ketorolac was compared to parecoxib in four studies and diclofenac in two studies. For our primary outcome, over both four and six hours there was no evidence of a difference between intravenous ketorolac and another NSAID (low-certainty and moderate-certainty evidence, respectively). Over four hours, four studies (337 participants) produced an RR of 1.04 (95% CI 0.89 to 1.21) and over six hours, six studies (603 participants) produced an RR of 1.06 (95% CI 0.95 to 1.19).

For time to rescue medication, low-certainty evidence from four studies (427 participants) suggested that participants receiving ketorolac waited an extra 35 minutes (mean median 331 minutes versus 296 minutes). For the number of participants using rescue medication, very low-certainty evidence from three studies (260 participants) compared ketorolac with another NSAID. The RR was 0.90 (95% CI 0.58 to 1.40), that is, there may be little or no difference between groups.

Ketorolac probably results in a slight increase in total adverse event rates compared with another NSAID (76% versus 68%, 5 studies, 516 participants; RR 1.11, 95% CI 1.00 to 1.23; NNTH 12.5, 95% CI 6.7 to infinite, moderate-certainty evidence). Serious AEs were rare. Low-certainty evidence from five studies (530 participants) did not demonstrate a difference in rates between ketorolac and another NSAID (RR 3.18, 95% CI 0.13 to 76.99). Only one of the five studies reported a single serious AE.

Authors' conclusions

The amount and certainty of evidence for the use of intravenous ketorolac as a treatment for postoperative pain varies across efficacy and safety outcomes and amongst comparators, from very low to moderate. The available evidence indicates that postoperative intravenous ketorolac administration may offer substantial pain relief for most patients, but further research may impact this estimate. Adverse events appear to occur at a slightly higher rate in comparison to placebo and to other NSAIDs. Insufficient information is available to assess whether intravenous ketorolac has a different rate of gastrointestinal or surgical-site bleeding, renal dysfunction, or cardiovascular events versus other NSAIDs. There was a lack of studies in cardiovascular surgeries and in elderly populations who may be at increased risk for adverse events.

PLAIN LANGUAGE SUMMARY

What are the benefits and risks of a single injection of ketorolac (an anti-inflammation medicine) for relieving short-term pain after surgery in adults?

Key messages

· Ketorolac may reduce short-term pain after surgery by 50% (half) or more in more people than a placebo (dummy treatment).
· There may be little to no difference between ketorolac and other anti-inflammation medicines in the number of people whose pain is reduced by half or more.
· Ketorolac probably causes slightly more unwanted effects than placebo and other anti-inflammation medicines; more evidence is required to establish if it causes serious unwanted effects.

Treating short-term pain after surgery

It is common for people to feel pain in the short term (within six hours) after surgery. Often, medicines called non-steroidal anti-inflammatory drugs (NSAIDs) are given to relieve this pain.

NSAIDS work by stopping the body's production of chemicals that cause inflammation and pain. A potential advantage of using NSAIDs is that they may limit the need for stronger pain-relief medicine such as opioids. Opioids can cause unwanted (adverse) events such as nausea and vomiting, constipation, breathing problems and allergic reactions. People may become addicted to opioids if they take a lot of them.

NSAIDs can also cause unwanted effects. These include bleeding at the site of the surgical wound, and potential injury to the kidneys and gut. It is therefore important to weigh the benefits and risks of NSAIDs when considering using them to reduce pain shortly after surgery.

What did we want to find out?

We wanted to find out about the benefits and risks of using a specific NSAID, ketorolac, for relief of short-term pain after surgery. Ketorolac can be given as an injection, which may be useful when patients cannot take medicines by mouth.

What did we do?

We searched for studies that involved adults (aged over 18) and compared a single injection of ketorolac against:

· a placebo (dummy treatment); or
· another treatment.

We compared and summarized the results of the studies and rated our confidence in the evidence, based on factors such as study methods and sizes.

What did we find?

We found 12 studies that involved 1905 people in total. The studies investigated the treatment of pain after surgery on the abdomen, pelvis, teeth, bones, joints and muscles. Most studies (10) treated people with a dose of 30 milligrams of ketorolac. They compared ketorolac against:

· a placebo;
· another NSAID; or
· an opioid.

Here we present the findings from comparisons between ketorolac and placebo or other NSAIDs.

Pain reduction

The evidence suggests that:

· around three times more people may have their pain reduced by 50% (half) or more within six hours of surgery when treated with ketorolac rather than placebo; and
· there could be little to no difference between ketorolac and other NSAIDS in the number of people with pain reduced by 50% or more within four or six hours of surgery.

Need for extra pain medicines (rescue medication)

Ketorolac could delay the need for rescue medication compared to placebo or other NSAIDs. The evidence is not robust enough to show if fewer people need rescue medicine when treated with ketorolac.

Adverse effects

Ketorolac probably causes slightly more adverse effects than placebo and other NSAIDS. Serious adverse effects (such as blood collecting in the muscles around the abdomen, causing severe pain) were rare in the studies we found; the evidence suggested there may be little to no difference in the number of serious adverse events between ketorolac and placebo or other NSAIDS.

What are the limitations of the evidence?

Studies were small, and most may have been conducted in ways that could introduce errors into their results. This limited our confidence in the evidence.

How up to date is this evidence?

The evidence is up to date to April 2020.

Summary of findings 1. Intravenous ketorolac compared to placebo for adults with acute postoperative pain

Intravenous ketorolac compared to placebo for adults with acute postoperative pain

Patient or population: adults (mean study ages 23 to 67 years) with acute postoperative pain after abdominal/pelvic, dental or orthopedic surgeries
Settings: hospital or community
Intervention: intravenous ketorolac (30 mg or 60 mg)
Comparison: placebo

Outcomes	Probable outcome with:		Relative effect and NNTB or NNTH (95% CI)	No of Participants (studies)	Certainty of the evidence (GRADE)	Comments
	Placebo	Ketorolac				
Number of participants with at least 50% pain relief over 4 hours	**192 per 1000**	**586 per 1000** (463 to 741)	**RR 2.81** (1.80 to 4.37) **NNTB** 2.4 (1.8 to 3.7)	658 (8 studies)	⊕⊖⊖⊖ **very low** [a,b,c]	-
Number of participants with at least 50% pain relief over 6 hours	**231 per 1000**	**592 per 1000** (497 to 705)	**RR 3.26** (1.93 to 5.51) **NNTB** 2.5 (1.9 to 3.7)	914 (10 studies)	⊕⊕⊖⊖ **low** [a,b]	-
Median time to use of rescue medication	**104 minutes**	**271 minutes**	Not applicable	633 (6 studies)	⊕⊕⊕⊖ **moderate** [a,d,e]	-
Number of participants using rescue medication over 4 or 6 hours post-interventions	**830 per 1000**	**531 per 1000** (456 to 606)	**RR 0.60** (0.36 to 1.00)	417 (5 studies)	⊕⊖⊖⊖ **very low** [a,b,c]	-
Number of participants reporting any adverse event	**647 per 1000**	**705 per 1000** (647 to 770)	**RR 1.09** (1.00 to 1.19) **NNTH** 16.7 (8.3 to infinite)	810 (8 studies)	⊕⊕⊕⊖ **moderate** [a]	-
Number of participants experiencing a serious adverse event	**11 per 1000**	**7 per 1000** (1 to 33)	**RR 0.62** (0.13 to 3.03)	703 (8 studies)	⊕⊕⊖⊖ **low** [a,f]	Studies underpowered to detect these events

CI: confidence interval; **NNTB:** number needed to treat for an additional beneficial outcome; **NNTH:** number needed to treat for an additional harmful outcome; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded once for serious study limitations due to unclear risk of bias in several domains.
[b]Downgraded once for inconsistency due to unexplained heterogeneity ($I^2 > 50\%$).
[c]Downgraded once for imprecision due to total number of events < 300.
[d]Downgraded once for imprecision due to being unable to estimate confidence intervals because of reporting of median data.
[e]Upgraded once for large magnitude of effect: time to rescue > 3 times longer in ketorolac group.
[f]Downgraded once for imprecision due to very low event rate.

Summary of findings 2. Intravenous ketorolac compared to another NSAID for adults with acute postoperative pain

Intravenous ketorolac compared to another NSAID for adults with acute postoperative pain

Patient or population: adults (mean study ages 23 to 67 years) with acute postoperative pain after abdominal/pelvic, dental or orthopedic surgeries
Settings: hospital or community
Intervention: intravenous ketorolac (30 mg)
Comparison: another NSAID (parecoxib or diclofenac)

Outcomes	Probable outcome with:		Relative effect and NNTB or NNTH (95% CI)	No of Participants (studies)	Certainty of the evidence (GRADE)	Comments
	Other NSAID	Ketorolac				
Number of participants with at least 50% pain relief over 4 hours	**630 per 1000**	**656 per 1000** (561 to 763)	**RR 1.04** (0.89 to 1.21)	337 (4 studies)	⊕⊕⊖⊖ **low** [a,b]	-
Number of participants with at least 50% pain relief over 6 hours	**626 per 1000**	**663 per 1000** (595 to 745)	**RR 1.06** (0.95 to 1.19)	603 (6 studies)	⊕⊕⊕⊖ **moderate** [a]	-
Median time to use of rescue medication	**296 minutes**	**331 minutes**	Not applicable	427 (4 studies)	⊕⊕⊖⊖ **low** [a,c]	-
Number of participants using rescue medication over 4 or 6 hours post interventions	**515 per 1000**	**474 per 1000** (381 to 582)	**RR 0.90** (0.58 to 1.40)	260 (3 studies)	⊕⊖⊖⊖ **very low** [a,b,d]	-

Number of participants reporting any adverse event	**683 per 1000**	**759 per 1000** (683 to 841)	**RR 1.11** (1.00 to 1.23) **NNTH** 12.5 (6.7 to infinite)	516 (5 studies)	⊕⊕⊕⊖ **moderate** [a]	-
Number of participants experiencing a serious adverse event	**0 per 1000**	**0 per 1000** (0 to 0)	**RR 3.18** (0.13 to 76.99)	530 (5 studies)	⊕⊕⊖⊖ **low** [a,e]	Studies underpowered to detect these events.

CI: confidence interval; **NNTB:** number needed to treat for an additional beneficial outcome; **NNTH:** number needed to treat for an additional harmful outcome; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded once for serious study limitations due to unclear risk of bias in several domains.
[b]Downgraded once for imprecision due to total number of events < 300.
[c]Downgraded once for imprecision due to being unable to estimate confidence intervals because of reporting of median data.
[d]Downgraded once for inconsistency due to unexplained heterogeneity (I^2 > 50%).
[e]Downgraded once for imprecision due to very low event rate.

BACKGROUND

The methodology and several sections of the text in this review are derived from a series of reviews published in the Cochrane Library that assess single or combined analgesic agents for postoperative pain, and from suggested wording from the Pain, Palliative and Supportive Care Cochrane Review Group (PaPaS CRG) (Derry 2016).

Description of the condition

Evidence indicates that around 80% of people experience postoperative pain and that 75% of people report pain of moderate or greater severity (Gan 2014). Surgeries of the upper and lower extremities, thoracic, abdominal, and back/spinal column surgeries have been associated with higher levels of pain (Sommer 2008). Many people receive suboptimal perioperative analgesia, which affects quality of life, functioning, and time to recovery, and places them at risk for developing acute postsurgical complications and persistent postsurgical pain (Chou 2016; Gan 2014). Populations at increased risk for inadequate treatment of perioperative pain include children, minorities, the elderly, and those with substance-use disorders (Anderson 2009; Brasher 2014; Chou 2016).

This review was based on a series of reviews published in the Cochrane Library. Cochrane's aim is to increase awareness of the range of analgesics that are potentially available, and present evidence for relative analgesic efficacy through indirect comparisons with placebo, in very similar trials performed in a standard manner, with very similar outcomes, and over the same duration. Such relative analgesic efficacy does not in itself determine choice of drug for any situation or person, but guides policy-making at the local level. The series covers all analgesics licensed for acute postoperative pain in the UK, and dipyrone, which is commonly used in Spain, Portugal, and Latin-American countries. The results have been examined in overviews of efficacy and harm (Moore 2015a; Moore 2015b), and related individual reviews include ibuprofen (Derry 2009), paracetamol (acetaminophen) (Toms 2008), ketoprofen and dexketoprofen (Gaskell 2017), codeine (Derry 2010), and combinations such as ibuprofen plus paracetamol (Derry 2013), ibuprofen plus codeine (Derry 2015), and paracetamol plus codeine (Toms 2009).

Description of the intervention

Acute pain trials

Single-dose trials in acute pain are commonly short in duration, rarely lasting longer than 12 hours. The numbers of participants are normally small, allowing no reliable conclusions to be drawn about safety. To show that the analgesic is working, it is necessary to compare the drug to a placebo control (McQuay 2005). There are clear ethical considerations in doing this. These ethical considerations are addressed by using acute pain situations where the pain is expected to go away, and by providing additional analgesia, commonly called rescue analgesia, if the pain has not diminished after about one hour. This is reasonable, because not all participants given an analgesic will have significant pain relief. Approximately 18% of participants given placebo will have significant pain relief (Moore 2006), and up to 50% may have inadequate analgesia with active medicines (Moore 2015b). Hence, the use of additional or rescue analgesia is important for all participants in the trials.

Clinical trials measuring the efficacy of analgesics in acute pain have been standardized over many years (McQuay 2012). Trials have to be randomized and double-blind. Typically, in the first few hours or days after an operation, people develop pain that is moderate to severe in intensity, and will then be given the test analgesic or placebo. Pain is measured using standard pain intensity scales immediately before the intervention, and then using pain intensity and pain relief scales over the following four to six hours for shorter-acting drugs, and up to 12 or 24 hours for longer-acting drugs. Pain relief of half the maximum possible pain relief or better (at least 50% pain relief) is typically regarded as a clinically useful outcome (Moore 2011). For people given rescue medication, it is usual for no additional pain measurements to be made, and for all subsequent measures to be recorded as initial pain intensity or baseline (zero) pain relief (baseline observation carried forward (BOCF)). This process ensures that analgesia from the rescue medication is not wrongly ascribed to the test intervention. In some trials, the last observation is carried forward (LOCF), which gives an inflated response for the test intervention compared to placebo, but the effect has been shown to be negligible over four to six hours (Moore 2005). People usually remain in the hospital or clinic for at least the first six hours following the intervention, with measurements supervised, although they may then be allowed home to make their own measurements in trials of longer duration. Knowing the relative efficacy of different analgesic drugs at various doses can be helpful (Moore 2015a).

Recommendations for non-steroidal anti-inflammatory drug use in postoperative guidelines

Treatment guidelines for acute pain developed by major professional organizations recommend a multimodal approach to analgesia, which routinely includes administration of both an opioid and one or more non-opioids, the latter of which frequently includes a non-steroidal anti-inflammatory drug (NSAID) or acetaminophen or both (Chou 2016; Schug 2020). Postoperative administration of NSAIDs has been shown to reduce patient requirements for opioids and, in turn, to reduce the incidence and severity of opioid-induced adverse events (AEs); however, NSAIDs do not typically offer adequate relief of severe pain when administered as a sole analgesic agent (Cepeda 2005).

Parenteral ketorolac

Parenteral analgesics may be required postoperatively if people are unable to tolerate oral medications. Until 2009, the only NSAID approved for intravenous (IV) administration for postoperative pain in the USA and many other countries was ketorolac. Ketorolac, an acetic acid derivative, can be administered by mouth, intranasally, or parenterally as either an IV or intramuscular (IM) injection (Lexicomp 2018). The IM route is not preferred, as drug absorption may be unreliable and the injection itself may be painful (Schug 2020). It is a potent analgesic but has only moderate anti-inflammatory properties (Grosser 2018). It has a rapid onset (30 to 60 minutes) and short duration of action (half-life of four to six hours). Typical IV doses are 15 mg or 30 mg every six hours, with 15 mg recommended in people over the age of 65 years. While oral bioavailability is estimated at 100%, oral administration in the postoperative setting is generally reserved for continuation of therapy initiated with IM or IV ketorolac. Recommended maximum duration of therapy varies by country, but a combined therapy

duration (oral and parenteral) of five days should not be exceeded (Lexicomp 2018).

Parenteral ketorolac has efficacy in reducing pain and opioid requirements (Cepeda 2005). Common AEs of systemic administration include somnolence, dizziness, headache, gastrointestinal (GI) pain, dyspepsia, nausea, and pain at the site of injection (Grosser 2018). Its acute safety profile includes increased risk of GI and operative-site bleeding and renal events, particularly with use beyond five days and in at-risk populations (such as older people) (Feldman 1997; Strom 1996). Although clinical evidence is lacking, concern for altered bone and ligament healing may also cause providers to avoid the use of ketorolac postoperatively (Harder 2003; Marquez-Lara 2016).

How the intervention might work

NSAIDs inhibit cyclo-oxygenase (COX) isoenzymes, thereby reducing the formation of prostaglandins that are responsible for pain and inflammation at a site of injury or disease (FitzGerald 2001). In addition to their peripheral effects, NSAIDs act in the spinal cord and central nervous system (CNS) to reduce pain even when inflammation is not present. They also act on inflammatory pathways other than those involving COX. Inhibition of COX may also play a role in the AE profile of NSAIDs. NSAIDs account for more reports of drug toxicity than any other agents (Hawkey 2002). Risk factors for toxicity include dose, duration of therapy, patient age, and pre-existing renal impairment. At least two forms of COX are expressed in tissues: COX-1 is responsible for the production of prostaglandins that play a predominately protective role in the GI tract, vascular system, and kidneys, and for the production of thromboxane A2, responsible for platelet aggregation and vasoconstriction (FitzGerald 2004). COX-2 is expressed constitutively in the vasculature, CNS, and kidneys, but in other organs it is induced after trauma (including surgery) and inflammation. Inhibition of the production of protective prostaglandins and thromboxane A2 may lead to GI, hematological, cardiovascular, and renal AEs. Postoperative patients are at greater risk of developing NSAID-induced acute kidney injury as they may be volume-depleted, as are older people, who rely on prostaglandins to maintain renal function. NSAIDs that selectively inhibit the COX-1 isoenzyme, such as ketorolac, may increase the incidence of GI bleeding and interfere more with platelet aggregation in comparison to NSAIDs that are selective for COX-2 or that have a balanced COX-1/COX-2 profile (FitzGerald 2001; FitzGerald 2004). Conversely, NSAIDs that are selective for COX-2 may confer an increased risk of cardiovascular events versus COX-1 selective agents. NSAIDs may also occasionally produce liver damage, particularly with long-term use (APS 2008).

Why it is important to do this review

Increasing concerns about the risks of excessive opioid use in the postoperative setting, and in particular the risk of people developing opioid use disorder, has led to greater emphasis on the importance of multimodal strategies that reduce opioid requirements (Chou 2016). NSAIDs are considered an integral part of a multimodal analgesic regimen, despite their unfavorable safety profile.

The approval of parenteral formulations of ibuprofen and diclofenac has expanded the menu of NSAIDs for treating postoperative pain in people who require IV analgesia (Bookstaver 2010; Daniels 2016; Scott 2012). Both NSAIDs are the subject of separate Cochrane Reviews (Ferguson 2018; McNicol 2018). Because of their balanced COX-1/COX-2 profile, they may be safer (although more expensive) options than ketorolac in this setting. It is therefore important to assess the risk:benefit profile of these individual agents.

The target audiences for this review include: perioperative caregivers who make decisions about postoperative pain management; and affected patients who wish to find information about the effectiveness and risks of a specific postoperative pain medication. We anticipate that the information from our review will be disseminated through respective publishing journals and medical literature databases.

OBJECTIVES

To assess the analgesic efficacy and adverse effects of single-dose intravenous ketorolac, compared with placebo or an active comparator, for moderate to severe postoperative pain in adults.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomized controlled trials (RCTs), with at least 10 participants randomly allocated to each treatment group. We only include trials that conducted a double-blind assessment of participant outcomes. We include multiple-dose studies if appropriate data from the first dose were available, and cross-over studies provided that data from the first phase were presented separately or could be obtained.

We exclude:

- non-randomized studies;
- review articles, case reports, and clinical observations;
- studies of experimental pain;
- studies of less than four hours' duration or studies that did not present data over four- to six-hours post-dose;
- studies where ketorolac was administered preoperatively or intraoperatively;
- studies where pain was not participant-reported.

For postpartum pain, we include studies if the pain investigated was due to episiotomy or caesarean section irrespective of the presence of uterine cramps; we exclude studies investigating pain due to uterine cramps alone.

We required full journal publication, with the exception of online clinical trial results, summaries of otherwise unpublished clinical trials, and abstracts with sufficient information to assess eligibility and sufficient data for analysis. For an abstract with insufficient data, we assumed that if the study was valid, the investigators would publish its data in full within three years. If not, we excluded without attempting to contact authors.

Types of participants

We included studies of adults (aged 18 years and above) with established postoperative pain of moderate-to-severe intensity following day surgery or inpatient surgery. For studies using a visual

analogue scale (VAS) (see Glossary: Appendix 1), we considered that pain intensity of more than 30 mm equates to pain of at least moderate intensity (Collins 1997). We excluded studies that included participants with mild pain, unless they presented data for those with moderate-to-severe pain separately.

Types of interventions

We included trials that delivered ketorolac, administered as a single IV dose, for the relief of acute postoperative pain, and compared to placebo or any active comparator.

Types of outcome measures

Primary outcomes

- Number of participants achieving at least 50% pain relief over a four-hour period and over a six-hour period.

Secondary outcomes

- Median or mean time to use of rescue medication.
- Number of participants using rescue medication over a four- or six-hour period.
- Withdrawals due to lack of efficacy, AEs, and for any cause.
- Participants reporting or experiencing any AE.
- Participants experiencing any serious adverse event (SAE). SAEs typically include any untoward medical occurrence or effect that at any dose results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, is a congenital anomaly or birth defect, is an 'important medical event' that may jeopardize the patient, or may require an intervention to prevent one of the above characteristics or consequences.
- Specific AEs associated with parenteral NSAIDs, that is, renal dysfunction, cardiovascular events, GI or operative site bleeding, and thrombophlebitis.
- Specific AEs associated with opioids. A reduction in opioid requirements with an effective analgesic may, in turn, reduce the incidence of opioid-induced AEs. We assessed the following opioid-related AEs: nausea, vomiting, nausea and vomiting, pruritus, respiratory depression, sedation, urinary retention, and allergic reaction/rashes.

Search methods for identification of studies

Electronic searches

We searched the following databases without language restrictions or restrictions on the time period covered.

- The Cochrane Central Register of Controlled Trials (CENTRAL), Issue 4 of 12, 2020, in the Cochrane Library.
- MEDLINE (via Ovid) 1946 to April 17th 2020.
- Embase (via Ovid) 1980 to 2020 week 16.
- LILACS (Bireme) to April 2020.

We used medical subject headings (MeSH) or equivalent and text word terms. We tailored searches to individual databases. The search strategies used can be found in Appendix 2.

Searching other resources

We searched www.clinicaltrials.gov and the World Health Organization International Clinical Trials Registry Platform (ICTRP) (apps.who.int/trialsearch/) for ongoing trials. In addition, we checked reference lists of reviews and retrieved articles for additional studies, and we performed citation searches on key articles. We contacted experts in the field for unpublished and ongoing trials. We contacted study authors for additional information where necessary. If a published protocol was not available, we did not contact study authors if the outcomes listed in their Methods section were those that we would expect from similar studies and if these outcomes were reported in full in the Results section.

Data collection and analysis

Selection of studies

Two review authors (a combination of EM, MF, and RS) independently determined eligibility by reading the abstract of each study identified by the search. Independent review authors eliminated studies that clearly did not satisfy inclusion criteria, and obtained full copies of the remaining studies. Two review authors (a combination of EM, MF, and RS) independently read and selected studies, and, in the event of disagreement, the third review author adjudicated. We did not anonymize the studies before assessment.

We include a PRISMA flow chart in the full review, which shows the status of identified studies (Moher 2009), as recommended in Section 11.2.1 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2021). We included studies in the review irrespective of whether measured outcome data were reported in a 'usable' way.

Data extraction and management

Two review authors (a combination of EM, MF, and RS) independently extracted data using a previously-piloted standard form and checked for agreement before entry into Review Manager 5 (Review Manager 2020). In the event of disagreement, the third review author adjudicated. We extracted the following information:

- study methods;
- study population;
- interventions;
- pain intensity scale used and baseline pain intensity;
- outcomes of interest. We extracted efficacy outcomes for the six hours post-administration of interventions. We extracted safety outcomes for the duration of the study.

We collated multiple reports of the same study, so that each study, rather than each report, was the unit of interest in the review. We collected information about the included studies in sufficient detail to complete a 'Characteristics of included studies' table.

Assessment of risk of bias in included studies

Two review authors (a combination of EM, MF, and RS) independently assessed risks of bias for each study, using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Chapter 8, Higgins 2011), and, in the event of disagreement, the third review author adjudicated. We completed a risk of bias table for each included study using the risk of bias tool in Review Manager 5 (Review Manager 2020).

We assessed the following for each study.

- Random sequence generation (checking for possible selection bias). We assessed the method used to generate the allocation sequence as: low risk of bias (any truly random process, e.g. random-number table; computer random-number generator); unclear risk of bias (method used to generate sequence not clearly stated). We excluded studies using a non-random process (e.g. odd or even date of birth; hospital or clinic record number).
- Allocation concealment (checking for possible selection bias). The method used to conceal allocation to interventions prior to assignment determines whether intervention allocation could have been foreseen in advance of or during recruitment, or changed after assignment. We assessed the methods as: low risk of bias (e.g. telephone or central randomization; consecutively-numbered sealed opaque envelopes); unclear risk of bias (method not clearly stated). We excluded studies that did not conceal allocation (e.g. open list).
- Blinding of participants and personnel (checking for possible performance bias). We assessed the methods used to blind study participants and personnel from knowledge of which intervention a participant received. We assessed methods as: low risk of bias (study stated that it was blinded and described the method used to achieve blinding, such as identical tablets matched in appearance or smell, or a double-dummy technique); unclear risk of bias (study stated that it was blinded but did not provide an adequate description of how it was achieved). We excluded studies that were not double-blind.
- Blinding of outcome assessment (checking for possible detection bias). In this review, pain-related outcomes were self-assessed, so that the same considerations apply to detection bias as performance bias.
- Incomplete outcome data (checking for possible attrition bias due to the amount, nature, and handling of incomplete outcome data). We assessed the methods used to deal with incomplete data as: low risk (fewer than 10% of participants did not complete the study or the study used intention-to-treat (ITT) analysis and imputed missing data using BOCF, or both); unclear risk of bias (used ITT analysis and imputed missing data using LOCF or did not describe methods of imputation); high risk of bias (used only 'completer' analysis).
- Selective reporting (checking for reporting bias). We assessed whether primary and secondary outcome measures were prespecified and whether these were consistent with those reported. We assessed reporting of results as having low risk of bias (e.g. the study protocol was available and all the study's prespecified outcomes of interest in the review were reported in the prespecified way; the study protocol was not available but it was clear that published reports included all expected outcomes, including those that were prespecified); high risk of bias (e.g. not all of the study's prespecified primary outcomes were reported; one or more primary outcomes were reported using measurements, analysis methods or subsets of data that were not prespecified); or unclear risk of bias (information insufficient to permit judgment of 'low risk' or 'high risk').
- Size of study (checking for possible biases confounded by small size). We assessed studies as being at low risk of bias (200 participants or more per treatment arm); unclear risk of bias (50 to 199 participants per treatment arm); high risk of bias (fewer than 50 participants per treatment arm).

Measures of treatment effect

We used the risk ratio (RR) to establish statistical difference, and the number needed to treat for an additional beneficial outcome (NNTB) with 95% confidence intervals (CIs), and pooled percentages as absolute measures of effect.

We used the following terms to describe adverse outcomes in terms of harm or prevention of harm.

- When fewer adverse outcomes occurred with treatment than with control (placebo or active), we used the term 'number needed to treat to prevent one additional harmful event' (NNTp).
- When more adverse outcomes occurred with treatment compared with control (placebo or active), we used the term 'number needed for one additional harmful event' (NNTH).

Unit of analysis issues

We accepted only randomization of individual participants. If two or more active treatment arms were compared with a placebo arm within the same meta-analysis, we avoided double-counting of participants in the placebo arm by splitting the total number between the active arms. If we identified multiple-dose studies, we used data for the most commonly-used dose only; and for cross-over studies, we used only data from the first treatment phase.

Dealing with missing data

One issue with missing data in these studies was from imputation using LOCF when a participant requests rescue medication. It has been shown that this does not affect results for up to six hours after taking study medication (Moore 2005). Where large amounts of data were missing, we reported this in our review and assessed such results with caution. We consulted the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2021) for guidance. Where papers reported results using more than one method of imputation, we analyzed data using the primary method reported and performed sensitivity analysis by entering data from secondary methods. We also attempted to assess differences between intervention groups in reasons for missing data and how these differences might bias results.

Assessment of heterogeneity

We assessed statistical heterogeneity by visually examining forest plots and quantified it using the I^2 statistic. The I^2 statistic is a reliable and robust test to quantify heterogeneity, since it does not depend on the number of trials or on the between-study variance. The I^2 statistic measures the extent of inconsistency among studies' results, and can be interpreted as the proportion of total variation in study estimates that is due to heterogeneity rather than sampling error. An I^2 value of greater than 50% is considered to indicate substantial heterogeneity (Deeks 2021). If heterogeneity was high (I^2 greater than 50%), we looked for possible causes including the influence of small studies.

Assessment of reporting biases

To assess the impact of reporting bias, we considered the number of additional participants needed in studies with zero effect (relative benefit of one) required to change the number needed to treat (NNT) for all statistically significant outcomes to an unacceptably high level (in this case the arbitrary NNT of 10) (Moore 2008). Where this number was fewer than 400 (equivalent to four studies with

100 participants per comparison, or 50 participants per group), we considered the results to be susceptible to publication bias and therefore unreliable (low-certainty evidence).

We also attempted to mitigate the potential for publication bias by searching clinical trial websites, and by contacting the manufacturers of parenteral ketorolac for an internal reference list of completed studies (see Searching other resources).

Data synthesis

For efficacy analyses, we used the number of participants in each treatment group who were randomized, received medication, and provided at least one post-baseline assessment. For safety analyses, we used the number of participants randomized to each treatment group who took the study medication.

For the primary outcome (number of participants achieving at least 50% pain relief over a four- to six-hour period), if numbers were not reported directly, we converted the mean total pain relief (TOTPAR), or summed pain intensity difference (SPID), VAS TOTPAR, or VAS SPID (see Glossary: Appendix 1) values for the active and placebo groups in each study to a percentage of maximum TOTPAR or a percentage of maximum SPID by division into the calculated maximum value (Cooper 1991). We then calculated the proportion of participants in each treatment group who achieved at least 50% maximum TOTPAR using verified equations (Moore 1996; Moore 1997a; Moore 1997b), and converted these proportions into the number of participants achieving at least 50% maximum TOTPAR by multiplying by the total number of participants in the treatment group. We used this information on the number of participants with at least 50% maximum TOTPAR for active and placebo groups to calculate RR and NNT.

We accepted the following pain measures for the calculation of TOTPAR or SPID (in order of priority: see Appendix 1):

- 5-point categorical pain relief scales with comparable wording to 'none', 'slight', 'moderate', 'good', and 'complete';
- 4-point categorical pain intensity scales with comparable wording to 'none', 'mild', 'moderate', and 'severe';
- VAS for pain relief;
- VAS for pain intensity.

If none of these measures were available, we planned to use the number of participants reporting 'very good or excellent' on a 5-point categorical global scale with the wording 'poor', 'fair', 'good', 'very good', and 'excellent' for the number of participants achieving at least 50% pain relief (Collins 2001).

For dichotomous outcomes, we calculated RR estimates with 95% CIs using the Mantel-Haenszel method in Review Manager 5 and RevMan Web (Review Manager 2020; RevMan Web 2021). We calculated NNTB and NNTH with 95% CIs using the pooled number of events and the method of Cook and Sackett (Cook 1995). We assumed a statistically significant difference from control when the 95% CI of the RR did not include the number one.

For the continuous outcome of time to rescue medication, we intended to pool mean scores using the inverse variance method in Review Manager 5 and RevMan Web (Review Manager 2020; RevMan Web 2021). However, the data were only available as medians in the relevant studies, so instead we calculated the mean of these medians and presented the analysis as such.

We used a fixed-effect model for all initial meta-analyses. If a meta-analysis had an I^2 score of greater than 50%, we reanalyzed data using a random-effects model and presented the analysis using this model (Deeks 2021, see Sensitivity analysis).

Subgroup analysis and investigation of heterogeneity

We analyzed different doses (15 mg, 30 mg, and 60 mg) separately, if there were sufficient data. We also planned to analyze different surgeries if there were sufficient data, as postoperative pain levels and analgesic efficacy may differ (Sommer 2008). We planned to use the Z test to explore whether there were differences between subgroups (Tramèr 1997), if appropriate.

Sensitivity analysis

For meta-analyses with an I^2 score greater than 50%, we reanalyzed data using a random-effects model. We preferentially present the data for these re-analyses within the Effects of interventions section rather than presenting them initially as fixed-effect analyses.

Summary of findings and assessment of the certainty of the evidence

Two review authors (EM, MF) independently rated the certainty of the evidence for each outcome. We used the GRADE system to rank the certainty of the evidence using GRADEprofiler Guideline Development Tool software (GRADEpro GDT 2015), and the guidelines provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2021). We reported our judgment on the certainty of evidence in the summary of findings tables.

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

- High: we are very confident that the true effect lies close to that of the estimate of the effect.
- Moderate: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different.
- Low: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
- Very low: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

The GRADE system uses the following criteria for assigning a certainty level to a body of evidence (Schünemann 2021).

- High: randomized trials; or double upgraded observational studies.
- Moderate: downgraded randomized trials; or upgraded observational studies.
- Low: double-downgraded randomized trials; or observational studies.

- Very low: triple-downgraded randomized trials; or downgraded observational studies; or case series/case reports.

Factors that may decrease the certainty level of a body of evidence are:

- limitations in the design and implementation of available studies suggesting high likelihood of bias;
- indirectness of evidence (indirect population, intervention, control, outcomes);
- unexplained heterogeneity or inconsistency of results (including problems with subgroup analyses);
- imprecision of results (wide CIs);
- high probability of publication bias.

Factors that may increase the certainty level of a body of evidence are:

- large magnitude of effect;
- all plausible confounding would reduce a demonstrated effect or suggest a spurious effect when results show no effect;
- dose–response gradient.

We decreased the grade rating by one (–1) or two (–2) (up to a maximum of –3 to 'very low') if we identified:

- serious (−1) or very serious (−2) limitation to study certainty;
- important inconsistency (−1);
- some (−1) or major (−2) uncertainty about directness;
- imprecise or sparse data (−1);
- high probability of reporting bias (−1).

We paid particular attention to:

- inconsistency, where point estimates varied widely across studies or CIs of studies showed minimal or no overlap (Guyatt 2011);
- potential for publication bias, based on the amount of unpublished data required to make the result clinically irrelevant (Moore 2008).

In addition, there may be circumstances where the overall rating for a particular outcome needs to be adjusted as recommended by GRADE guidelines (Guyatt 2013a). For example, if there were so few data that the results are highly susceptible to the random play of chance, or if studies used LOCF imputation in circumstances where there were substantial differences in AE withdrawals, one would have no confidence in the result, and would need to downgrade the certainty of the evidence by three levels, to very low certainty. In circumstances where there were no data reported for an outcome, we reported the level of evidence as very low certainty (Guyatt 2013b).

Summary of findings tables

We include two summary of findings tables to present the main findings for comparisons with placebo and with an active comparator (another NSAID), in a transparent and simple tabular format. In particular, we included key information about the certainty of the evidence (using GRADE), the magnitude of effect of the interventions examined, and the sum of available data on the following outcomes:

- number of participants achieving at least 50% pain relief over a four-hour period and over a six-hour period;
- median or mean time to use of rescue medication;
- number of participants using rescue medication over a four- or six-hour period;
- participants reporting any AE;
- participants experiencing any SAE.

RESULTS

Description of studies

See Characteristics of included studies; Characteristics of excluded studies; Characteristics of studies awaiting classification; and Characteristics of ongoing studies tables.

Results of the search

Our literature search yielded 1499 references from CENTRAL, 1011 references from MEDLINE, 1528 references from Embase, and 6 from LILACS (a total of 2484 after de-duplication). We reviewed the abstracts associated with these references and identified 100 potentially relevant studies, determining that the remaining references clearly did not meet our inclusion criteria. After full-text review, we excluded 81 studies that did not meet our inclusion criteria. Our search of clinical trial websites yielded 70 ongoing or completed trials from ClinicalTrials.gov and 531 studies from the WHO ICTRP. From these, we found no studies in addition to those already identified from our database searches (Figure 1).

Figure 1. Study flow diagram.

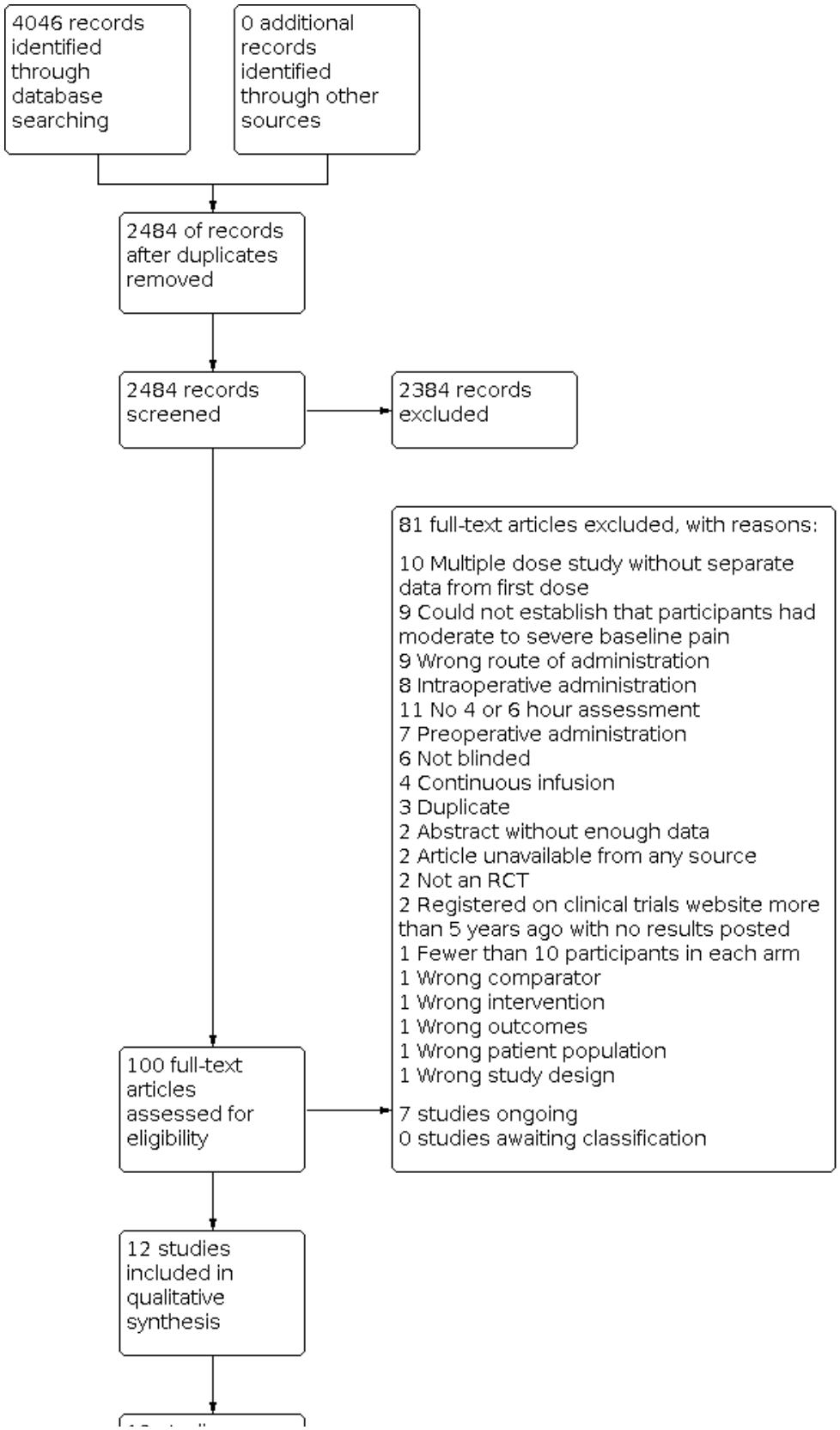
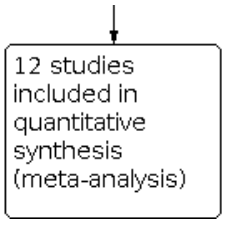


Figure 1. (Continued)



Included studies

Twelve studies fulfilled our inclusion criteria (Balestrieri 1997; Barton 2002; Bikhazi 2004; Christensen 2011; Gan 2012; Gonzalez 1994; Mehlisch 2003; Moodie 2013; Parke 1995; Rasmussen 2002; Romundstad 2004; Zhou 2001). All but one study (Gonzalez 1994) compared ketorolac with placebo. Six studies used another NSAID arm (Barton 2002; Bikhazi 2004; Christensen 2011; Gan 2012; Mehlisch 2003; Rasmussen 2002) and four included an opioid arm (Barton 2002; Bikhazi 2004; Gonzalez 1994; Rasmussen 2002).

Eight trials were conducted in the USA (Balestrieri 1997; Barton 2002; Bikhazi 2004; Christensen 2011; Gan 2012; Mehlisch 2003; Rasmussen 2002; Zhou 2001), one in Mexico (Gonzalez 1994), one in New Zealand (Moodie 2013), one in England (Parke 1995) and one in Norway (Romundstad 2004). Total enrollment ranged from 53 to 353 participants, with the number of participants in each study receiving ketorolac ranging from 17 to 83, placebo 25 to 82, another NSAID 29 to 255 and an opioid 40 to 60. Where reported, mean study population ages ranged from 22.5 years (Mehlisch 2003), to 67.4 years, (Rasmussen 2002), with most studies having mean ages between 40 and 45 years. The ages of participants generally reflected the type of surgical procedure; for example Mehlisch 2003 using a dental model enrolled younger participants, whereas orthopedic procedures enrolled older participants. Two studies enrolled participants undergoing dental surgery (third molar extraction; Christensen 2011; Mehlisch 2003); five studies enrolled participants undergoing abdominal/pelvic surgeries (Balestrieri 1997; Barton 2002; Bikhazi 2004; Gan 2012; Gonzalez 1994); and five studies assessed participants undergoing orthopedic procedures (Moodie 2013; Parke 1995; Rasmussen 2002; Romundstad 2004; Zhou 2001).

Nine studies were funded in part or entirely by the manufacturers of one of the interventions; one study was funded by a grant (Zhou 2001). Two studies did not report funding (Gonzalez 1994; Romundstad 2004).

Study designs were similar: participants received one of the assigned interventions after reporting moderate-to-severe pain postoperatively, and outcomes such as pain relief, pain intensity difference, or time to use of rescue medication were assessed. The exception was Balestrieri 1997, where participants were scheduled to receive interventions regardless of report of postoperative pain. In this study participants in both groups had mean categorical pain intensity of 2.3 at baseline (2 = moderate).

In most studies the dose of ketorolac administered was 30 mg. Balestrieri 1997 administered 60 mg and Zhou 2001 administered both 15 and 30 mg doses.

Ongoing studies

Seven trials were ongoing at the time of completion of our review. One study published its protocol in a medical journal (Claus 2019). The other studies are available on clinical trial websites (Irct201607271674N 2016; Irct2017041033350N 2017; Irct20171003036530N 2018; Irct20180909040979N 2019; NCT02700451; NCT03823534). Claus 2019 is primarily a safety trial. Its primary outcome is to demonstrate that the use of ketorolac does not decrease thoracolumbar spinal fusion rates postoperatively. It intends to enroll at least 300 participants in each arm (ketorolac or placebo). The remaining six are efficacy studies with targeted enrollments ranging from 60 to 300 participants and primary outcomes assessing pain intensity and opioid use. Ketorolac doses range from 15 mg in participants over 65 years to 30 mg in younger participants. In addition to orthopedic and abdominal populations (Irct201607271674N 2016; Irct2017041033350N 2017; Irct20171003036530N 2018; NCT02700451; NCT03823534), pain after coronary artery bypass graft (Irct20180909040979N 2019) will also be assessed.

Excluded studies

Eighty-one studies did not meet all of our inclusion criteria (Figure 1). Common reasons included multiple-dose studies that did not present data from the first dose separately, studies where we could not establish that all participants had moderate-to-severe pain at baseline, and studies with ineligible route or timing of administration. We excluded two trials posted on clinical trial websites as they had started enrolling participants more than five years ago, but had still not posted results (NCT00293631; NCT00845754). We excluded two studies as the corresponding publication was not available from any source (Brown 1988; Hegazy 2003).

Risk of bias in included studies

Our findings are summarized in Figure 2 and Figure 3.

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

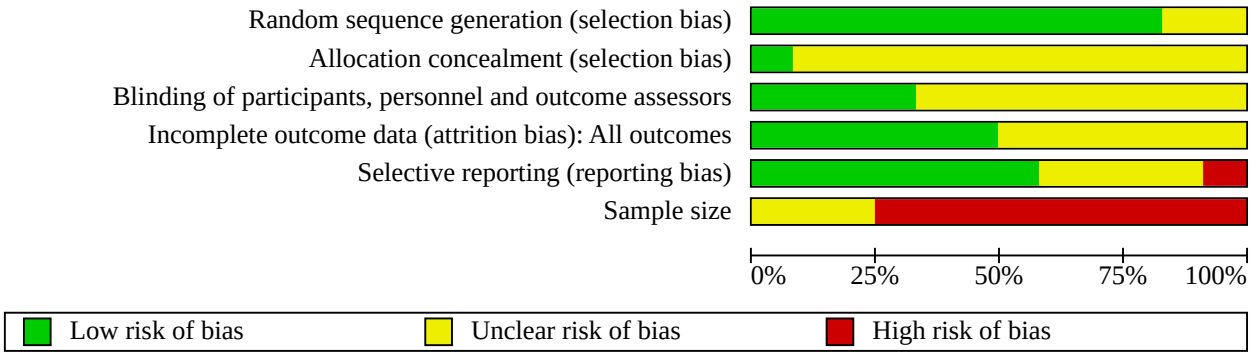
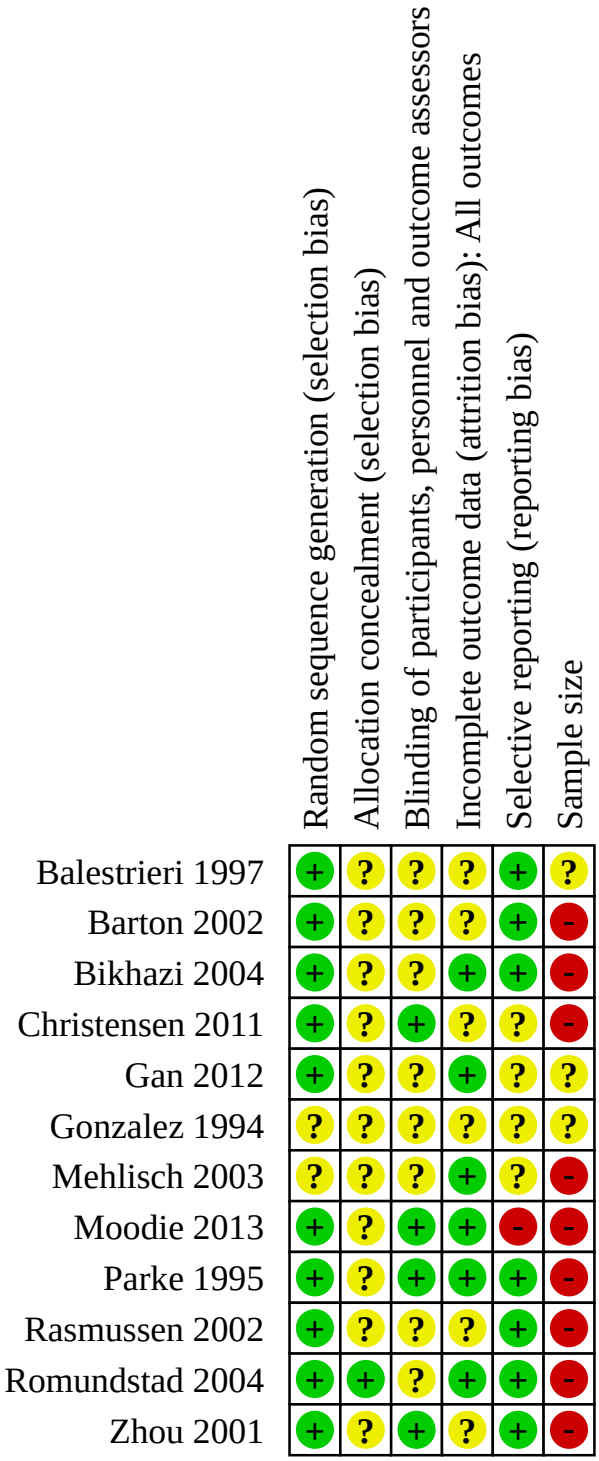


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Random sequence generation

All studies reported that they were randomized, and all but two described adequate methods of randomization, that is by computer-generated numbers or a table of random numbers. Gonzalez 1994 and Mehlisch 2003 offered no description of how randomization was performed.

Allocation concealment

Only one study described adequate allocation concealment (Romundstad 2004). Participants in this study were assigned according to information in opaque envelopes marked with consecutive patient numbers only. In the remaining articles, allocation concealment was not mentioned.

Blinding

Four studies described adequate methods of blinding both investigators and participants (Christensen 2011; Moodie 2013; Parke 1995; Zhou 2001). Although none of the articles explicitly stated that the interventions were indistinguishable from each other, methods used to ensure blinding were described in sufficient detail (e.g. double-dummy technique) for us to believe that neither the investigator nor the study participant would have been able to discriminate interventions based on their appearance. We assessed the remaining studies as having an unclear risk of bias, either because they did not describe methods of blinding in any way, because their descriptions were inadequate for us to determine whether investigators or participants would have been able to distinguish interventions, or because they only described how participants were blinded. One study (Romundstad 2004) appeared to have used adequate methods to blind participants and investigators, but most were able to guess if they had received or administered, respectively, an active or placebo intervention.

Incomplete outcome data

We assessed six studies as having a low risk (Bikhazi 2004; Gan 2012; Mehlisch 2003; Moodie 2013; Parke 1995; Romundstad 2004), and the remaining six studies as having an unclear risk of attrition bias. For the former, ITT analyses were used or all participants completed the study, or both. Missing data were appropriately imputed. For the latter, this was primarily because they did not describe how missing data were imputed. Gonzalez 1994 did not present AE data separately for each intervention group. Withdrawal rates were generally low across studies.

Selective reporting

Seven of the 12 studies had a low risk of reporting bias. While published protocols were generally not available for these studies, all outcomes listed in their Methods section were those that we would expect from similar studies and were reported in full in the Results section. We assessed one study as having a high risk of bias. In Moodie 2013, secondary outcomes assessed were inconsistent between the published protocol and study report. We assessed the remaining four studies as having unclear risk of bias, mostly due to incomplete reporting of secondary outcomes, such as only displaying some results graphically.

Other potential sources of bias

The major threat to reliability was the small size of the studies. Only three studies enrolled at least 50 participants in each arm and we assessed these as having an unclear risk of bias due to sample size (Balestrieri 1997; Gan 2012; Gonzalez 1994). The highest number of participants in a single ketorolac group was 83 in Balestrieri 1997. The remaining studies had fewer than 50 participants in at least one arm of the study, with Moodie 2013 administering ketorolac to only 17 participants. We assessed these studies as having a high risk of bias.

Effects of interventions

See: **Summary of findings 1** Intravenous ketorolac compared to placebo for adults with acute postoperative pain; **Summary of findings 2** Intravenous ketorolac compared to another NSAID for adults with acute postoperative pain

See Summary of findings 1 for outcomes for the main comparison, ketorolac versus placebo, and Summary of findings 2 for the comparison of ketorolac versus another NSAID. All 12 included studies provided usable data for analysis. However, we did not use all data in meta-analysis, either because there was only one study for a given outcome, or there were too few participants or events for a given outcome.

1. Ketorolac versus placebo

Proportion of participants achieving at least 50% postoperative pain relief over a four-hour period and over a six-hour period

Only two studies reported numbers of participants achieving this outcome directly, and only over the six-hour time period (Gan 2012; Romundstad 2004). Gan 2012 reported the number of participants achieving at least 30% pain relief; we used this as a surrogate value. For the remaining studies we derived numbers, using the equations described earlier (Data synthesis) from tables or figures. Eight studies (658 participants) compared ketorolac 30 mg (Barton 2002; Bikhazi 2004; Mehlisch 2003; Moodie 2013; Rasmussen 2002; Romundstad 2004; Zhou 2001) or 60 mg (Balestrieri 1997) versus placebo over four hours post-administration of interventions.

- The proportion of participants with at least 50% pain relief with ketorolac was 57% (177/309, range 35% to 82%).
- The proportion of participants with at least 50% pain relief with placebo was 19% (67/349, range 0 to 39%).
- The relative benefit of treatment compared with placebo was 2.81 (95% confidence interval (CI) 1.80 to 4.37); the number needed to treat for an additional beneficial outcome (NNTB) for one additional participant to benefit compared with placebo was 2.4 (95% CI 1.8 to 3.7) (Analysis 1.1).

Ten studies (914 participants) compared ketorolac 30 mg (Barton 2002; Bikhazi 2004; Christensen 2011; Gan 2012; Mehlisch 2003; Moodie 2013; Rasmussen 2002; Romundstad 2004; Zhou 2001), or 60 mg (Balestrieri 1997), versus placebo over six hours post-administration of interventions.

- The proportion of participants with at least 50% pain relief with ketorolac was 61% (266/438, range 36% to 77%).
- The proportion of participants with at least 50% pain relief with placebo was 23% (110/476, range 0 to 55%).

- The relative benefit of treatment compared with placebo was 3.26 (95% CI 1.93 to 5.51); the NNTB for one additional participant to benefit compared with placebo was 2.5 (95% CI 1.9 to 3.7) (Analysis 1.2).

We assessed the certainty of evidence for this outcome as very low over four hours, and low over six hours. We downgraded certainty over four hours based on unclear risk of bias for several domains among the included studies (study limitations), unexplained heterogeneity among studies (important inconsistency), and a low total number of participants in the analysis (imprecision). We downgraded certainty over six hours due to unclear risk of bias for several domains among the included studies (study limitations) and unexplained heterogeneity among studies.

Time to use of rescue medication

This outcome examined the time from taking study medication to use of rescue medication. A longer time to use of rescue medication indicates a longer duration of analgesia from the assigned intervention. Not all studies reported relevant data; of those that did, all but one (Romundstad 2004) reported median times to remedication, rather than means.

For the comparison of IV ketorolac versus placebo, the median time to use of rescue medication was 271 minutes for ketorolac and 104 minutes for placebo (6 studies, 633 participants) (Balestrieri 1997; Bikhazi 2004; Gan 2012; Mehlisch 2003; Rasmussen 2002; Zhou 2001). In almost all of these studies, time to rescue was longer in those participants assigned to ketorolac. We judged the certainty of evidence as moderate, downgrading once for both unclear risk of bias for several domains among the included studies (study limitations) and for imprecision, and upgrading once for large magnitude of effect.

Number of participants using rescue medication over a four- or six-hour period

This outcome assessed the need for rescue analgesia in the period immediately after administering the assigned interventions.

Five studies (417 participants) included comparisons of ketorolac with placebo (Barton 2002; Bikhazi 2004; Christensen 2011; Parke 1995 Zhou 2001).

- The proportion of participants using rescue medication with ketorolac was 54% (105/194, range 26% to 93%).
- The proportion of participants using rescue medication with placebo was 83% (185/223, range 73% to 97%).
- The risk ratio of treatment compared with placebo was 0.60 (95% CI 0.36 to 1.00), that is, there is no evidence of a difference (Analysis 1.3). This meta-analysis had substantial heterogeneity, as demonstrated by an I^2 score of 95%.

We judged the certainty of evidence for this outcome as very low, due to downgrading once for each of unclear risk of bias for several domains among the included studies (study limitations), unexplained heterogeneity (I^2 = 95%) and the low total number of events (imprecision).

Withdrawals due to adverse events, lack of efficacy, and for any cause

In addition to study limitations, numbers of participants withdrawing were generally low, and reasons for withdrawal were inconsistently reported. We therefore judged the certainty of evidence for these outcomes to be very low.

- The proportion of participants withdrawing due to AEs was 2% (11/452) with ketorolac versus 2% (8/493) with placebo (Analysis 1.4: RR 1.31, 95% CI 0.56 to 3.06; 10 studies, 945 participants).
- The proportion of participants withdrawing due to lack of efficacy was 3% (10/339) with ketorolac versus 3% (12/359) with placebo (Analysis 1.5; RR 0.81, 95% CI 0.36 to 1.78; 7 studies, 698 participants). Most withdrawals occurred in one study (Gan 2012).
- The proportion of participants withdrawing for any cause was 6% (19/307) with ketorolac versus 7% (24/327) with placebo (Analysis 1.6; RR 0.80, 95% CI 0.47 to 1.36; 7 studies, 634 participants). Most withdrawals occurred in one study (Gan 2012), primarily due to participants' requests.

Participants experiencing any adverse event

Not all studies reported the number of participants experiencing any AE. The time over which AEs were measured varied. In one multiple-dose study (Gan 2012), AEs were measured through the end of the study (five to nine days after baseline observations).

Eight studies (810 participants) included comparisons of ketorolac versus placebo (Balestrieri 1997; Barton 2002; Bikhazi 2004; Gan 2012; Mehlisch 2003; Moodie 2013; Rasmussen 2002; Zhou 2001).

- The proportion of participants reporting an AE with ketorolac was 74% (286/385).
- The proportion of participants reporting an AE with placebo was 65% (275/425).
- The risk ratio of treatment compared with placebo was 1.09 (95% CI 1.00 to 1.19); the NNTH was 16.7 (95% CI 8.3 to infinite) (Analysis 1.7).

We assessed the certainty of evidence for comparisons with placebo as moderate, based on unclear risk of bias in several domains for the included studies (study limitations).

Participants experiencing any serious adverse event

In those studies that reported them, SAEs were very rare (Analysis 1.8). We assessed the certainty of evidence for this outcome as low, based on the very low event rates (imprecision) and unclear risk of bias for several domains in the included studies (study limitations). Eight studies (703 participants) did not demonstrate a difference in SAE rates between ketorolac and placebo (RR 0.62, 95% CI 0.13 to 3.03) (Barton 2002; Bikhazi 2004; Christensen 2011; Gan 2012; Mehlisch 2003; Moodie 2013; Parke 1995; Romundstad 2004). Only one participant administered ketorolac suffered an SAE (Gan 2012). The participant experienced an abdominal hematoma, which was considered to be possibly treatment-related. Four participants receiving placebo experienced an SAE: appendicitis, which was assessed as being unrelated to therapy (Christensen 2011); a left knee joint hematoma in one participant; a wound infection in the right hip with cellulitis in one participant (both considered procedure-related); and thrombus formation in the peroneal vein, which was resolved with thrombolysis

therapy (Moodie 2013). No participants receiving another NSAID experienced an SAE. Two participants receiving an opioid suffered an SAE: pulmonary emboli and persistent nausea and vomiting, both of which were considered unrelated to treatment.

Specific adverse events

Methods of assessment and the reporting of specific AEs were inconsistent across studies, as was the time over which the information was collected. Our AEs of interest were NSAID-related (renal dysfunction, cardiovascular events, gastrointestinal or operative-site bleeding, and thrombophlebitis) or opioid-related (nausea, vomiting, nausea and vomiting, pruritus, respiratory depression, sedation, urinary retention, and allergic reaction/rashes). These AEs occurred infrequently in all groups, with the exception of nausea, vomiting, itching and sedation amongst the opioid-related AEs. Other than for these four outcomes, there were insufficient data for meta-analysis. As with our analysis of SAEs, we assessed the certainty of evidence for the four meta-analyses as low. Where there were so few events or studies that meta-analysis was precluded, we assessed the certainty of evidence as very low.

Renal dysfunction

Only one study reported assessing renal dysfunction (Gan 2012). No participants in either of the intervention groups experienced this AE.

Cardiovascular events

In the two studies that reported cardiovascular events (Balestrieri 1997; Gan 2012), 13% (21/165) of participants receiving ketorolac experienced an event versus 11% (18/158) of participants receiving placebo. Most of the AEs occurred in Balestrieri 1997. Cardiovascular events in this study were defined as bradycardia, tachycardia, hypotension, and hypertension. In the other study in which cardiovascular events occurred (not defined), none were considered to be treatment-related (Gan 2012) (Analysis 1.9).

Gastrointestinal bleeding

In the one study that reported gastrointestinal bleeding, 1% of participants (1/82) receiving ketorolac experienced clinically significant bleeding versus none of those receiving placebo (Gan 2012).

Operative-site bleeding

Two studies reported operative-site bleeding (Gan 2012; Zhou 2001). Four per cent (4/110) of those receiving ketorolac experienced this AE versus 1% (1/131) of those receiving placebo (Analysis 1.10).

Thrombophlebitis

Both studies that assessed thrombophlebitis used a six-point scale (grade 0 = "no reaction" to grade 5 = "thrombosis with overt infection") and defined events as occurring in participants with a score of more than 1 (Christensen 2011; Gan 2012). No events occurred in Christensen 2011. In Gan 2012 7% (6/82) receiving ketorolac versus 12% (9/76) receiving placebo were assessed as experiencing this AE (Analysis 1.11).

Nausea, vomiting or both

Eight studies (798 participants) compared rates of nausea with ketorolac versus placebo (Balestrieri 1997; Barton 2002; Bikhazi 2004; Gan 2012; Mehlisch 2003; Parke 1995; Rasmussen 2002; Romundstad 2004).

- The proportion of participants reporting nausea with ketorolac was 34% (138/402, range 12% to 67%).
- The proportion of participants reporting nausea with placebo was 39% (154/396, range 16% to 78%).
- The risk ratio of treatment compared with placebo was 0.88 (95% CI 0.75 to 1.04); there was no evidence of a difference (Analysis 1.12).

Seven studies (724 participants) compared rates of vomiting with ketorolac versus placebo (Balestrieri 1997; Barton 2002; Bikhazi 2004; Gan 2012; Mehlisch 2003; Rasmussen 2002; Romundstad 2004).

- The proportion of participants reporting vomiting with ketorolac was 13% (47/365, range 5% to 27%).
- The proportion of participants reporting vomiting with placebo was 15% (55/359, range 4% to 27%).
- The risk ratio of treatment compared with placebo was 0.84 (95% CI 0.59 to 1.20); there was no evidence of a difference (Analysis 1.13).

No studies reported nausea and vomiting as a combined outcome.

Pruritus

Five studies (574 participants) compared rates of pruritus with ketorolac versus placebo (Balestrieri 1997; Barton 2002; Bikhazi 2004; Gan 2012; Rasmussen 2002).

- The proportion of participants reporting pruritus with ketorolac was 7% (21/290, range 4% to 12%).
- The proportion of participants reporting pruritus with placebo was 8% (24/284, range 7% to 12%).
- The risk ratio of treatment compared with placebo was 0.86 (95% CI 0.49 to 1.50); there was no evidence of a difference (Analysis 1.14).

Respiratory depression

Incidence of respiratory depression was only reported in two studies (Balestrieri 1997; Rasmussen 2002). Neither study defined how it was assessed. In combination, four of 125 participants receiving ketorolac and nine of 121 receiving placebo experienced this side effect (Analysis 1.15).

Sedation

Six studies (566 participants) compared rates of sedation with ketorolac versus placebo (Balestrieri 1997; Barton 2002; Bikhazi 2004; Mehlisch 2003; Rasmussen 2002; Romundstad 2004).

- The proportion of participants reporting sedation with ketorolac was 5% (14/283, range 0 to 7%).
- The proportion of participants reporting sedation with placebo was 10% (30/283, range 0 to 18%).
- The risk ratio of treatment compared with placebo was 0.47 (95% CI 0.25 to 0.86); the NNTp for one additional participant not to report sedation compared with placebo was 16.7 (95% CI 10 to 100) (Analysis 1.16).

Urinary retention

Only one study reported this safety outcome. Bikhazi 2004 reported that 2/42 participants receiving ketorolac and 5/45 receiving placebo experienced urinary retention.

Allergic reaction/rashes

No study reported this outcome.

2. Ketorolac versus another NSAID

Proportion of participants achieving at least 50% postoperative pain relief over a four-hour period and over a six-hour period

Four studies provided data for the comparison of IV ketorolac 30 mg versus another NSAID over four hours (Barton 2002; Bikhazi 2004; Mehlisch 2003; Rasmussen 2002).

- The proportion of participants with at least 50% pain relief with ketorolac was 65% (112/172, range 51% to 76%).
- The proportion of participants with at least 50% pain relief with another NSAID was 63% (104/165, range 55% to 80%).
- The relative benefit of treatment compared with another NSAID was 1.04 (95% CI 0.89 to 1.21); there was no evidence of a difference (Analysis 2.1).

Six studies (603 participants) compared ketorolac 30 mg, versus another NSAID over six hours (Barton 2002; Bikhazi 2004; Christensen 2011; Gan 2012; Mehlisch 2003; Rasmussen 2002).

- The proportion of participants with at least 50% pain relief with ketorolac was 66% (199/301, range 46% to 77%).
- The proportion of participants with at least 50% pain relief with another NSAID was 63% (189/302, range 53% to 76%).
- The relative benefit of treatment compared with another NSAID was 1.06 (95% CI 0.95 to 1.19); there was no evidence of a difference (Analysis 2.2).

We assessed the certainty of evidence for this outcome as low over four hours and moderate over six hours, based on unclear risk of bias for several domains among the included studies over both time periods (study limitations) and the low total number of events over four hours (imprecision).

Time to use of rescue medication

For the comparison of IV ketorolac versus another NSAID, the median time to use of rescue medication was 331 minutes for ketorolac and 296 minutes for another NSAID (4 studies, 427 participants) (Bikhazi 2004; Gan 2012; Mehlisch 2003; Rasmussen 2002). In none of the studies was there evidence of a difference between ketorolac and another NSAID. We judged the certainty of evidence as low, based on risk of bias in the included studies and imprecision of findings.

Number of participants using rescue medication over a four- or six-hour period

Only three studies provided usable data for ketorolac versus another NSAID (parecoxib or diclofenac) (Barton 2002; Bikhazi 2004; Christensen 2011).

- The proportion of participants using rescue medication with ketorolac was 48% (63/130).
- The proportion of participants using rescue medication with another NSAID was 52% (67/130).
- The risk ratio of ketorolac compared with another NSAID was 0.90 (95% CI 0.58 to 1.40; participants = 260), that is, there is no evidence of a difference (Analysis 2.3).

We judged the certainty of evidence for this outcome as very low, due to unclear risk of bias for several domains among the included studies (study limitations), unexplained heterogeneity (I^2 = 65%) and the low total number of events (imprecision).

Withdrawals due to adverse events, lack of efficacy, and for any cause

In addition to study limitations, numbers of participants withdrawing were generally low, and reasons for withdrawal were inconsistently reported. We therefore judged the certainty of evidence for these outcomes to be very low.

- The proportion of participants withdrawing due to AEs was 3% (8/262) with ketorolac versus 3% (9/269) with another NSAID (Analysis 2.4; RR 0.87, 95% CI 0.35 to 2.19; 5 studies, 531 participants).
- The proportion of participants withdrawing due to lack of efficacy was 4% (6/166) with ketorolac versus 5% (8/170) with another NSAID (Analysis 2.5; (RR 0.80, 95% CI 0.29 to 2.19; 3 studies, 336 participants). All of the withdrawals occurred in a single study (Gan 2012).
- The proportion of participants withdrawing for any cause was 8% (17/216) with ketorolac versus 11% (25/221) with another NSAID (Analysis 2.6; RR 0.72, 95% CI 0.41 to 1.26; 4 studies, 437 participants). Again, most withdrawals occurred in one study (Gan 2012), primarily due to participants' requests.

Participants experiencing any adverse event

Five studies reported the number of participants experiencing any AE (Barton 2002; Bikhazi 2004; Gan 2012; Mehlisch 2003; Rasmussen 2002).

- The proportion of participants reporting an AE with ketorolac was 76% (195/257).
- The proportion of participants reporting an AE with another NSAID was 68% (177/259).
- The risk ratio of treatment compared with another NSAID was 1.11 (95% CI 1.00 to 1.23); the NNTH was 12.5 (95% CI 6.7 to infinite) (Analysis 2.7).

We assessed the certainty of evidence for comparisons with another NSAID as moderate, based on unclear risk of bias in several domains for the included studies (study limitations).

Participants experiencing any serious adverse event

In those studies that reported them, SAEs were very rare (Analysis 2.8). We assessed the certainty of evidence for this outcome as low, based on the very low event rates and unclear risk of bias for several domains in the included studies.

Low-certainty evidence from five studies (530 participants) did not demonstrate a difference in SAE rates between ketorolac and another NSAID (RR 3.18, 95% CI 0.13 to 76.99) (Barton 2002; Bikhazi 2004; Christensen 2011; Gan 2012; Mehlisch 2003). Only one participant given ketorolac suffered an SAE (Gan 2012).

The participant experienced an abdominal hematoma, which was considered to be possibly treatment-related. No participants receiving another NSAID experienced an SAE.

Specific adverse events

Methods of assessment and the reporting of specific AEs were inconsistent across studies, as was the time over which the information was collected. Our AEs of interest were NSAID-related (renal dysfunction, cardiovascular events, gastrointestinal or operative-site bleeding, and thrombophlebitis) or opioid-related (nausea, vomiting, nausea and vomiting, pruritus, respiratory depression, sedation, urinary retention, and allergic reaction/rashes). These AEs occurred infrequently in all groups, with the exception of nausea, vomiting, itching and sedation amongst the opioid-related AEs. Other than for these four outcomes, there were insufficient data for meta-analysis. As with our analysis of SAEs, we assessed the certainty of evidence for the four meta-analyses as low. Where there were so few events or studies that meta-analysis was precluded, we assessed the certainty of evidence as very low.

Renal dysfunction

Only one study reported assessing renal dysfunction (Gan 2012). No participants in either of the intervention groups experienced this AE.

Cardiovascular events

In the one study that reported cardiovascular events (Gan 2012), 6% (5/82) of participants receiving ketorolac experienced an event versus 5% (4/87) of those receiving another NSAID. None were considered to be treatment-related.

Gastrointestinal bleeding

In the one study that reported gastrointestinal bleeding, 1% of participants (1/82) receiving ketorolac experienced clinically significant bleeding versus none of those on another NSAID (Gan 2012).

Operative-site bleeding

One study reported operative-site bleeding (Gan 2012). Two per cent (2/82) of those receiving ketorolac experienced this AE versus no participants (0/87) receiving another NSAID.

Thrombophlebitis

Both studies that assessed thrombophlebitis used a six-point scale (grade 0 = "no reaction" to grade 5 = "thrombosis with overt infection") and defined events as occurring in participants with a score of more than 1 (Christensen 2011; Gan 2012). No events occurred in Christensen 2011. In Gan 2012 7% (6/82) receiving ketorolac versus 3% (3/87) receiving another NSAID were assessed as experiencing this AE (Analysis 2.9).

Nausea, vomiting or both

Five studies (516 participants) compared rates of nausea with another NSAID (Barton 2002; Bikhazi 2004; Gan 2012; Mehlisch 2003; Rasmussen 2002) .

- The proportion of participants reporting nausea with ketorolac was 26% (68/257, range 19% to 41%).
- The proportion of participants reporting nausea with another NSAID was 23% (59/259, range 12% to 32%).
- The risk ratio of treatment compared with another NSAID was 1.16 (95% CI 0.86 to 1.56); there was no evidence of a difference (Analysis 2.10).

Five studies (516 participants) compared rates of vomiting with another NSAID (Barton 2002; Bikhazi 2004; Gan 2012; Mehlisch 2003; Rasmussen 2002) .

- The proportion of participants reporting vomiting with ketorolac was 11% (29/257, range 5% to 27%).
- The proportion of participants reporting vomiting with another NSAID was 8% (21/259, range 2% to 24%).
- The risk ratio of treatment compared with another NSAID was 1.36 (95% CI 0.81 to 2.28); there was no evidence of a difference (Analysis 2.11).

No studies reported nausea and vomiting as a combined outcome.

Pruritus

Four studies (415 participants) compared rates of pruritus with another NSAID (Barton 2002; Bikhazi 2004; Gan 2012; Rasmussen 2002).

- The proportion of participants reporting pruritus with ketorolac was 5% (11/207, range 4% to 7%).
- The proportion of participants reporting pruritus with another NSAID was 6% (13/208, range 0 to 12%).
- The risk ratio of treatment compared with another NSAID was 0.85 (95% CI 0.40 to 1.84); there was no evidence of a difference (Analysis 2.12).

Respiratory depression

Incidence of respiratory depression was only reported in one study (Rasmussen 2002). Two of 42 participants receiving ketorolac and two of 42 receiving another NSAID experienced this side effect.

Sedation

Four studies (347 participants) compared rates of sedation with another NSAID (Barton 2002; Bikhazi 2004; Mehlisch 2003; Rasmussen 2002) .

- The proportion of participants reporting sedation with ketorolac was 6% (11/175, range 4% to 7%).
- The proportion of participants reporting sedation with another NSAID was 2% (4/172, range 0 to 5%).
- The risk ratio of treatment compared with another NSAID was 2.51 (95% CI 0.86 to 7.35); there was no evidence of a difference (Analysis 2.13).

Urinary retention

Only one study reported this safety outcome. Bikhazi 2004 reported that 2/42 participants receiving ketorolac and 0 of 41 receiving another NSAID experienced urinary retention.

Allergic reaction/rashes

No study reported this outcome.

3. Ketorolac versus an opioid

Proportion of participants achieving at least 50% postoperative pain relief over a four-hour period and over a six-hour period

Three studies (243 participants) provided data for the comparison of IV ketorolac 30 mg with an opioid over four hours and six hours (Barton 2002; Bikhazi 2004; Rasmussen 2002).
Over four hours:

- The proportion of participants with at least 50% pain relief with ketorolac was 64% (79/124, range 51% to 76%).
- The proportion of participants with at least 50% pain relief with an opioid was 36% (43/119, range 26% to 55%).
- The relative benefit of treatment compared with an opioid was 1.75 (95% CI 1.34 to 2.28); the NNTB for one additional participant to benefit compared with an opioid was 3.7 (95% CI 2.6 to 6.7) (Analysis 3.1).

Over six hours:

- The proportion of participants with at least 50% pain relief with ketorolac was 58% (72/124, range 46% to 71%).
- The proportion of participants with at least 50% pain relief with an opioid was 30% (36/119, range 19% to 50%).
- The relative benefit of treatment compared with an opioid was 1.90 (95% CI 1.40 to 2.56); the NNTB for one additional participant to benefit compared with an opioid was 3.7 (95% CI 2.6 to 6.3) Analysis 3.2).

We assessed the certainty of evidence for this outcome as low over both four hours and six hours, based on unclear risk of bias for several domains among the included studies (study limitations) and the low total number of participants analyzed (imprecision).

Time to use of rescue medication

Only two studies compared ketorolac 30 mg IV with an opioid (4 mg IV morphine) for this outcome. Bikhazi 2004 demonstrated that participants receiving IV ketorolac had a longer time to rescue than those participants receiving morphine (370 minutes versus 295 minutes, P < 0.05, 80 participants). Similarly, Rasmussen 2002 demonstrated that participants receiving ketorolac waited more than twice as long before requesting rescue (275 minutes versus 127 minutes, P < 0.05). Due to study limitations and imprecision (lack of data), we assessed the certainty of evidence as low.

Number of participants using rescue medication over a four- to six-hour period

Only two studies provided usable data for ketorolac 30 mg versus an opioid (morphine 4 mg) (Barton 2002; Bikhazi 2004).

- The proportion of participants using rescue medication with ketorolac was 61% (51/83).
- The proportion of participants using rescue medication with morphine was 79% (63/80).
- The risk ratio of ketorolac compared with an opioid was 0.72 (95% CI 0.25 to 2.04), that is, there is no evidence of a difference (Analysis 3.3). This meta-analysis had substantial heterogeneity, as demonstrated by an I^2 score of 94%.

We judged the certainty of evidence for this outcome as very low, due to unclear risk of bias for several domains among the included studies (study limitations), unexplained heterogeneity (I^2 = 94%) and the low total number of events (imprecision).

Withdrawals due to adverse events, lack of efficacy, and for any cause

Numbers of participants withdrawing were generally low, and reasons for withdrawal were inconsistently reported. We therefore judged the certainty of evidence for these outcomes to be very low.

There were only two studies that contributed data to each of these outcomes for this comparison. Number of events were low across all outcomes and similar between groups (Analysis 3.4; Analysis 3.5; Analysis 3.6).

Participants experiencing any adverse event

Three studies reported the number of participants experiencing any AE (Barton 2002; Bikhazi 2004; Rasmussen 2002).

- The proportion of participants reporting an AE with ketorolac was 74% (92/125).
- The proportion of participants reporting an AE with an opioid was 83% (103/124).
- The risk ratio of treatment compared with an opioid was 0.89 (95% CI 0.67 to 1.18); there was no evidence of a difference (Analysis 3.7).

We assessed the certainty of evidence for comparisons with an opioid as low, based on unclear risk of bias in several domains for the included studies (study limitations), and also the low total number of events (imprecision).

Participants experiencing any serious adverse event

In those studies that reported them, SAEs were very rare (Analysis 3.8). We assessed the certainty of evidence for this outcome as low, based on the very low event rates and unclear risk of bias for several domains in the included studies.

Two studies (165 participants) did not demonstrate a difference in SAE rates between ketorolac and an opioid (RR 0.20, 95% CI 0.01 to 4.14) (Barton 2002; Bikhazi 2004). No participants given ketorolac suffered an SAE. Two participants receiving an opioid suffered an SAE: pulmonary emboli and persistent nausea and vomiting, both of which were considered unrelated to treatment.

Specific adverse events

Methods of assessment and the reporting of specific AEs were inconsistent across studies, as was the time over which the information was collected. Our AEs of interest were NSAID-related (renal dysfunction, cardiovascular events, gastrointestinal or operative-site bleeding, and thrombophlebitis) or opioid-related (nausea, vomiting, nausea and vomiting, pruritus, respiratory depression, sedation, urinary retention, and allergic reaction/rashes). These AEs occurred infrequently in all groups, with the exception of nausea, vomiting, itching and sedation amongst the opioid-related AEs. Other than for these four outcomes, there were insufficient data for meta-analysis. As with our analysis of SAEs, we assessed the certainty of evidence for the four meta-analyses as low. Where there were so few events or studies that meta-analysis was precluded, we assessed the certainty of evidence as very low.

Nausea, vomiting or both

Four studies (369 participants) compared rates of nausea with an opioid (Barton 2002; Bikhazi 2004; Gonzalez 1994; Rasmussen 2002).

- The proportion of participants reporting nausea with ketorolac was 20% (37/185, range 7% to 41%).
- The proportion of participants reporting nausea with an opioid was 25% (46/184, range 17% to 31%).
- The risk ratio of treatment compared with an opioid was 0.80 (95% CI 0.55 to 1.17); there was no evidence of a difference (Analysis 3.9).

Four studies (369 participants) compared rates of vomiting with an opioid (Barton 2002; Bikhazi 2004; Gonzalez 1994; Rasmussen 2002).

- The proportion of participants reporting vomiting with ketorolac was 11% (20/185, range 3% to 27%).
- The proportion of participants reporting vomiting with an opioid was 13% (24/184, range 8% to 24%).
- The risk ratio of treatment compared with an opioid was 0.84 (95% CI 0.48 to 1.44); there was no evidence of a difference (Analysis 3.10).

No studies reported nausea and vomiting as a combined outcome.

Pruritus

Three studies (249 participants) compared rates of pruritus with an opioid (Barton 2002; Bikhazi 2004; Rasmussen 2002).

- The proportion of participants reporting pruritus with ketorolac was 6% (8/125, range 5% to 7%).
- The proportion of participants reporting pruritus with an opioid was 9% (11/124, range 7% to 12%).
- The risk ratio of treatment compared with an opioid was 0.73 (95% CI 0.30 to 1.74); there was no evidence of a difference (Analysis 3.11).

Respiratory depression

Incidence of respiratory depression was only reported in one study (Rasmussen 2002). Two of 42 participants receiving ketorolac and five of 42 participants receiving an opioid experienced this side effect.

Sedation

Three studies (249 participants) compared rates of sedation with an opioid (Barton 2002; Bikhazi 2004; Rasmussen 2002).

- The proportion of participants reporting sedation with ketorolac was 7% (9/125, range all 7%).
- The proportion of participants reporting sedation with an opioid was 10% (13/124, range 5% to 17%).
- The risk ratio of treatment compared with an opioid was 0.69 (95% CI 0.31 to 1.55); there was no evidence of a difference (Analysis 3.12).

Urinary retention

Only one study reported this safety outcome. Bikhazi 2004 reported that 2/42 participants receiving ketorolac and 2/40 participants receiving an opioid experienced urinary retention.

Allergic reaction/rashes

No study reported this outcome.

Subgroup analysis, sensitivity analysis, and investigation of heterogeneity

Dosing

Where there were sufficient data, we planned to analyze the effect on our primary outcomes of different doses of ketorolac separately. Three different doses were used: 15 mg, 30 mg and 60 mg. Almost all studies administered 30 mg, so there were not enough data for a subgroup analysis. Balestrieri 1997 administered only 60 mg (subsequent doses in this multiple-dose study were 30 mg) and Zhou 2001 had both 15 mg and 30 mg arms. Balestrieri 1997 compared ketorolac with placebo only. However, the RR versus placebo was not higher (better) in this study versus any of the other studies included over either four or six hours post-interventions, in part because of the high placebo response in this study. In Zhou 2001, there was no evidence of a difference in the number of participants achieving at least 50% pain relief with 15 mg versus 30 mg, respectively over four hours (15/28 versus 16/27) or over six hours (14/28 versus 15/27).

Type of surgery

We split the various surgeries that participants underwent into three subgroups: abdominal/pelvic; dental (third molar extraction); and orthopedic. For comparisons of ketorolac with placebo over four and six hours for our primary outcome, the z test demonstrated differences between subgroups (Analysis 1.17; Analysis 1.18). Ketorolac appeared to be most effective in dental surgery and least effective in abdominal surgery. For comparisons versus other NSAIDs, subgroup analysis (Analysis 2.14; Analysis 2.15) did not show differences between subgroups. There were insufficient data to perform a subgroup analysis for comparisons with an opioid.

Heterogeneity

For our primary outcome analyses, studies generally enrolled similar numbers of participants. Substantial heterogeneity, as demonstrated by I^2 scores of greater than 50%, occurred only in comparisons of ketorolac versus placebo. Analysis 1.1, number of participants with at least 50% pain relief over four hours, had an I^2 of 65%. In this analysis, two studies, Mehlisch 2003; and Romundstad 2004, had no participants in the placebo groups that achieved this outcome. Removal of these studies reduced the I^2 to32%. However, removal of these studies from the same comparison over six hours (Analysis 1.2) did not reduce the I^2 score. As noted above, subgroup analysis by surgery did show differences between subgroups. However, heterogeneity remained high (I^2 = 53%) in the orthopedic subgroup over four hours and in the abdominal/pelvic analysis over six hours (I^2 = 71%). Removal of the one study (Balestrieri 1997) that used a higher dose of ketorolac also did not reduce heterogeneity in Analysis 1.1 or Analysis 1.2.

Sensitivity analysis

For meta-analyses with an I^2 score of greater than 50%, we re-analyzed the data using a random-effects model and presented these analyses preferentially. There were no large changes in the effect size when converting from fixed-effect to random-effects models; however, one analysis that had previously demonstrated superiority of ketorolac over placebo (Analysis 1.3), and one that demonstrated superiority of ketorolac versus an opioid (Analysis 3.3), no longer demonstrated a difference (P = 0.05 and P = 0.53, respectively). Both analyses were for the outcome of number of participants requiring rescue medication over four to six hours. For Analysis 1.3, comparing ketorolac with placebo, Barton 2002, had a very similar event rate in the ketorolac and placebo groups. The reasons for this similarity are unclear. Of note, the median *time* to rescue was longer in those receiving ketorolac in this study, as noted in Effects of interventions. For Analysis 3.3, comparing ketorolac versus an opioid, there were only two studies and a low total number of participants, so this analysis was more susceptible to chance.

DISCUSSION

Summary of main results

We found 12 studies for inclusion in this review. Study designs were similar, in that most required participants to report moderate-to-severe pain postoperatively before being assigned to one of the planned intervention groups. Most were single-dose studies that measured pain relief or pain intensity difference after an intervention was administered. Doses of ketorolac varied among studies, but in 11 studies a 30 mg dose was administered, which represents the dose typically used in clinical practice in patients under the age of 65 years (those over 65 years typically receive 15 mg). One study used a dose of 15 mg separately from a 30 mg dose arm, and one study used a 60 mg single dose. For studies assessing multiple-dose regimens, we assessed outcomes based only on the first dose administered. The similarity of study designs, and the drugs administered in the comparator arms, was reflected in the fact that most analyses did not display substantial heterogeneity, which we defined as an I^2 score of greater than 50%. However, comparison of ketorolac and placebo for our primary outcomes displayed substantial heterogeneity over both four and six hours. In these analyses, there were no obvious explanations for the differences in event rates among studies, but subgroup analyses based on type of surgery suggest that event rates may be higher in dental surgery, specifically third molar extraction, and lowest in abdominal or pelvic surgeries. Although it has been suggested that NSAIDs are more effective in dental models, this has not been demonstrated conclusively (Barden 2004). Conversely, NSAIDs are thought to be less effective in treating visceral pain; presumably the latter would be a major component of abdominal and pelvic surgeries. Of note, pooled analyses of the outcome 'number of participants using rescue over 4 - 6 hours post-interventions' displayed heterogeneity in all three comparisons (placebo, NSAID and opioid). Informal subgroup analyses by type of surgery for this outcome did not suggest that this was the source of heterogeneity. Although not part of our planned analysis, subgroup analysis by specific NSAID did reduce heterogeneity for this outcome from an I^2 score of 65% to 0%.

The results of the studies available for IV ketorolac versus placebo suggest that more participants achieved at least 50% pain relief with ketorolac. For the same outcome, ketorolac appears to be similar to other NSAIDs (parecoxib or diclofenac), and superior to an opioid (morphine 4 mg). Limited evidence suggests that ketorolac has a similar safety profile to all three comparator groups.

Efficacy

Analysis of our primary outcome, defined as participants achieving at least 50% maximum pain relief over both four and six hours, demonstrated that ketorolac was superior to placebo and the opioid morphine at a dose of 4 mg, and similar to other NSAIDs, specifically parecoxib and diclofenac. Limited analysis of the most commonly-used dose, 30 mg, versus 15 mg or 60 mg arms, based on data from only two studies, did not suggest a dose-response effect. The relative benefit of ketorolac compared with placebo over four hours was 2.81 (95% CI 1.80 to 4.37). Around three times as many participants achieved at least 50% pain relief in the ketorolac group compared with those receiving placebo. The NNTB for one additional participant to benefit compared with placebo was 2.4 (95% CI 1.8 to 3.7), which indirectly compares favorably with oral analgesics used in the same setting (Moore 2015a), and similarly to other parenteral NSAIDs, which were 20 mg of parenteral parecoxib (Lloyd 2009) and 37.5 mg of parenteral diclofenac (McNicol 2018). Of note, parecoxib is not available in the USA. A systematic review of the only other commercially-available NSAID, ibuprofen, is ongoing (Ferguson 2018). The percentage of participants achieving at least 50% maximum pain relief with ketorolac was similar over six hours versus over four hours, suggesting that ketorolac has a relatively long duration of action. Parenteral ketorolac also demonstrated lower (that is, superior) NNTBs over four and six hours versus those found in a Cochrane Review of parenteral formulations of paracetamol (acetaminophen) for postoperative pain, where NNTBs were 5 and 6 over four and six hours, respectively (McNicol 2016). Direct comparison of ketorolac with other NSAIDs within this review suggested similar efficacy over both four and six hours (RR 1.04, 95% CI 0.89 to 1.21 and RR 1.06, 95% CI 0.95 to 1.19, respectively). Limited evidence, based on three studies, demonstrated that ketorolac 30 mg was superior to morphine 4 mg over both four and six hours, with NNTs of 3.7 (95% CI 2.6 to 6.7) and 3.7 (95% CI 2.6 to 6.3), respectively. This is somewhat unexpected, in that opioids are generally considered to be more effective in reducing pain than NSAIDs, but could possibly be related to a relatively small comparison dose of morphine.

For secondary efficacy outcomes, median time to rescue medication was longer in those receiving ketorolac versus those receiving placebo. Head-to-head comparisons with another NSAID for these outcomes showed similar efficacy. In comparisons with an opioid, very limited evidence from only two studies showed that participants waited longer for rescue medication. Lastly, there were an insufficient number of events to allow us to perform pooled analyses of the number of participants withdrawing from a trial due to lack of efficacy.

Safety

Total AE rates were slightly higher in those receiving ketorolac versus placebo or another NSAID (although differences are unlikely to be clinically significant), but were similar when comparing ketorolac with an opioid. There was a lack of data for our planned analyses of specific AEs associated with NSAID use, comprising renal dysfunction, cardiovascular events, gastrointestinal bleeding, operative-site bleeding, and thrombophlebitis. This likely reflects

the relatively low frequency with which these events occur, particularly in studies of short duration and low participant enrollment. Probably because of the greater incidence of opioid-related side effects in general, there were more data available for these outcomes for comparisons between ketorolac and placebo or other comparators. Opioid-related outcomes were analyzed to assess whether a reduction in requirement for rescue opioid in turn resulted in a reduction in the rate of occurrence of opioid-related events. However, ketorolac was only shown to be safer than placebo for one outcome, sedation, where fewer than half as many participants reported this AE versus placebo. There was no evidence that ketorolac had different event rates versus other NSAIDs or versus opioids for all of the opioid-related AEs. It is unclear if this reflects a genuine lack of difference, or is simply due to a lack of data.

Only one participant experienced an SAE (an abdominal hematoma) when administered ketorolac, which was assessed as possibly related to the intervention (Gan 2012). Lastly, withdrawals due to AEs were very rare in all groups, as these generally take more time to develop than the very short study period would permit.

Overall completeness and applicability of evidence

There were a reasonable number of studies, participants and events for meta-analyses of our primary outcomes when comparing ketorolac with placebo. The data were less robust for comparisons with other NSAIDs or with opioids. For secondary efficacy outcomes, there were fewer data available, with the exception of time to rescue medication, when comparing ketorolac with placebo. Safety outcomes generally had a small number of studies, participants, and events for most analyses. The limited data prevented us from interpreting safety data with any confidence. Adverse events, particularly those that occur rarely or develop after multiple doses, may be better captured in epidemiological studies. Such studies have assessed rates of renal dysfunction, bleeding, delayed bone healing and reduced spinal fusion with short-term use of ketorolac (Chan 2014; Feldman 1997; Gobble 2014; Glassman 1998; Marquez-Lara 2016; Riggin 2013; Strom 1996).

Included studies reported data from comparisons of ketorolac with both placebo and with active controls administered at standard routine dosing to treat postoperative pain. The studies covered a range of commonly-performed surgeries, but no studies were conducted in people undergoing cardiovascular surgeries, and only two studies described surgeries performed as 'major'. The lack of studies in major surgeries may explain the limited data for reduction in opioid consumption and, in turn, opioid-induced AEs, as opioids would be expected to be a larger component of the postoperative regimen in more invasive procedures. While the use of opioids in the postoperative period has declined in recent years due to advances in multimodal analgesic regimens and awareness and concerns for the safety of opioids, most of the included studies were performed in the 1990s or early 2000s. Earlier studies may not fully reflect current practice, as opioid dosing may have been more liberal and multimodal analgesic regimens were less frequently administered.

The lack of studies in cardiovascular surgeries is perhaps not surprising, given guidelines from regulatory organizations that recommend NSAIDs be contraindicated immediately postoperatively in people undergoing coronary artery bypass surgery (Jenkins 2005). However, an ongoing study (Irct20180909040979N 2019) intends to assess outcomes in this population.

The mean age of participants across studies was generally low, but three studies in orthopedic surgery (Moodie 2013; Rasmussen 2002; Zhou 2001) assessed participants with an average age of over 60 years. However, only one of these studies used the dose typically suggested for this population (Zhou 2001). It has been recommended that ketorolac be avoided in elderly people due to safety concerns, specifically for renal and gastrointestinal AEs (Beers 2019).

Quality of the evidence

When assessing the certainty of findings using GRADE, we ranked certainty as ranging from very low to moderate for efficacy outcomes, but generally ranked the certainty of the evidence as low across safety outcomes, as shown in Summary of findings 1 and Summary of findings 2. 'Low certainty' means that our confidence in the effect estimate is limited, and the true effect may be substantially different from the estimate of the effect. Many individual studies had an unclear risk of bias for issues such as allocation concealment and blinding, and a high risk of bias for sample size, and none of the trials was unequivocally at low risk of bias for all criteria. The lack of clarity for many of the risks of bias may be due to the reporting standards or space limitations of journals rather than any fundamental flaws in the methodology of the studies. Where a study was also posted to a clinical trial website, we sought additional data to further inform assessments. For the outcomes for which we were able to perform pooled analysis, we further downgraded the certainty of evidence due to issues with imprecision (wide confidence intervals) or sparse data (low overall numbers of participants, events, or both) and important inconsistency (unexplained heterogeneity of results).

Potential biases in the review process

We tried to minimize the potential for publication bias related to unpublished or unidentified studies by assessing clinical trial registries and multiple databases, respectively. We also assessed the impact publication bias may have on our findings.

For analysis of our primary outcome of pain relief, we used the number of participants with 30% pain relief, rather than at least 50% pain relief, for one study (Analysis 1.2; Analysis 2.2) (Gan 2012), as these were the only data available for this study. Not surprisingly, more participants achieved at least 30% pain relief in this study than the proportion of those achieving at least 50% in the other studies included in these analyses. However, NNTBs for 30% and 50% pain relief have been shown to be similar over six hours when effective analgesics are compared with placebo (Moore 1997c; Moore 2005), given that event rates tend to change proportionally in both groups when different cutpoints of pain relief are measured.

We did not assess time to onset of analgesia as an efficacy outcome. This was not a frequently-assessed outcome in our included studies. However, this may be an important outcome for patients.

For some AEs we did not predefine assessment criteria for inclusion in a meta-analysis. Instead we typically reported them as they were defined in the included studies. For example, Balestrieri 1997 defined cardiovascular events as bradycardia, tachycardia, hypotension, and hypertension, whereas cardiovascular events

would usually be defined as stroke, myocardial infarction, etc. This may have led to over- (or under-) counting of events. Other AEs, such as vomiting, may be less vulnerable to assessor interpretation.

We are not aware of additional potential biases.

Agreements and disagreements with other studies or reviews

We are aware of two other systematic reviews and meta-analyses of ketorolac for postoperative pain, both of which compared ketorolac to placebo only (De Oliveira 2012; Smith 2000). The former also included studies where ketorolac was administered before the end of surgery and assessed different efficacy outcomes, such as pain scores at four hours and opioid consumption in IV morphine equivalents. As with our analysis, reductions in opioid consumption were generally not accompanied by reductions in opioid-related AEs. Smith 2000 did not include any studies where ketorolac was administered intravenously; instead the eight included parenteral studies administered ketorolac intramuscularly. For the outcome of participants with at least 50% pain relief at four to six hours, the percentage of participants achieving this in the ketorolac and placebo groups was similar to our review, and the NNT was slightly higher compared to our findings (3.4 versus 2.6). Assessment of AE rates was similar to our findings.

AUTHORS' CONCLUSIONS

Implications for practice

For adults with moderate-to-severe postoperative pain

The amount and quality of evidence for the use of IV ketorolac for treating postoperative pain varies from very low to moderate for efficacy outcomes and is generally low for safety outcomes. The evidence we have indicates that postoperative administration of IV ketorolac may offer good pain relief for most patients, but further research may impact this estimate. Adverse events appear to occur at a slightly higher rate versus placebo and other non-steroidal anti-inflammatory drugs (NSAIDs), but at a similar rate to opioids, but information from randomized trials is insufficient to assess whether ketorolac has a different rate of gastrointestinal or operative-site bleeding, renal dysfunction, or cardiovascular events when compared with other NSAIDs, or if it reduces opioid-related adverse events.

For clinicians

The amount and quality of evidence for the use of IV ketorolac for treating postoperative pain varies from very low to moderate for efficacy outcomes and is generally low for safety outcomes. The evidence we have indicates that postoperative administration of IV ketorolac offers good pain relief for most patients, but further research may impact this estimate. Adverse events appear to occur at a slightly higher rate versus placebo and other NSAIDs, but at a similar rate to opioids, but information from randomized trials is insufficient to assess whether ketorolac has a different rate of gastrointestinal or operative-site bleeding, renal dysfunction, or cardiovascular events when compared with other NSAIDs, or if it reduces opioid-related adverse events.

For policymakers

The amount and quality of evidence for the use of IV ketorolac for treating postoperative pain varies from very low to moderate for efficacy outcomes, and policymakers should exercise caution when recommending its use in postoperative guidelines. The evidence we have indicates that postoperative administration of IV ketorolac offers good pain relief for most patients, but further research may impact this estimate. Adverse events appear to occur at a slightly higher rate versus placebo and other NSAIDs, but at a similar rate to opioids, but information from randomized trials is insufficient to assess whether ketorolac has a different rate of gastrointestinal or operative-site bleeding, renal dysfunction, or cardiovascular events when compared with other NSAIDs, or if it reduces opioid-related adverse events.

For funders of the intervention

The amount and quality of evidence for the use of IV ketorolac for treating postoperative pain varies from very low to moderate for efficacy outcomes and is generally low for safety outcomes. The evidence we have indicates that postoperative administration of IV ketorolac offers good pain relief for most patients, but further research may impact this estimate. Adverse events appear to occur at a slightly higher rate versus placebo and other NSAIDs, but at a similar rate to opioids, but information from randomized trials is insufficient to assess whether ketorolac has a different rate of gastrointestinal or operative-site bleeding, renal dysfunction, or cardiovascular events when compared with other NSAIDs, or if it reduces opioid-related adverse events. At this time, parenteral ketorolac is available as a generic product, whereas the other widely-available parenteral NSAIDs, ibuprofen and diclofenac, are generally only available as brand-name products. We did not aim to determine whether potential cost savings of generic ketorolac are offset by possible differences in safety or efficacy when parenteral ibuprofen or diclofenac are used instead.

Implications for research

General

While more studies are required to be able to more accurately estimate the efficacy and safety of parenteral ketorolac, there is a lack of studies specifically in cardiovascular surgeries and in elderly populations.

Design

The studies included in our review were designed to detect differences in efficacy between interventions. However, further studies that compare different doses of ketorolac may establish whether doses lower than those currently used are equally effective, particularly in elderly patients, where data from non-randomized studies demonstrate higher adverse event rates. Studies should be large enough to produce precise estimates of effect in order to meaningfully reduce uncertainty. Serious adverse events and adverse events associated with NSAIDs were rare or very rare. There are several epidemiological studies that may more accurately determine the adverse profile of ketorolac, particularly for renal dysfunction, bleeding, cardiovascular events and delay of bone-healing postoperatively.

Outcomes

Endpoints and the pain scoring scales used to assess them in these studies have been extensively validated. Most studies assessed pain relief after administration of each intervention, an outcome shown to be clinically important to patients. Studies conducting cost-benefit analyses may determine whether the reduced cost

of parenteral ketorolac versus brand-name parenteral diclofenac and ibuprofen is offset by increased adverse event rates and subsequently increased overall costs of care.

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Tramèr 1997

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References to other published versions of this review

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McNicol ED, Ferguson MC, Gallagher S, Schumann R. Single-dose intravenous ketorolac for acute postoperative pain in adults. *Cochrane Database of Systematic Reviews* 2019, Issue 2. Art. No: CD013263. [DOI: 10.1002/14651858.CD013263]

CHARACTERISTICS OF STUDIES

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

Balestrieri 1997

Study characteristics	
Methods	Randomized, double-blind, placebo controlled, parallel, multiple dose, multicenter Efficacy and safety monitored over 24 h postoperatively. Intervention administered on awakening in PACU. Next 3 doses administered 6, 12 and 18 h after first dose
Participants	Type of surgery: total abdominal hysterectomy or myomectomy **Ketorolac group**

Balestrieri 1997 *(Continued)*

	Entered/completing: 83/68 Age (mean, SD): 44 ± 7.7 Sex (male, %): 0 **Placebo group** Entered/completing: 82/66 Age (mean, SD): 43 ± 9.5 Sex (male, %): 0 **Setting:** Washington D.C., USA **Dates Conducted:** not specified
Interventions	**Ketorolac:** 60 mg IV (administration details not reported). Subsequent doses (not analyzed for this review of 30 mg) **Placebo:** Saline (administration details not reported)
Outcomes	Primary (as specified in study): not specified Secondary: Pain intensity: categorical (0 = none, 3 = severe) and VAS (0 = none, 100 = worst pain possible) at baseline, 15 and 30 minutes, and every hour until 6 h Pain on coughing assessed similarly at baseline, 2, 4 and 6 h Adverse events at baseline, 2, 6 and 24 h. Categorized as mild, moderate or severe. Assessed in a blinded manner Drug tolerability and overall ratings (0 = fair, 4 = excellent) Ease of nursing care (0 = very difficult, 4 = minimal) Recovery milestones: readiness for and actual discharge from PACU; length of hospital stay Time to first use of morphine and total morphine use
Source of funding	Supported in part by a grant from Hoffman-La Roche Inc., Nutley, NJ. Author COIs not reported.
Were treatment groups comparable at baseline?	No evidence of a difference between groups for demographic variables (age, weight, height, BMI). Categorical pain intensity was not statistically different between groups before first postoperative dose, ranging from 2 to 2.3
Notes	Third group that received intraoperative ketorolac not included in this review. Both included groups received placebo (saline) intraoperatively

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computerized random-numbers table
Allocation concealment (selection bias)	Unclear risk	Not mentioned

Balestrieri 1997 *(Continued)*

Blinding of participants, personnel and outcome assessors	Unclear risk	Not described. Placebo group received saline
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	"Forty-nine patients were excluded from the efficacy analysis because of an early revision of protocol and of protocol violations, leaving 199 patients for the efficacy analyses". Later reported as 34 subjects. 32 withdrew for other reasons (lack of efficacy, adverse events): numbers were balanced between groups
Selective reporting (reporting bias)	Low risk	All relevant efficacy and safety outcomes reported in full in results section
Sample size	Unclear risk	N = 83 in ketorolac group vs. 82 in placebo group

Barton 2002

Study characteristics	
Methods	Multicenter, double-blinded, placebo- and active controlled. Participants evaluated up to 24 h post-dose or until receiving rescue analgesia. Interventions administered on postoperative day 1 after participants reported a pain intensity of ≥ 45 mm on a 0 - 100 VAS and a categorical pain intensity of moderate or severe, within 6 h after discontinuation of patient-controlled analgesia
Participants	Type of surgery: total abdominal hysterectomy (95 - 100% in each group) or myomectomy (0 - 5% in each group). Between 38 - 41% of participants in each treatment group had severe pain at baseline, with mean VAS pain intensity ranging from 66.3 to 69.4 **Ketorolac group** Entered/completing: 41/41 Age (mean, SD): 40.8 (range 27 - 52) Sex (male, %): 0 **Placebo group** Entered/completing: 42/39 Age (mean, SD): 41.0 (29 - 63) Sex (male, %): 0 **Parecoxib group** Entered/completing: 38/38 Age (mean, SD): 42.0 (29 - 65) Sex (male, %): 0 **Morphine group** Entered/completing: 42/42 Age (mean, SD): 40.7 (25 - 61) Sex (male, %): 0 **Setting:** Salt Lake City, Utah, USA

Barton 2002 *(Continued)*

	Dates Conducted: not specified
Interventions	**Ketorolac:** 30 mg single dose at report of moderate or severe pain; administration details not specified **Placebo:** as with ketorolac; solution and administration details not specified **Parecoxib:** 40 mg as with ketorolac; administration details not specified **Morphine:** 4 mg as with ketorolac; administration details not specified
Outcomes	Primary (as specified in study): not specified Efficacy outcomes assessed until 24 h or rescue analgesia; AEs assessed for duration of the study Time to onset of perceptible and meaningful analgesia Pain relief and TOTPAR Pain intensity difference and SPID Time to and number of participants needing rescue medication Global evaluation of intervention Adverse events by observation and indirect questioning; physical examination changes; vital signs; clinical laboratory values
Source of funding	Supported by Pharmacia Corporation, Skokie, Illinois. Author COIs not reported
Were treatment groups comparable at baseline?	Yes: demographic (age, weight) and clinical (surgical procedure, baseline pain intensity). Baseline pain intensity was ranked moderate in 59% to 62% across groups; 38% to 41% severe. Average VAS was 66 to 69 at baseline
Notes	2 strengths of parecoxib assessed: 20 mg and 40 mg. 40 mg data used here. After surgery, morphine or meperidine PCA was initiated until no later than 12:00 PM on the first postsurgical day. Any participant that had VAS ≥ 45 and a categorical pain intensity of moderate to severe within 6 hours of PCA discontinuation was randomized

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants, personnel and outcome assessors	Unclear risk	Quote: "All participants were blinded to the identity of the treatments until all study data had been collated in a database". Comment: No mention of interventions appearing identical
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	LOCF used for missing data as a result of participants taking rescue medication or withdrawing from the study. Isolated missing data imputed by linear interpolation
Selective reporting (reporting bias)	Low risk	All outcomes described in Methods reported in full in Results. Pain relief and PID data presented graphically only
Sample size	High risk	< 50 participants in each arm

Bikhazi 2004

Study characteristics	
Methods	Active and placebo-controlled, 6-center, single- and multiple-dose study, of up to 5 days duration. Intervention administered on postoperative day 1 after discontinuation of PCA and report of pain ≥ 45/100
Participants	Type of surgery: elective total abdominal hysterectomy (with or without salpingo-oophorectomy or minor bladder repair; 60 - 80% in each group) or myomectomy (11 - 17% in each group) through a low transverse or low midline incision under general anesthesia. Incidental appendectomy and/or abdominal lipectomy were allowed as collateral surgical procedures if the same incision was used. Non-lactating women aged 18 to 64 years, with a body weight of ≥ 50 kg Between 31 - 40% of participants in each treatment group had severe pain at baseline, with mean VAS pain intensity ranging from 60.8 to 64.5 **Ketorolac group** Entered/completing: 42/42 Age (mean, SD): 44.7 ± 8.2 Sex (male, %): 0 **Placebo group** Entered/completing: 45/44 Age (mean, SD): 43.3 ± 6.8 Sex (male, %): 0 **Morphine group** Entered/completing: 40/38 Age (mean, SD): 43.4 ± 7.0 Sex (male, %): 0 **Parecoxib group** Entered/completing: 41/41 Age (mean, SD): 42.0 ± 6.4 Sex (male, %): 0 **Setting:** Miami, Florida, USA **Dates Conducted:** not specified
Interventions	**Ketorolac:** 30 mg (no further details) **Placebo:** no details **Morphine:** 4 mg IV (no further details) **Parecoxib:** 40 mg IV (no further details)
Outcomes	Primary (as specified in study): not specified Time to perceptible and meaningful pain relief (categorical)

Bikhazi 2004 *(Continued)*

	Pain intensity (categoric and VAS) and relief (categoric) at 15, 30, and 45 minutes and 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, 16, and 24 hours after administration of intervention or just before the participant received rescue medication Time to rescue or remedication Global evaluation of study drug (excellent, good, fair, poor) at the end of the treatment period or just before rescue analgesia or remedication Adverse events by observation and indirect questioning; physical examination changes; vital signs; clinical laboratory.
Source of funding	Sponsored by Pfizer Global Pharmaceuticals and Pharmacia Corporation. Author COIs not reported.
Were treatment groups comparable at baseline?	Yes: demographic (age, race, weight) and clinical (baseline pain intensity, surgical procedure, duration of surgery, time from end of surgery until first dose of intervention)
Notes	Study also included a parecoxib 20 mg arm and a multiple dose phase (neither included here)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants, personnel and outcome assessors	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	< 10% of participants did not complete the study
Selective reporting (reporting bias)	Low risk	All outcomes outlined in Methods reported in full in Results
Sample size	High risk	All arms had < 50 participants

Christensen 2011

Study characteristics

Methods	Randomized, double-blind, placebo and active controlled, parallel, single dose, multicenter. Efficacy monitored over 24 h post-intervention; safety monitored over 9 days post-intervention. Intervention administered at first report of moderate-to-severe postoperative pain
Participants	Type of surgery: Third molar extraction (1 or more extractions, 1 of which was a fully or partially impacted mandibular third molar requiring bone removal) **Ketorolac group** Entered/completing: 47/47 Age (mean, SD): not reported

Christensen 2011 *(Continued)*

	Sex (male, %): not reported **Placebo group** Entered/completing: 51/51 Age (mean, SD): not reported Sex (male, %): not reported **Diclofenac 3.75 mg, 9.4 mg, 18.75 mg, 37.5 mg and 75 mg groups** Entered/completing: 51/51 for each group Age (mean, SD): not reported Sex (male, %): not reported **Setting:** Multiple sites, USA **Dates Conducted:** not specified
Interventions	**Ketorolac:** 30 mg single IV bolus injection over 15 seconds **Placebo:** unspecified solution administered in same manner **Diclofenac:** 3.75 mg, 9.4 mg, 18.75 mg, 37.5 mg or 75 mg administered in same manner
Outcomes	Primary (as specified in study): TOTPAR over 0 - 6 h in the ITT population Secondary: Time-specific PR (VAS and categorical) Peak PR (VAS and categorical) SPID over 0 - 2, 0 - 4, 0 - 6, 0 - 8, 0 - 10, 0 - 12, and 0 - 24 h (VAS and categorical) Time-specific PID (VAS and categorical) Peak PID (VAS and categorical) Summed PR intensity differences (SPRID) over 0 - 2, 0 - 4, 0 - 6, 0 - 8, 0 - 10, 0 - 12, and 0 - 24 h (VAS and categorical) Time to administration of rescue medication Proportion of participants requiring rescue medication Time to meaningful pain relief Time to perceptible pain relief Patient global evaluation Safety
Source of funding	Sponsored by Javelin Pharmaceuticals Inc (manufacturers of IV diclofenac). Author COIs not reported
Were treatment groups comparable at baseline?	Yes: demographic (age, sex, ethnic origin, height, weight) and clinical (degree of molar impaction, surgical time and trauma, baseline pain) variables
Notes	Used 37.5 mg dose arm for meta-analysis
Risk of bias	

Christensen 2011 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: “computer-generated randomization schedule”
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants, personnel and outcome assessors	Low risk	Quote: “A third party doser who had no contact with patients except when dosing administered study treatment prepared the syringe with appropriate study treatment using a blind label within 1 hour of dosing”.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	ITT analysis performed on all participants for both efficacy and safety. Methods of data imputation not described
Selective reporting (reporting bias)	Unclear risk	All outcomes specified in Methods reported in Results. Data and SDs not reported for all dose levels for every outcome
Sample size	High risk	47 participants in ketorolac group; 51 participants in each diclofenac group and in placebo group.

Gan 2012

Study characteristics	
Methods	Multicenter, multiple-dose, multiple-day, randomized, double-blind, active- and placebo-controlled, parallel-group phase 3 study. Efficacy assessed through Day 5 or discharge. Safety assessed 30 days post-baseline. Intervention administered when participant reported moderate to severe postoperative pain within 6 hours of completing surgery
Participants	Type of surgery: Abdominal or pelvic (hysterectomy, general abdominal, inguinal hernia, myomectomy, partial colectomy, general pelvic, salpingo-oophorectomy, ventral hernia, other) Mean baseline VAS 67 - 70/100 & comparable among groups; acetaminophen/opioids/other NSAIDs/PCA not permitted; shorting-acting barbiturates or benzodiazepines were allowed with sufficient washout prior to assessment; rescue medication was available (IV morphine 5 - 7.5 mg) **Ketorolac group** Entered/completing: 82/67 Age (mean, SD): 42.9 ± 11.42 Sex (male, %): 15 (18.3%) **Placebo group** Entered/completing: 76/57 Age (mean, SD): 42.8 ± 9.66 Sex (male, %): 15 (19.7%) **Diclofenac group** Entered/completing: 87/68 Age (mean, SD): 43.3 ± 10.83

Gan 2012 *(Continued)*

	Sex (male, %): 19 (21.8%) **Setting:** Multiple sites, USA **Dates Conducted:** May 2006-November 2007
Interventions	**Ketorolac:** 30 mg/1 ml IV bolus administered when participant reported moderate to severe postoperative pain within 6 h of completing surgery. Doses repeated every 6 h until end of study or participant withdrawal **Placebo:** As with ketorolac. Nature of placebo not specified **Diclofenac:** 37.5 mg/1 ml as with ketorolac
Outcomes	Primary (as specified in study): SPID 0 - 48 h post-first dose of study drug Secondary: SPID over 0 to 24 h TOTPAR for the 0- to 24- and 0- to 48-h intervals (0 to 72, 0 to 96, and 0 to 120 h as well, if data permitted) Proportion of participants with clinically-meaningful (≥ 30%) reduction in PI (vs baseline, using 0 to 100 mm VAS) PID at each scheduled assessment Time from administration of study drug to administration of rescue medication Frequency and amount of rescue medication Patient-reported global evaluation of the study drug at 24 and 48 h on a 5-point categorical scale (“excellent,” “very good,” “good,” “fair,” and “poor”) Safety: physical exam, labs, vitals, ECG, thrombophlebitis, AEs
Source of funding	Javelin Pharmaceuticals, Inc., Cambridge, MA (now Hospira, Inc., Lake Forest, IL following acquisition in 2010) Tong J. Gan was compensated for participating in industry-sponsored clinical trial Stephen E. Daniels was compensated for participating in industry-sponsored clinical trial Neil Singla was compensated for participating in industry-sponsored clinical trial Douglas A. Hamilton was a full-time Chief Operating Officer for sponsor (Javelin Pharmaceuticals, Inc., now Hospira, Inc.) during this trial Daniel B. Carr was a full-time Chief Medical Officer for sponsor (Javelin Pharmaceuticals, Inc., now Hospira, Inc.) during this trial
Were treatment groups comparable at baseline?	Yes: demographic (age, sex, ethnicity, height, weight) and surgical (time to first doses of intervention, surgical procedure, baseline PI) variables
Notes	Opioids were not administered as part of the postoperative analgesic regimen – only allowed as rescue medication. Rescue medication (bolus IV morphine 5 mg, titrated up to 7.5 mg after 30 min if analgesia was inadequate) was available upon participant request, up to once every 3 hours any time after administration of the initial dose of study drug, but participants were encouraged to wait at least 1 hour after study medication injection Data from 37.5 mg diclofenac dose (highest in the study) chosen for all outcomes

Risk of bias

Bias	Authors' judgement	Support for judgement

Gan 2012 *(Continued)*

Random sequence generation (selection bias)	Low risk	Computer-generated random code
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants, personnel and outcome assessors	Unclear risk	Quote: "clinical staff and patients were blinded to study drug assignment". Comment: No further details
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT population. For PI and PR, if rescue medication was administered within 3 h of the next scheduled assessment, WOCF from the preceding 6 hours. If the assessments necessary to do this were unavailable, assessments were imputed using BOCF. For withdrawals due to AEs or lack of efficacy, BOCF
Selective reporting (reporting bias)	Unclear risk	Protocol available on ClinicalTrials.gov. All prespecified outcomes reported in full except: PID for each stated time point and grade of thrombophlebitis
Sample size	Unclear risk	Ketorolac N = 82 Placebo N = 76 Diclofenac N = 87

Gonzalez 1994

Study characteristics	
Methods	Multiple-dose, parallel-group, active-controlled. Outcomes assessed through 24 h. Interventions administered when participants required "strong parenteral analgesics" for moderate to severe pain while in the recovery room immediately after surgery
Participants	Type of surgery: "Major". "A large majority of the patients had undergone abdominal surgery" **Ketorolac group** Entered/completing: 60/60 Age (mean, SD): 42.0 ± 16.4 Sex (male, %): 29, 48.4% **Butorphanol group** Entered/completing: 60/60 Age (mean, SD): 44.5 ± 12.9 Sex (male, %): 14, 23.4% **Setting:** Mexico City, Mexico **Dates Conducted:** not specified
Interventions	**Ketorolac:** 30 mg every 6 hours for 24 h; no other details **Butorphanol:** 2 mg as with ketorolac
Outcomes	Primary (as specified in study): Unclear (order of outcomes changed between Introduction and Results)

Gonzalez 1994 *(Continued)*

	Secondary: All outcomes assessed at 1, 6, 10, 12, 18 and 24 h Pain intensity (0 = none, 3 = severe) Pain relief (0 = none, 3 = complete) Ventilatory function (oxygen saturation via pulse oximeter) Side effects
Source of funding	Not reported. Author COIs not reported
Were treatment groups comparable at baseline?	Baseline pain 2.8 and 2.6 for ketorolac and butorphanol, respectively. Sex distribution was "significantly" different between groups. Age, weight, height and baseline pain were similar. No additional information about type of surgeries, other than noting that most surgeries were abdominal
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants, personnel and outcome assessors	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not clear if all participants contributed data at all time points for all outcomes. No data presented for pain intensity. AEs not described per arm other than for nausea and vomiting
Selective reporting (reporting bias)	Unclear risk	All outcomes mentioned in Methods reported in Results, although pain and oxygen saturation presented graphically only
Sample size	Unclear risk	60 participants in each arm

Mehlisch 2003

Study characteristics

Methods	Single-center, placebo- and active-controlled, dose-ranging study. Interventions administered upon participant report of moderate to severe pain within 6 h of surgery. Efficacy outcomes assessed over 24 h post-administration or until rescue medication
Participants	Type of surgery: extraction of 2 or more impacted third molars (1 of which was mandibular) requiring bone removal **Ketorolac group** Entered/completing: 50/48 Age (mean, SD): 22.5 (no SD reported)

Mehlisch 2003 *(Continued)*

	Sex (male, %): 14 (28%) **Placebo group** Entered/completing: 50/50 Age (mean, SD): 23.4 Sex (male, %): 12 (24%) **Parecoxib group** Entered/completing: 51/50 Age (mean, SD): 22.5 Sex (male, %): 14 (27%) **Setting:** unspecified single site, USA **Dates Conducted:** not specified
Interventions	**Ketorolac:** 30 mg x 1 dose (no administration details) **Placebo:** no details **Parecoxib:** 20 mg x 1 dose (no administration details)
Outcomes	Primary (as specified in study): PID and pain relief via categorical scales at 15, 30, and 45 min; 1 h, 1.5 h, then hourly until 12 h and again at 16 and 24 h after administration of study drug or until rescue medication taken Time to onset of analgesia – time to perceptible analgesia and time to meaningful pain relief via 2 stopwatches Time to and proportion of participants requiring rescue medication Secondary: Global evaluation (anchors poor through excellent) Safety (number and frequency of AEs, changes in clinical laboratory findings; changes in vital signs and physical examination findings during the 24 h assessment period and up to 9 days post-treatment
Source of funding	Sponsored by Pharmacia Corporation, Skokie, IL. Author COIs not reported.
Were treatment groups comparable at baseline?	Yes: demographic (age, sex, race, weight) and clinical (degree of bony impaction, baseline pain intensity - ranging from 52 - 57% for moderate pain and 43 - 48% for severe pain) other than degree of surgical trauma (more severe in ketorolac and placebo groups)
Notes	Several doses of parecoxib were assessed. We chose the 20 mg dose as it is the dose closest to (but lower than) that used in practice. Data on other doses not presented here

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not mentioned

Mehlisch 2003 *(Continued)*

Blinding of participants, personnel and outcome assessors	Unclear risk	Participants blinded via double-dummy design. Blinding of investigators not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	< 10% of participants did not complete the study. Isolated missing data were imputed by linear interpolation
Selective reporting (reporting bias)	Unclear risk	Participants also recorded pain intensity using a VAS scale, but no results using this scale reported; proportion of participants requiring rescue medication reported, but not mentioned in Methods. All other outcomes mentioned in Methods reported in full in Results
Sample size	High risk	50 participants enrolled in ketorolac arm, but only 48 included in analysis. Placebo n = 50, parecoxib n = 50

Moodie 2013

Study characteristics	
Methods	Phase 2, single-center, placebo and active controlled, parallel group. On the morning after surgery and following the discontinuation of PCA for at least 30 minutes, participants had to have a minimum score of 40 mm on a 100-mm VAS pain assessment. Interventions administered at the start of the treatment period. Efficacy assessed over 8 h after intervention, safety over 30 days
Participants	Type of surgery: total hip or knee replacement **Ketorolac group** Entered/completing: 17/17 Age (mean, SD): 63.4, 8.0 Sex (male, %): 4 (23.5%) **Placebo group** Entered/completing: 36/35 Age (mean, SD): 61.6, 10.0 Sex (male, %): 28 (77.8%) **Setting:** Hamilton, New Zealand **Dates Conducted:** December 2008-February 2010
Interventions	**Ketorolac:** 30 mg bolus **Placebo:** as with ketorolac
Outcomes	Primary (as specified in study): SPID4 Secondary: Pain intensity 0.5, 1, 1.5, 2, 3, 4, 6, and 8 h Difference between groups in pain intensity over time

Moodie 2013 *(Continued)*

	Global quality of analgesia (1 = poor, 5 = excellent) Number of participants requiring rescue Adverse events through 24 h Serious adverse events through 30 days
Source of funding	Sponsored by KAI Pharmaceuticals, Inc., manufacturers of KAI-1678, including writing of study report. Dr. Pickthorn, Dr. Huang, and Dr. Bell were employees and stockholders of KAI Pharmaceuticals, Inc
Were treatment groups comparable at baseline?	Yes; for demographic (age, BMI) with exception of sex (23.5% male in ketorolac group vs 77.8% in placebo group) and clinical (surgery type (hip or knee), time to start of infusion, mean baseline pain intensity) variables
Notes	Investigational product KAI-1678 (PKC inhibitor) also administered. Not included in this extraction

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was stratified based on surgical procedure (total hip vs total knee replacement). Subjects were randomized 2:2:1 to KAI-1678, Placebo, or Ketorolac, respectively".
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants, personnel and outcome assessors	Low risk	Quote: "A double-dummy design was used with each subject receiving both an SQ infusion (KAI-1678 or saline) and an intravenous (IV) injection (ketorolac or saline) during the treatment period to ensure blinding".
Incomplete outcome data (attrition bias) All outcomes	Low risk	2 populations were defined: the MITT population and the evaluable population. The MITT population consisted of all participants who were randomized and received any amount of study medication. Safety analyses were also performed on the MITT population. Randomized participants who received study drug for at least 30 minutes without technical problems and had a baseline pain intensity score with at least 1 valid (i.e. participant did not receive rescue analgesics) post-baseline pain intensity score comprised the evaluable population. Missing data were imputed using LOCF. Efficacy analyses were performed on the evaluable population. Only 1 participant in the placebo group did not complete evaluations
Selective reporting (reporting bias)	High risk	Protocol available: ClinicalTrials.gov/ct2/show/NCT01015235. Secondary outcomes inconsistent between protocol and manuscript
Sample size	High risk	N = 17 ketorolac N = 36 placebo Predefined interim analysis determined enrolment > 110 (as planned) was not necessary

Parke 1995

Study characteristics

Parke 1995 *(Continued)*

Methods	Parallel, active and placebo-controlled, single-center. Pain assessed through 6 h; safety assessed through 24 h after surgery. Interventions administered upon participant report of moderate or severe pain (score of 2 or 3 on a VRS) within 2 h of the end of surgery
Participants	Type of surgery: major orthopedic (total hip or knee replacement; lumbar spine; shoulder reconstruction; internal fixation of fractures; miscellaneous) **Ketorolac group** Entered/completing: 38/37 Age (mean, SD): median 59 (no range reported) Sex (male, %): 17 (45%) **Placebo group** Entered/completing: 37/37 Age (mean, SD): median 56 (no range reported) Sex (male, %): 22 (59%) **Setting:** Reading, UK **Dates Conducted:** not specified
Interventions	**Ketorolac:** 30 mg/1 ml injection into a cannula flushed with saline **Placebo:** 0.9% saline 1 ml as with ketorolac
Outcomes	Primary (as specified in study): not specified Secondary: Verbal ordinal scale (0 - 100; every 2 min for 10 min after the injection, then every 5 min for 45 min, then at 1 h and hourly up to 6 h) and VRS (0 - 3; at 30 min, 45 min, 1 h, and then hourly up to 6 h) pain intensity Time to onset of analgesia (50% reduction in baseline pain scores occurring in 25% of patients) Proportion of participants whose pain decreased at 30 min by 1 point or more on the VRS Time to rescue analgesia Pain relief (0 = very poor, 4 = excellent) Overall acceptability of medication (0 = very poor, 4 = excellent) Vital signs (baseline, 45 min, 1 h, 2 h, and 24 h after the injections) Adverse events (at 24 h post surgery)
Source of funding	Syntex Research, Maidenhead (no details). Author COIs not reported.
Were treatment groups comparable at baseline?	Not explicitly stated, but demographics (age, weight) and clinical (intraoperative fentanyl dose, baseline pain) variables all appear similar between groups. Median duration of surgery was 73 min with IV ketorolac vs 55 min with placebo. Type of surgery varied, for IV ketorolac 43.2% had total hip replacement (29.7% placebo), and 35% had lumbar spine surgery (29.7% placebo). 8/37 (21.6%) in the placebo arm had internal fixation of fracture (vs 2.7% of IV ketorolac)
Notes	Third group administered 30 mg ketorolac IM (not included here)

Parke 1995 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated numbers table
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants, personnel and outcome assessors	Low risk	Quote: "All injections were drawn into opaque syringes from coded ampoules. Both patients and observers were unaware of the nature of the study medications administered".
Incomplete outcome data (attrition bias) All outcomes	Low risk	No mention of methods for accommodating missing data, but appears that all participants (other than one who was incorrectly included) completed the study and contributed data at all time points. Pain assessment was discontinued when a participant requested further analgesia
Selective reporting (reporting bias)	Low risk	All outcomes described in Methods reported in full in Results
Sample size	High risk	37 participants in both groups

Rasmussen 2002

Study characteristics	
Methods	Placebo and active controlled, multi-center, single-dose. Efficacy and safety assessed up to 24 h post interventions. Interventions administered on postoperative Day 1, after participants reported moderate to severe pain within 6 h of discontinuation of IV PCA
Participants	Type of surgery: Orthopedic (unilateral total knee replacement) **Ketorolac group** Entered/completing: 42/41 Age (mean, SD): 64.5 ± 10.7 Sex (male, %): 7, 17% **Placebo group** Entered/completing: 39/37 Age (mean, SD): 64.7 ± 10.1 Sex (male, %): 19, 49% **Parecoxib group** Entered/completing: 42/36 Age (mean, SD): 67.4 ± 8.3 Sex (male, %): 14, 33% **Morphine group**

Rasmussen 2002 *(Continued)*

	Entered/completing: 42/39 Age (mean, SD): 65.3 ± 9.4 Sex (male, %): 16, 38% **Setting:** Multiple sites, USA **Dates Conducted:** not specified
Interventions	**Ketorolac:** 30 mg, no further details **Placebo:** not specified **Parecoxib:** 40 mg, no further details **Morphine:** 4 mg, no further details
Outcomes	Primary (as specified in study): not specified Secondary: Median time to onset of analgesia (perceptible pain relief) Elicited pain intensity and pain relief (up to 24 h post-interventions, or until rescue medication) PID and SPID Global evaluation Median time to, and number of participants requiring rescue medication Adverse events and vital signs (up to 24 h post-interventions)
Source of funding	Pharmacia Corporation. 2 authors were employees of the sponsor
Were treatment groups comparable at baseline?	Yes: demographic (age, weight, race) except for sex, clinical (baseline pain intensity)
Notes	A fifth group received parecoxib 20 mg IV (not reported in this review). After surgery, participants received PCA until the first postoperative day. Rescue medication was permitted

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants, personnel and outcome assessors	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	MITT analysis (randomized participants who received study drug but who did not take rescue medication or withdraw from the study before 1 h pain assessment, did not take prohibited medication, did not have protocol violation, and did not miss 2 consecutive pain assessments in first 2 h). LOCF used for participants withdrawing or taking rescue medication. Most participants required

Rasmussen 2002 *(Continued)*

		rescue medication within 24 h assessment period. Unclear how random missing data were imputed
Selective reporting (reporting bias)	Low risk	All outcomes discussed in Methods reported in full in Results
Sample size	High risk	< 50 participants in each group

Romundstad 2004

Study characteristics	
Methods	Single-dose, parallel, active and placebo-controlled. Efficacy assessed over 72 h; safety assessed over 24 h. Interventions administered on the day after surgery if the participants reported need of an analgesic and had moderate to severe pain (> 2 on a 0 - 4 category verbal pain intensity scale)
Participants	Type of surgery: orthopedic (hip surgery, hip arthroplasty; femoral surgery, femoral rotational osteotomia, ankle surgery, ankle arthrodesis) **Ketorolac group** Entered/completing: 25/25 Age (mean, SD): 46, 16 Sex (male, %): 3 (12%) **Placebo group** Entered/completing: 25/25 Age (mean, SD): 42, 12 Sex (male, %): 7 (28%) **Methylprednisolone group** Entered/completing: 25/25 Age (mean, SD): 48, 15 Sex (male, %): 10 (40%) **Setting:** Oslo, Norway **Dates Conducted:** not specified
Interventions	**Ketorolac:** 30 mg diluted with saline to 10 ml and administered over 10 min **Placebo:** as with ketorolac **Methylprednisolone:** as with ketorolac
Outcomes	Primary (as specified in study): not specified Secondary: Present pain intensity (VAS, 0 = no pain, 100 = unbearable pain) at 15, 30 and 60 min, and then at 2, 3, 4, 5, 6 and 24 h after administration of the study medication

Romundstad 2004 *(Continued)*

	Pain relief (categorical, 0 = no relief, 4 = complete relief) at 15, 30 and 60 min, and then each hour until 6 h after the study medication was given The proportion of participants in each group, having > 50% of maximum obtainable total pain relief from 0 to 6 h (> 50% max TOTPAR) The proportion of participants in each group reporting at least 50% pain relief for longer than 4 h Time to rescue medication (ketobemidone) Opioid consumption (ketobemidone) up to 72 h Time to onset of perceptible and meaningful pain relief Side effects (open questions) through 6 h Unblinding (participants and observer asked 'Do you think the test medication was an active drug or placebo?')
Source of funding	Not reported. Author COIs not reported
Were treatment groups comparable at baseline?	Yes for demographic (age, sex, weight, height) and clinical variables (type and duration of surgery, anesthesia, and postoperative treatment). No significant differences were found in time from end of surgery to test drug administration. Baseline average (SD) pain intensity at start of test drug was 59 (21) for ketorolac, 63 (16) for methylprednisolone and 71 (18) for placebo
Notes	For 62 participants, postoperative pain relief before inclusion was epidural analgesia until 6 AM. The epidural was supplemented with IV ketobemidone as needed. 13 participants received only ketobemidone IV before they were given the test drug Rescue medication was ketobemidone 2 - 5 mg IV with paracetamol 1 g orally for the first dose of rescue. Thereafter, paracetamol was administered every 6 h Ages 17 and above. Mean age was > 40 in all groups

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	List of random numbers
Allocation concealment (selection bias)	Low risk	Block size and randomization code was not revealed to the investigators until all measurements and calculations had been entered into the database. Assignment according to information in opaque envelopes marked with consecutive patient numbers only
Blinding of participants, personnel and outcome assessors	Unclear risk	The test drugs were prepared by a doctor or nurse not in contact with the observer or participant, by diluting the active drugs with saline to fill a 10-ml syringe, marked with participant number and neutral information only. However, most participants and observers were able to guess if they had received active or placebo
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants completed the study. For those needing rescue analgesic before 6 h, subsequent data imputed using LOCF for pain intensity and 0 entered for pain relief
Selective reporting (reporting bias)	Low risk	No reference to protocol listed in text. All outcomes mentioned in Methods reported in Results in full
Sample size	High risk	25 in each arm

Zhou 2001

Study characteristics	
Methods	Double-dummy, placebo- and active-controlled, single-center Medication administered on postoperative day 1 when baseline pain reached moderate to severe intensity, after temporary discontinuation of PCA. Study period of 6 h
Participants	Type of surgery: orthopedic (total hip or knee replacement) **Ketorolac 30 mg group** Entered/completing: 28/27 Age (mean, SD): 60.6 ± 11.1 Sex (male, %): 6 (22%) **Ketorolac 15 mg group** Entered/completing: 29/28 Age (mean, SD): 64.2 ± 15.3 Sex (male, %): 8 (29%) **Placebo group** Entered/completing: 55/52 Age (mean, SD): 60.9 ± 12.4 Sex (male, %): 21 (40%) **Propacetamol group** Entered/completing: 60/57 Age (mean, SD): 61.4 ± 12.0 Sex (male, %): 21 (37%) **Setting:** Dallas, Texas, USA **Dates Conducted:** not specified
Interventions	**Ketorolac:** 30 mg or 15 mg over 2 min **Propacetamol:** 2 g over 15 min **Placebo:** saline, administered over 2 min or 15 min
Outcomes	Primary (as specified in study): Pain intensity (VRS, VAS) and pain relief scores (categorical) at rest, and derived summary measures Secondary: Time to onset of and number of participants experiencing analgesia (double-stopwatch method) Pain intensity with activity (VRS, VAS) Time to, number of participants requesting, and consumption of rescue medication (morphine via PCA) Global evaluation (categorical)

Zhou 2001 *(Continued)*

	Vital signs Sedation and nausea (VAS), other AEs
Source of funding	Supported in part by a grant from UPSA Inc., France, and in part by the White Mountain Institute (a non-for profit public charity) in Los Altos, CA. Author COIs not reported
Were treatment groups comparable at baseline?	Yes: demographic (age, height, weight, sex), anesthetic (ASA status, type of anesthesia) and surgical characteristics (type of surgery, total morphine dose, pain intensity). Baseline pain intensity (VRS) at rest was 2.2 to 2.3 among groups. Baseline VAS at rest was 58 to 63.9 among groups
Notes	PCA was available as rescue medication

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated schedule
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants, personnel and outcome assessors	Low risk	All study medication solutions prepared by a hospital pharmacist who was not involved in the data collection. Double-dummy technique employed
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	172 participants were initially randomized; 164 received the study medication and were included in the intention-to-treat analysis. No mention of how missing data were imputed
Selective reporting (reporting bias)	Low risk	All outcomes described in Methods reported in full in Results, other than sedation, nausea and vomiting, and vital signs (reported as not significantly different between groups)
Sample size	High risk	28 and 27 participants in ketorolac 15 mg and 30 mg groups, respectively N = 57 propacetamol; N = 52 placebo

AE = adverse event; ASA = American Society of Anesthesiologists physical status classification system; BMI: body mass index; CA = California; COI = conflict of interest; ECG = electrocardiogram; h = hour; IL = Illinois; ITT = intention-to-treat; IV = intravenous; kg = kilograms; LOCF = last observation carried forward; MA = Massachusetts; mg = milligrams; min = minutes; MITT = modified intention-to-treat; ml = milliliter; mm: millimeter; N/n = number; NJ = New Jersey; PACU = post-anesthesia care unit; PCA = patient-controlled analgesia; PI = pain intensity; PID = pain intensity difference; PR = pain relief; SD = standard deviation; SPID = summed pain intensity difference; SPRID = summed pain relief intensity differences; TOTPAR = total pain relief; VAS = visual analog scale; VRS = verbal rating scale; WOCF = worst observation carried forward.

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

Study	Reason for exclusion
Anderson 1993	Ineligible route of administration
Aziz 2003	Intraoperative administration
Babaeva 1997	Ineligible route of administration

Study	Reason for exclusion
Beliaeva 1995	Ineligible route of administration
Bloomfield 1988	Ineligible route of administration
Bosek 1994	Intraoperative administration
Boussofara 2006	Continuous infusion
Brown 1988	Article unavailable from any source
Brown 1990	Multiple- dose study without separate data from first dose
Carretta 1996	Ineligible route of administration
Cassinelli 2008	Intraoperative administration
Castillo 2017	Preoperative administration
Coloma 2000	Preoperative administration
Conti 2007	Multiple-dose study without separate data from first dose
Crespo 1994	Multiple-dose study without separate data from first dose
Duttchen 2017	Ineligible comparator
Dwarica 2020	Not blinded
Eftekharian 2017	We could not establish that participants had moderate to severe baseline pain
Fletcher 1995	Ineligible outcomes
Forrest 2002	Ineligible study design
Gan 2017	Duplicate
Garcia-Harel 2005	Multiple-dose study without separate data from first dose
Gilron 2000	< 10 participants in each arm
Greco 1994	Preoperative administration
Hegazy 2003	Article unavailable
Irct20140519017756N 2018	Not blinded
Irct20171111037369N 2018	Not blinded
Irct20180425039418N 2018	Not blinded
Iyer 2019a	No 4- or 6-hour assessment
Iyer 2019b	Duplicate
Izquierdo 1995	Not blinded

Study	Reason for exclusion
Kumar 1996	We could not establish that participants had moderate to severe baseline pain
Lee 2002	Ineligible patient population
Lee 2007	No 4- or 6-hour assessment
Lowder 2003	We could not establish that participants had moderate to severe baseline pain
Moeller 2012	No 4- or 6-hour assessment
NCT00293631	Registered on clinical trials website more than 5 years ago with no results posted
NCT00507026	Multiple-dose study without separate data from first dose
NCT00845754	Registered on clinical trials website more than 5 years ago with no results posted
NCT00868348	Ineligible route of administration
NCT01514175	Preoperative administration
NCT01901393	We could not establish that participants had moderate to severe baseline pain
NCT03178539	Intraoperative administration
NCT03331315	Not blinded
O'Hara 1997	Continuous infusion
Olle 2000	Intraoperative administration
Oriol-Lopez 2018	Preoperative administration
Pace 2009	Abstract without enough data
Parker 1994	Intraoperative administration
Patrocinio 2007	No 4- or 6-hour assessment
Pavy 2001	Continuous infusion
Peirce 1990	Multiple-dose study without separate data from first dose
Perttunen 1999	Preoperative administration
Petrov 2009	Ineligible route of administration
Pichard 2009	Not an RCT
Pickett 2016	No 4- or 6-hour assessment
Putland 1999	Preoperative administration
Raithatha 1996	Ineligible intervention
Rakowski 2013	No 4- or 6-hour assessment

Study	Reason for exclusion
Rakowski 2019	No 4- or 6-hour assessment
Ranucci 1999	Intraoperative administration
Rautela 1998	Ineligible route of administration
Ready 1994	Multiple-dose study without separate data from first dose
Reuben 1995	No 4- or 6-hour assessment
Reuben 1997	We could not establish that participants had moderate to severe baseline pain
Reuben 1998	We could not establish that participants had moderate to severe baseline pain
Schlachta 2007	No 4- or 6-hour assessment
See 1995	Not an RCT
Sevarino 1994	We could not establish that participants had moderate to severe baseline pain
Shah 2017	Ineligible route of administration
Singh 1997	We could not establish that participants had moderate to severe baseline pain
Singla 2018	Abstract without enough data
Thagaard 2007	Intraoperative administration
Trowbridge 2016	Duplicate
Trowbridge 2018	No 4- or 6-hour assessment
Twersky 1995	Multiple-dose study without separate data from first dose
Varrassi 1999	We could not establish that participants had moderate to severe baseline pain
Vergara 1998	Multiple-dose study without separate data from first dose
Wig 2008	No 4- or 6-hour assessments
Wong 1993	Multiple-dose study without separate data from first dose
Xu 2016	Continuous infusion

RCT = randomized controlled trial

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

Claus 2019

Study name	The effect of ketorolac on posterior thoracolumbar spinal fusions: a prospective double-blinded randomized placebo-controlled trial protocol
Methods	Multi-hospital, prospective, double-blinded, placebo-controlled, parallel

Claus 2019 *(Continued)*

Participants	Adults aged 18 – 80 years who elect to undergo posterior thoracolumbar spinal fusion at 2 sites in secondary and tertiary care settings. Estimated enrolment: 600
Interventions	Active intervention: ketorolac 15 mg IV every 6 hours for 48 hours in addition to multimodal pain regimen; placebo
Outcomes	Fusion rates, postoperative opioid use, pain scores, length of stay
Starting date	03 October 2017
Contact information	Dr Chad F Claus: chadfclaus@gmail.com
Notes	

Irct201607271674N 2016

Study name	Effect of intravenous ketorolac on postoperative pain in mandibular fracture surgery
Methods	Double-blind, parallel, placebo-controlled, single-dose, Phase 2
Participants	Adults aged 16 - 47 years scheduled to undergo mandibular fractured surgery. Estimated enrolment: 50
Interventions	IV ketorolac 30 mg for 30 s at end of the operation in post-anesthesia care unit immediately upon the onset of pain; placebo
Outcomes	Intensity of postoperative pain Immediately after surgery to 4 hours after surgery, opioid use, postoperative complications of ketorolac
Starting date	21 April 2015
Contact information	Hamid Reza Eftekharian: eftekharhr@sums.ac.ir
Notes	

Irct2017041033350N 2017

Study name	Effect of ketorolac and paracetamol on pain control after inguinal hernia surgery
Methods	Double-blind, parallel, active comparator, Phase 2
Participants	Adults aged 20 - 50 years; American Society of Anesthesiologists (ASA) physical status classification system I and II, undergoing inguinal hernia surgery. Target sample size: 74
Interventions	Ketorolac (maximal dosage of 120 mg daily) 1 hour after fentanyl injection; paracetamol (15 mg/ kg every 6 hours, maximal dosage of 60 mg/ kg, daily) 1 hour after fentanyl injection
Outcomes	Pain intensity up to 6 h post-interventions
Starting date	05 May 2017
Contact information	Dr. Ali Mahmoud Janlou: mahmoud.janlou@goums.ac.ir

Irct2017041033350N 2017 *(Continued)*

Notes	

Irct20171003036530N 2018

Study name	The comparison of efficacy and side effects of IV (intravenous) ibuprofen and intravenous ketorolac in laparoscopic cholecystectomy patients
Methods	Triple-blind active-controlled, parallel, single-center, Phase 3
Participants	Adults aged 20 - 60 years undergoing laparoscopic cholecystectomy surgery. Target sample size: 90
Interventions	IV ketorolac 30 mg at zero, 8 and 16 h after surgery; IV ibuprofen 80 mg at intervals of zero, 8 and 16 h after surgery
Outcomes	Abdominal and shoulder pain, nausea and vomiting, loss of consciousness, up to 24 h postoperatively
Starting date	05 May 2018
Contact information	Dr Ali Mohamadian: sagarmehrmed@yahoo.com
Notes	

Irct20180909040979N 2019

Study name	Comparison of the effect of intravenous ketorolac and paracetamol on pain after coronary artery bypass graft surgery
Methods	Double-blind active-controlled, parallel, single-center, Phase 2 - 3
Participants	Adults aged 30 - 70 years undergoing coronary artery bypass. Target sample size: 60
Interventions	Ketorolac 0.5 mg / kg in 100 ml of normal saline for 30 minutes, every 6 h up to 24 h; paracetamol 10 mg / kg diluted in 100 ml of normal saline for 30 minutes every 6 h up to 24 h
Outcomes	Primary: postoperative pain control, arterial oxygen saturation drop, blood pressure changes, chest tube discharge. Secondary: arrhythmia, duration of ventilator dependence
Starting date	23 September 2019
Contact information	Fatemeh Javaherforoosh zadeh: f_javaherforoosh@yahoo.com
Notes	

NCT02700451

Study name	Post-op acetaminophen vs NSAID use on lumbar spinal fusion outcomes
Methods	Quadruple-blind active- and placebo-controlled, parallel, single-center

NCT02700451 *(Continued)*

Participants	Adults aged 18 - 75 undergoing 1 or 2 level lumbar spinal fusion through posterior or lateral approach. Estimated enrolment: 300
Interventions	Ketorolac IV 30 mg (ages 18 - 64 years) or 15 mg (ages 65 - 75 years); acetaminophen 1000 mg IV; normal saline IV. All every 6 h for 48 h in addition to patient-controlled analgesia and oral opioids as needed
Outcomes	Primary: perioperative opioid use. Secondary: 26 outcomes including opioid use, pain intensity and adverse events
Starting date	March 2016
Contact information	Evangelia Zgonis
Notes	

NCT03823534

Study name	Post-op pain control for prophylactic intramedullary nailing
Methods	Double-blind, placebo-controlled, parallel, single-center, Phase 3
Participants	Adults aged over 18 years with femoral shaft or neck bone lesion undergoing prophylactic placement of intramedullary femoral nails. Estimated enrolment: 60
Interventions	Ketorolac IV 30 mg (ages 18 - 64 years) or 15 mg (ages 65 and above); placebo. Both every 6 h over the course of the first 24 hours after surgery
Outcomes	Primary: opioid use. Secondary: pain intensity, limb function
Starting date	20 February 2019
Contact information	David Greenberg, MD: david.greenberg@health.slu.edu
Notes	

h = hour(s); IV = intravenous; kg = kilogram; mg = milligram; NSAID = nonsteroidal antiinflammatory drug; s = seconds

DATA AND ANALYSES

Comparison 1. Ketorolac versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Number of participants with at least 50% pain relief at 4 hours	8	658	Risk Ratio (M-H, Random, 95% CI)	2.81 [1.80, 4.37]
1.2 Number of participants with at least 50% pain relief at 6 hours	10	914	Risk Ratio (M-H, Random, 95% CI)	3.26 [1.93, 5.51]

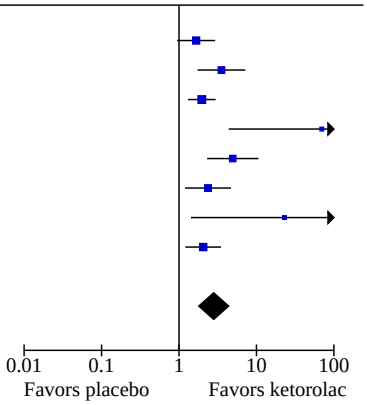
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.3 Number of participants using rescue medication over 4 to 6 hours post interventions	5	417	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.36, 1.00]
1.4 Number of participants withdrawing due to adverse events	10	945	Risk Ratio (M-H, Fixed, 95% CI)	1.31 [0.56, 3.06]
1.5 Number of participants withdrawing due to lack of efficacy	7	698	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.36, 1.78]
1.6 Number of participants withdrawing for any cause	7	634	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.47, 1.36]
1.7 Number of participants reporting any adverse event	8	810	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [1.00, 1.19]
1.8 Number of participants reporting a serious adverse event	8	703	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.13, 3.03]
1.9 Number of participants experiencing a cardiovascular event	2	323	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.63, 2.03]
1.10 Number of participants experiencing operative site bleeding	2	241	Risk Ratio (M-H, Fixed, 95% CI)	3.78 [0.67, 21.26]
1.11 Number of participants experiencing thrombophlebitis	2		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.12 Number of participants reporting nausea	8	798	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.75, 1.04]
1.13 Number of participants experiencing vomiting	7	724	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.59, 1.20]
1.14 Number of participants reporting pruritus	5	574	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.49, 1.50]
1.15 Number of participants experiencing respiratory depression	2	246	Risk Ratio (M-H, Fixed, 95% CI)	0.42 [0.14, 1.33]
1.16 Number of participants experiencing sedation	6	566	Risk Ratio (M-H, Fixed, 95% CI)	0.47 [0.25, 0.86]
1.17 Number of participants with at least 50% pain relief at 4 hours: subgroup analysis	8	658	Risk Ratio (M-H, Random, 95% CI)	2.81 [1.80, 4.37]
1.17.1 Abdominal/pelvic	3	300	Risk Ratio (M-H, Random, 95% CI)	2.13 [1.47, 3.08]
1.17.2 Dental	1	98	Risk Ratio (M-H, Random, 95% CI)	69.73 [4.39, 1107.05]
1.17.3 Orthopedic	4	260	Risk Ratio (M-H, Random, 95% CI)	3.04 [1.67, 5.53]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.18 Number of participants with at least 50% pain relief at 6 hours: subgroup analysis	10	914	Risk Ratio (M-H, Random, 95% CI)	3.26 [1.93, 5.51]
1.18.1 Abdominal/pelvic	4	458	Risk Ratio (M-H, Random, 95% CI)	1.81 [1.21, 2.73]
1.18.2 Dental	2	196	Risk Ratio (M-H, Random, 95% CI)	22.72 [6.64, 77.67]
1.18.3 Orthopedic	4	260	Risk Ratio (M-H, Random, 95% CI)	3.22 [1.90, 5.46]

Analysis 1.1. Comparison 1: Ketorolac versus placebo, Outcome 1: Number of participants with at least 50% pain relief at 4 hours

Study or Subgroup	Ketorolac Events	Ketorolac Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Balestrieri 1997	24	68	14	66	16.6%	1.66 [0.95 , 2.93]
Barton 2002	26	41	7	39	14.3%	3.53 [1.74 , 7.19]
Bikhazi 2004	32	42	17	44	19.0%	1.97 [1.31 , 2.97]
Mehlisch 2003	33	48	0	50	2.3%	69.73 [4.39 , 1107.05]
Moodie 2013	14	17	6	36	13.6%	4.94 [2.30 , 10.60]
Rasmussen 2002	21	41	8	37	14.8%	2.37 [1.20 , 4.69]
Romundstad 2004	11	25	0	25	2.3%	23.00 [1.43 , 370.27]
Zhou 2001	16	27	15	52	17.1%	2.05 [1.21 , 3.49]
Total (95% CI)		**309**		**349**	**100.0%**	**2.81 [1.80 , 4.37]**
Total events:	177		67			

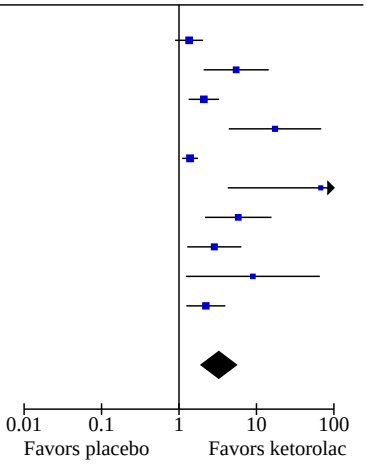
Heterogeneity: Tau² = 0.23; Chi² = 20.08, df = 7 (P = 0.005); I² = 65%
Test for overall effect: Z = 4.56 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 1.2. Comparison 1: Ketorolac versus placebo, Outcome 2: Number of participants with at least 50% pain relief at 6 hours

Study or Subgroup	Ketorolac Events	Ketorolac Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Balestrieri 1997	32	68	23	66	13.7%	1.35 [0.89 , 2.05]
Barton 2002	23	41	4	39	9.9%	5.47 [2.08 , 14.39]
Bikhazi 2004	30	42	15	44	13.4%	2.10 [1.33 , 3.30]
Christensen 2011	32	47	2	51	7.4%	17.36 [4.40 , 68.49]
Gan 2012	63	82	42	76	14.5%	1.39 [1.10 , 1.76]
Mehlisch 2003	32	48	0	50	2.9%	67.65 [4.26 , 1074.69]
Moodie 2013	11	17	4	36	9.8%	5.82 [2.17 , 15.65]
Rasmussen 2002	19	41	6	37	11.1%	2.86 [1.28 , 6.38]
Romundstad 2004	9	25	1	25	4.7%	9.00 [1.23 , 65.85]
Zhou 2001	15	27	13	52	12.6%	2.22 [1.25 , 3.97]
Total (95% CI)		**438**		**476**	**100.0%**	**3.26 [1.93 , 5.51]**
Total events:	266		110			

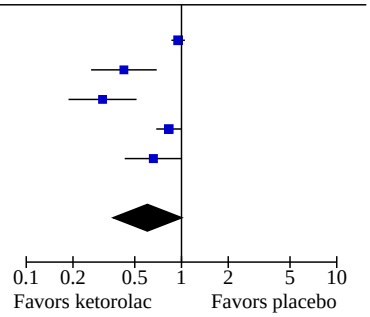
Heterogeneity: Tau² = 0.48; Chi² = 55.55, df = 9 (P < 0.00001); I² = 84%
Test for overall effect: Z = 4.42 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 1.3. Comparison 1: Ketorolac versus placebo, Outcome 3: Number of participants using rescue medication over 4 to 6 hours post interventions

Study or Subgroup	Ketorolac Events	Ketorolac Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Barton 2002	38	41	38	39	22.1%	0.95 [0.86 , 1.05]
Bikhazi 2004	13	42	32	44	18.5%	0.43 [0.26 , 0.69]
Christensen 2011	12	47	42	51	18.3%	0.31 [0.19 , 0.51]
Parke 1995	29	37	35	37	21.7%	0.83 [0.69 , 1.00]
Zhou 2001	13	27	38	52	19.3%	0.66 [0.43 , 1.01]
Total (95% CI)		**194**		**223**	**100.0%**	**0.60 [0.36 , 1.00]**
Total events:	105		185			

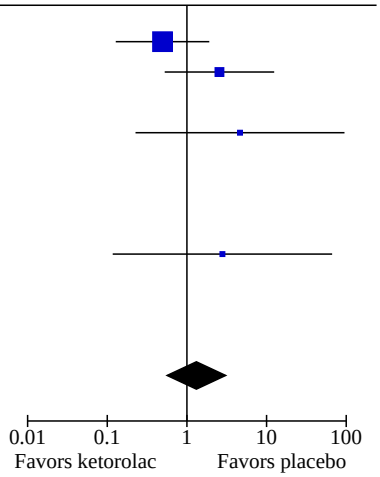
Heterogeneity: Tau² = 0.30; Chi² = 80.82, df = 4 (P < 0.00001); I² = 95%
Test for overall effect: Z = 1.95 (P = 0.05)
Test for subgroup differences: Not applicable



Analysis 1.4. Comparison 1: Ketorolac versus placebo, Outcome 4: Number of participants withdrawing due to adverse events

Study or Subgroup	Ketorolac Events	Ketorolac Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Balestrieri 1997	3	83	6	82	66.7%	0.49 [0.13 , 1.91]
Barton 2002	5	41	2	42	21.8%	2.56 [0.53 , 12.46]
Christensen 2011	0	47	0	51		Not estimable
Gan 2012	2	82	0	76	5.7%	4.64 [0.23 , 95.10]
Mehlisch 2003	0	50	0	50		Not estimable
Moodie 2013	0	17	0	36		Not estimable
Parke 1995	0	37	0	37		Not estimable
Rasmussen 2002	1	42	0	39	5.7%	2.79 [0.12 , 66.54]
Romundstad 2004	0	25	0	25		Not estimable
Zhou 2001	0	28	0	55		Not estimable
Total (95% CI)		**452**		**493**	**100.0%**	**1.31 [0.56 , 3.06]**
Total events:	11		8			

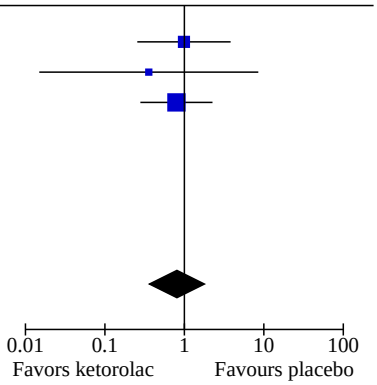
Heterogeneity: Chi² = 3.58, df = 3 (P = 0.31); I² = 16%
Test for overall effect: Z = 0.63 (P = 0.53)
Test for subgroup differences: Not applicable



Analysis 1.5. Comparison 1: Ketorolac versus placebo, Outcome 5: Number of participants withdrawing due to lack of efficacy

Study or Subgroup	Ketorolac Events	Ketorolac Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Balestrieri 1997	4	83	4	82	31.6%	0.99 [0.26 , 3.82]
Bikhazi 2004	0	42	1	45	11.4%	0.36 [0.01 , 8.52]
Gan 2012	6	82	7	76	57.0%	0.79 [0.28 , 2.26]
Parke 1995	0	37	0	37		Not estimable
Rasmussen 2002	0	42	0	39		Not estimable
Romundstad 2004	0	25	0	25		Not estimable
Zhou 2001	0	28	0	55		Not estimable
Total (95% CI)		**339**		**359**	**100.0%**	**0.81 [0.36 , 1.78]**
Total events:	10		12			

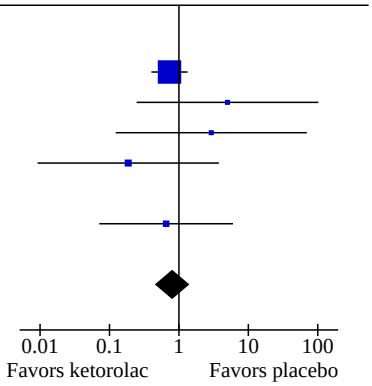
Heterogeneity: Chi² = 0.34, df = 2 (P = 0.84); I² = 0%
Test for overall effect: Z = 0.53 (P = 0.59)
Test for subgroup differences: Not applicable



Analysis 1.6. Comparison 1: Ketorolac versus placebo, Outcome 6: Number of participants withdrawing for any cause

Study or Subgroup	Ketorolac Events	Ketorolac Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bikhazi 2004	0	42	0	45		Not estimable
Gan 2012	15	82	19	76	77.8%	0.73 [0.40 , 1.33]
Mehlisch 2003	2	50	0	50	2.0%	5.00 [0.25 , 101.58]
Parke 1995	1	38	0	37	2.0%	2.92 [0.12 , 69.54]
Rasmussen 2002	0	42	2	39	10.2%	0.19 [0.01 , 3.76]
Romundstad 2004	0	25	0	25		Not estimable
Zhou 2001	1	28	3	55	8.0%	0.65 [0.07 , 6.01]
Total (95% CI)		**307**		**327**	**100.0%**	**0.80 [0.47 , 1.36]**
Total events:	19		24			

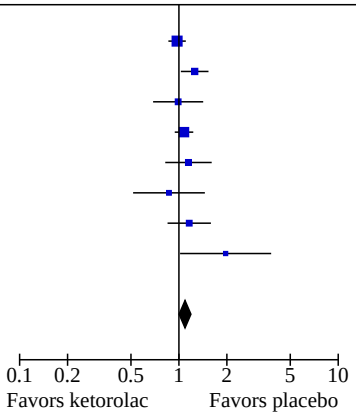
Heterogeneity: Chi² = 3.08, df = 4 (P = 0.54); I² = 0%
Test for overall effect: Z = 0.83 (P = 0.41)
Test for subgroup differences: Not applicable



Analysis 1.7. Comparison 1: Ketorolac versus placebo, Outcome 7: Number of participants reporting any adverse event

Study or Subgroup	Ketorolac Events	Ketorolac Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Balestrieri 1997	70	83	71	82	26.9%	0.97 [0.86 , 1.10]
Barton 2002	38	41	31	42	11.5%	1.26 [1.03 , 1.53]
Bikhazi 2004	24	42	26	45	9.5%	0.99 [0.69 , 1.42]
Gan 2012	72	82	62	76	24.2%	1.08 [0.94 , 1.23]
Mehlisch 2003	31	50	27	50	10.2%	1.15 [0.82 , 1.61]
Moodie 2013	9	17	22	36	5.3%	0.87 [0.52 , 1.45]
Rasmussen 2002	30	42	24	39	9.4%	1.16 [0.85 , 1.59]
Zhou 2001	12	28	12	55	3.0%	1.96 [1.02 , 3.79]
Total (95% CI)		**385**		**425**	**100.0%**	**1.09 [1.00 , 1.19]**
Total events:	286		275			

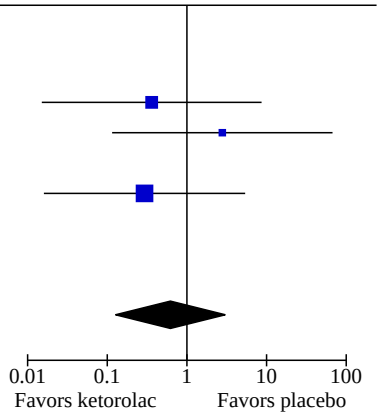
Heterogeneity: Chi² = 9.44, df = 7 (P = 0.22); I² = 26%
Test for overall effect: Z = 2.04 (P = 0.04)
Test for subgroup differences: Not applicable



Analysis 1.8. Comparison 1: Ketorolac versus placebo, Outcome 8: Number of participants reporting a serious adverse event

Study or Subgroup	Ketorolac Events	Ketorolac Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Barton 2002	0	41	0	42		Not estimable
Bikhazi 2004	0	42	0	45		Not estimable
Christensen 2011	0	47	1	51	33.9%	0.36 [0.02 , 8.65]
Gan 2012	1	82	0	76	12.2%	2.78 [0.12 , 67.30]
Mehlisch 2003	0	50	0	50		Not estimable
Moodie 2013	0	17	3	36	53.9%	0.29 [0.02 , 5.39]
Parke 1995	0	37	0	37		Not estimable
Romundstad 2004	0	25	0	25		Not estimable
Total (95% CI)		**341**		**362**	**100.0%**	**0.62 [0.13 , 3.03]**
Total events:	1		4			

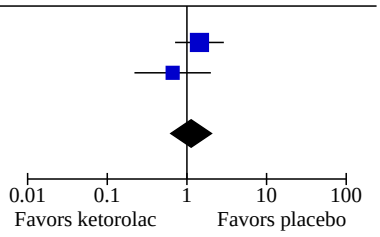
Heterogeneity: Chi² = 1.22, df = 2 (P = 0.54); I² = 0%
Test for overall effect: Z = 0.59 (P = 0.56)
Test for subgroup differences: Not applicable



Analysis 1.9. Comparison 1: Ketorolac versus placebo, Outcome 9: Number of participants experiencing a cardiovascular event

Study or Subgroup	Ketorolac Events	Ketorolac Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Balestrieri 1997	16	83	11	82	60.4%	1.44 [0.71 , 2.91]
Gan 2012	5	82	7	76	39.6%	0.66 [0.22 , 2.00]
Total (95% CI)		**165**		**158**	**100.0%**	**1.13 [0.63 , 2.03]**
Total events:	21		18			

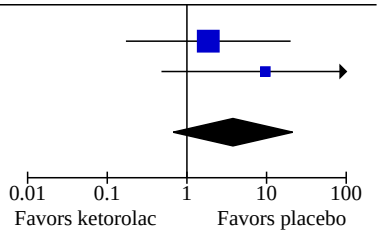
Heterogeneity: Chi² = 1.35, df = 1 (P = 0.25); I² = 26%
Test for overall effect: Z = 0.41 (P = 0.68)
Test for subgroup differences: Not applicable



Analysis 1.10. Comparison 1: Ketorolac versus placebo, Outcome 10: Number of participants experiencing operative site bleeding

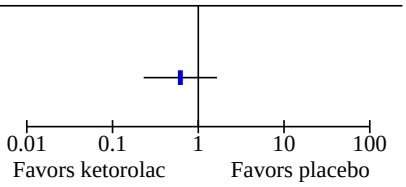
Study or Subgroup	Ketorolac Events	Ketorolac Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Gan 2012	2	82	1	76	75.3%	1.85 [0.17 , 20.03]
Zhou 2001	2	28	0	55	24.7%	9.66 [0.48 , 194.53]
Total (95% CI)		**110**		**131**	**100.0%**	**3.78 [0.67 , 21.26]**
Total events:	4		1			

Heterogeneity: Chi² = 0.72, df = 1 (P = 0.40); I² = 0%
Test for overall effect: Z = 1.51 (P = 0.13)
Test for subgroup differences: Not applicable



Analysis 1.11. Comparison 1: Ketorolac versus placebo, Outcome 11: Number of participants experiencing thrombophlebitis

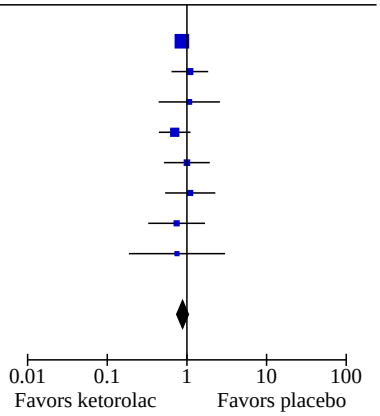
Study or Subgroup	Ketorolac Events	Ketorolac Total	Placebo Events	Placebo Total	Risk Ratio M-H, Fixed, 95% CI
Christensen 2011	0	47	0	51	Not estimable
Gan 2012	6	82	9	76	0.62 [0.23 , 1.65]



Analysis 1.12. Comparison 1: Ketorolac versus placebo, Outcome 12: Number of participants reporting nausea

Study or Subgroup	Ketorolac Events	Ketorolac Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Balestrieri 1997	56	83	64	82	41.4%	0.86 [0.72 , 1.04]
Barton 2002	17	41	16	42	10.2%	1.09 [0.64 , 1.85]
Bikhazi 2004	8	42	8	45	5.0%	1.07 [0.44 , 2.60]
Gan 2012	22	82	29	76	19.4%	0.70 [0.44 , 1.11]
Mehlisch 2003	13	50	13	50	8.4%	1.00 [0.52 , 1.94]
Parke 1995	11	37	10	37	6.4%	1.10 [0.53 , 2.27]
Rasmussen 2002	8	42	10	39	6.7%	0.74 [0.33 , 1.69]
Romundstad 2004	3	25	4	25	2.6%	0.75 [0.19 , 3.01]
Total (95% CI)		**402**		**396**	**100.0%**	**0.88 [0.75 , 1.04]**
Total events:	138		154			

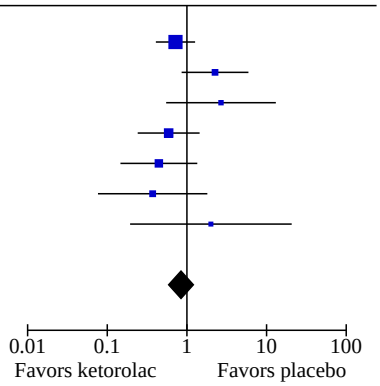
Heterogeneity: Chi² = 2.49, df = 7 (P = 0.93); I² = 0%
Test for overall effect: Z = 1.47 (P = 0.14)
Test for subgroup differences: Not applicable



Analysis 1.13. Comparison 1: Ketorolac versus placebo, Outcome 13: Number of participants experiencing vomiting

Study or Subgroup	Ketorolac Events	Ketorolac Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Balestrieri 1997	16	83	22	82	39.8%	0.72 [0.41 , 1.27]
Barton 2002	11	41	5	42	8.9%	2.25 [0.86 , 5.92]
Bikhazi 2004	5	42	2	45	3.5%	2.68 [0.55 , 13.07]
Gan 2012	7	82	11	76	20.5%	0.59 [0.24 , 1.44]
Mehlisch 2003	4	50	9	50	16.2%	0.44 [0.15 , 1.35]
Rasmussen 2002	2	42	5	39	9.3%	0.37 [0.08 , 1.80]
Romundstad 2004	2	25	1	25	1.8%	2.00 [0.19 , 20.67]
Total (95% CI)		**365**		**359**	**100.0%**	**0.84 [0.59 , 1.20]**
Total events:	47		55			

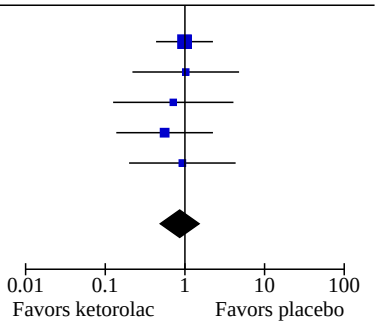
Heterogeneity: Chi² = 9.78, df = 6 (P = 0.13); I² = 39%
Test for overall effect: Z = 0.94 (P = 0.35)
Test for subgroup differences: Not applicable



Analysis 1.14. Comparison 1: Ketorolac versus placebo, Outcome 14: Number of participants reporting pruritus

Study or Subgroup	Ketorolac Events	Ketorolac Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Balestrieri 1997	10	83	10	82	41.5%	0.99 [0.43 , 2.25]
Barton 2002	3	41	3	42	12.2%	1.02 [0.22 , 4.78]
Bikhazi 2004	2	42	3	45	12.0%	0.71 [0.13 , 4.07]
Gan 2012	3	82	5	76	21.4%	0.56 [0.14 , 2.25]
Rasmussen 2002	3	42	3	39	12.8%	0.93 [0.20 , 4.33]
Total (95% CI)		**290**		**284**	**100.0%**	**0.86 [0.49 , 1.50]**
Total events:	21		24			

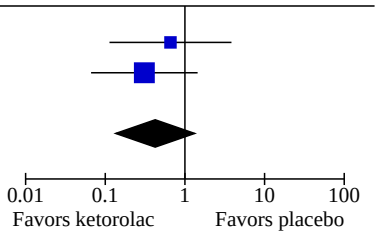
Heterogeneity: Chi² = 0.59, df = 4 (P = 0.96); I² = 0%
Test for overall effect: Z = 0.53 (P = 0.60)
Test for subgroup differences: Not applicable



Analysis 1.15. Comparison 1: Ketorolac versus placebo, Outcome 15: Number of participants experiencing respiratory depression

Study or Subgroup	Ketorolac Events	Ketorolac Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Balestrieri 1997	2	83	3	82	32.7%	0.66 [0.11 , 3.84]
Rasmussen 2002	2	42	6	39	67.3%	0.31 [0.07 , 1.44]
Total (95% CI)		**125**		**121**	**100.0%**	**0.42 [0.14 , 1.33]**
Total events:	4		9			

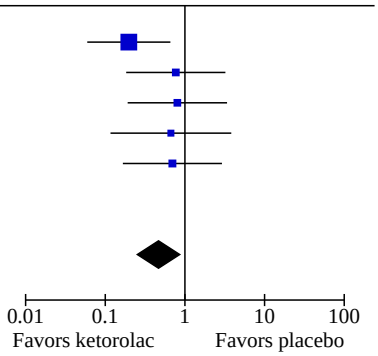
Heterogeneity: Chi² = 0.40, df = 1 (P = 0.53); I² = 0%
Test for overall effect: Z = 1.48 (P = 0.14)
Test for subgroup differences: Not applicable



Analysis 1.16. Comparison 1: Ketorolac versus placebo, Outcome 16: Number of participants experiencing sedation

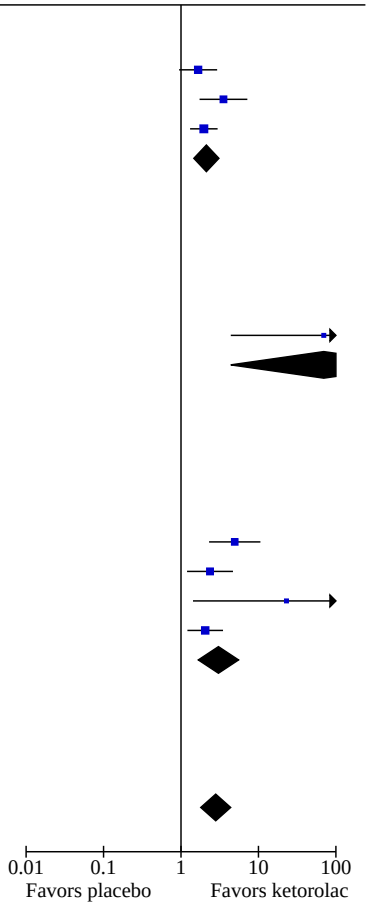
Study or Subgroup	Ketorolac Events	Ketorolac Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Balestrieri 1997	3	83	15	82	50.2%	0.20 [0.06 , 0.66]
Barton 2002	3	41	4	42	13.1%	0.77 [0.18 , 3.22]
Bikhazi 2004	3	42	4	45	12.9%	0.80 [0.19 , 3.38]
Mehlisch 2003	2	50	3	50	10.0%	0.67 [0.12 , 3.82]
Rasmussen 2002	3	42	4	39	13.8%	0.70 [0.17 , 2.92]
Romundstad 2004	0	25	0	25		Not estimable
Total (95% CI)		**283**		**283**	**100.0%**	**0.47 [0.25 , 0.86]**
Total events:	14		30			

Heterogeneity: Chi² = 3.44, df = 4 (P = 0.49); I² = 0%
Test for overall effect: Z = 2.45 (P = 0.01)
Test for subgroup differences: Not applicable

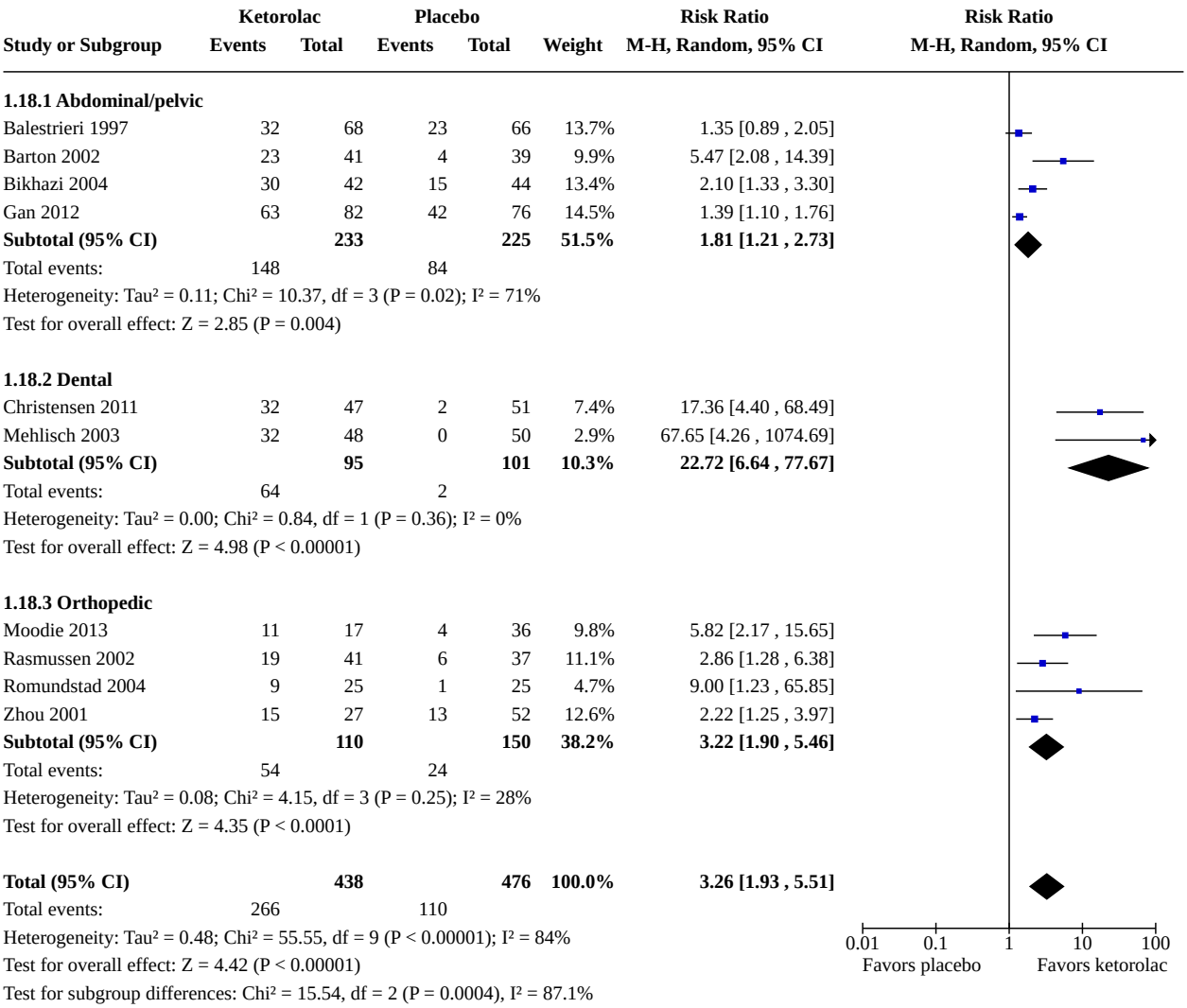


Analysis 1.17. Comparison 1: Ketorolac versus placebo, Outcome 17: Number of participants with at least 50% pain relief at 4 hours: subgroup analysis

Study or Subgroup	Ketorolac Events	Ketorolac Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
1.17.1 Abdominal/pelvic						
Balestrieri 1997	24	68	14	66	16.6%	1.66 [0.95 , 2.93]
Barton 2002	26	41	7	39	14.3%	3.53 [1.74 , 7.19]
Bikhazi 2004	32	42	17	44	19.0%	1.97 [1.31 , 2.97]
Subtotal (95% CI)		**151**		**149**	**49.9%**	**2.13 [1.47 , 3.08]**
Total events:	82		38			
Heterogeneity: Tau² = 0.03; Chi² = 2.84, df = 2 (P = 0.24); I² = 30%						
Test for overall effect: Z = 3.97 (P < 0.0001)						
1.17.2 Dental						
Mehlisch 2003	33	48	0	50	2.3%	69.73 [4.39 , 1107.05]
Subtotal (95% CI)		**48**		**50**	**2.3%**	**69.73 [4.39 , 1107.05]**
Total events:	33		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.01 (P = 0.003)						
1.17.3 Orthopedic						
Moodie 2013	14	17	6	36	13.6%	4.94 [2.30 , 10.60]
Rasmussen 2002	21	41	8	37	14.8%	2.37 [1.20 , 4.69]
Romundstad 2004	11	25	0	25	2.3%	23.00 [1.43 , 370.27]
Zhou 2001	16	27	15	52	17.1%	2.05 [1.21 , 3.49]
Subtotal (95% CI)		**110**		**150**	**47.8%**	**3.04 [1.67 , 5.53]**
Total events:	62		29			
Heterogeneity: Tau² = 0.18; Chi² = 6.37, df = 3 (P = 0.09); I² = 53%						
Test for overall effect: Z = 3.65 (P = 0.0003)						
Total (95% CI)		**309**		**349**	**100.0%**	**2.81 [1.80 , 4.37]**
Total events:	177		67			
Heterogeneity: Tau² = 0.23; Chi² = 20.08, df = 7 (P = 0.005); I² = 65%						
Test for overall effect: Z = 4.56 (P < 0.00001)						
Test for subgroup differences: Chi² = 6.70, df = 2 (P = 0.04), I² = 70.1%						



Analysis 1.18. Comparison 1: Ketorolac versus placebo, Outcome 18: Number of participants with at least 50% pain relief at 6 hours: subgroup analysis



Comparison 2. Ketorolac versus other NSAID

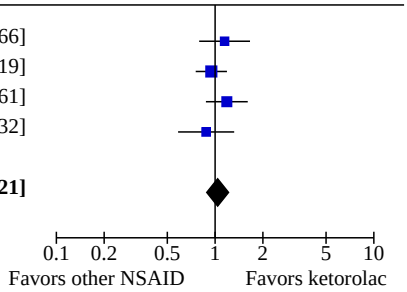
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Number of participants with at least 50% pain relief at 4 hours	4	337	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.89, 1.21]
2.2 Number of participants with at least 50% pain relief at 6 hours	6	603	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.95, 1.19]
2.3 Number of participants using rescue medication over 4 to 6 hours post interventions	3	260	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.58, 1.40]
2.4 Number of participants withdrawing due to adverse events	5	531	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.35, 2.19]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.5 Number of participants withdrawing due to lack of efficacy	3		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.6 Number of participants withdrawing for any cause	4	437	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.41, 1.26]
2.7 Number of participants reporting any adverse event	5	516	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [1.00, 1.23]
2.8 Number of participants reporting a serious adverse event	5		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.9 Number of participants experiencing thrombophlebitis	2		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.10 Number of participants reporting nausea	5	516	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [0.86, 1.56]
2.11 Number of participants experiencing vomiting	5	516	Risk Ratio (M-H, Fixed, 95% CI)	1.36 [0.81, 2.28]
2.12 Number of participants reporting pruritus	4	415	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.40, 1.84]
2.13 Number of participants experiencing sedation	4	347	Risk Ratio (M-H, Fixed, 95% CI)	2.51 [0.86, 7.35]
2.14 Number of participants with at least 50% pain relief at 4 hours: subgroup analysis	4	337	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.89, 1.21]
2.14.1 Abdominal/pelvic	2	162	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.84, 1.26]
2.14.2 Dental	1	98	Risk Ratio (M-H, Fixed, 95% CI)	1.19 [0.88, 1.61]
2.14.3 Orthopedic	1	77	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.58, 1.32]
2.15 Number of participants with at least 50% pain relief at 6 hours: subgroup analysis	6	603	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.95, 1.19]
2.15.1 Abdominal/pelvic	3	330	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.91, 1.21]
2.15.2 Dental	2	196	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [0.93, 1.43]
2.15.3 Orthopedic	1	77	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.56, 1.38]

Analysis 2.1. Comparison 2: Ketorolac versus other NSAID, Outcome 1: Number of participants with at least 50% pain relief at 4 hours

Study or Subgroup	Ketorolac Events	Ketorolac Total	Other NSAID Events	Other NSAID Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Barton 2002	26	41	21	38	20.6%	1.15 [0.79 , 1.66]
Bikhazi 2004	32	42	33	41	31.5%	0.95 [0.75 , 1.19]
Mehlisch 2003	33	48	29	50	26.8%	1.19 [0.88 , 1.61]
Rasmussen 2002	21	41	21	36	21.1%	0.88 [0.58 , 1.32]
Total (95% CI)		**172**		**165**	**100.0%**	**1.04 [0.89 , 1.21]**
Total events:	112		104			

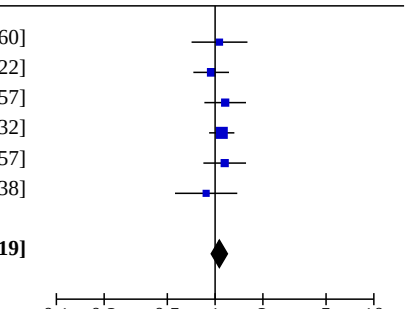
Heterogeneity: Chi² = 2.30, df = 3 (P = 0.51); I² = 0%
Test for overall effect: Z = 0.46 (P = 0.65)
Test for subgroup differences: Not applicable



Analysis 2.2. Comparison 2: Ketorolac versus other NSAID, Outcome 2: Number of participants with at least 50% pain relief at 6 hours

Study or Subgroup	Ketorolac Events	Ketorolac Total	Other NSAID Events	Other NSAID Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Barton 2002	23	41	20	38	11.0%	1.07 [0.71 , 1.60]
Bikhazi 2004	30	42	31	41	16.7%	0.94 [0.73 , 1.22]
Christensen 2011	32	47	30	51	15.3%	1.16 [0.86 , 1.57]
Gan 2012	63	82	60	86	31.1%	1.10 [0.92 , 1.32]
Mehlisch 2003	32	48	29	50	15.1%	1.15 [0.84 , 1.57]
Rasmussen 2002	19	41	19	36	10.8%	0.88 [0.56 , 1.38]
Total (95% CI)		**301**		**302**	**100.0%**	**1.06 [0.95 , 1.19]**
Total events:	199		189			

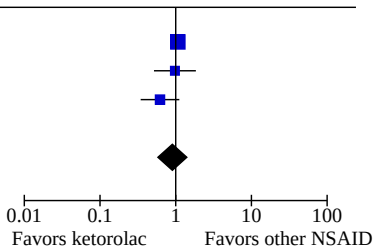
Heterogeneity: Chi² = 2.18, df = 5 (P = 0.82); I² = 0%
Test for overall effect: Z = 1.03 (P = 0.30)
Test for subgroup differences: Not applicable



Analysis 2.3. Comparison 2: Ketorolac versus other NSAID, Outcome 3: Number of participants using rescue medication over 4 to 6 hours post interventions

Study or Subgroup	Ketorolac Events	Ketorolac Total	Other NSAID Events	Other NSAID Total	Weight	Risk Ratio M-H, Random, 95% CI
Barton 2002	38	41	33	38	48.6%	1.07 [0.92 , 1.24]
Bikhazi 2004	13	42	13	41	24.7%	0.98 [0.52 , 1.85]
Christensen 2011	12	47	21	51	26.7%	0.62 [0.34 , 1.12]
Total (95% CI)		**130**		**130**	**100.0%**	**0.90 [0.58 , 1.40]**
Total events:	63		67			

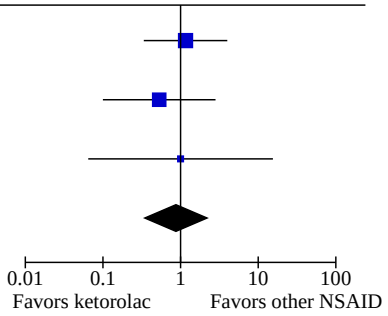
Heterogeneity: Tau² = 0.10; Chi² = 5.67, df = 2 (P = 0.06); I² = 65%
Test for overall effect: Z = 0.46 (P = 0.65)
Test for subgroup differences: Not applicable



Analysis 2.4. Comparison 2: Ketorolac versus other NSAID, Outcome 4: Number of participants withdrawing due to adverse events

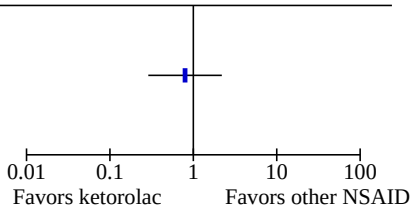
Study or Subgroup	Ketorolac Events	Ketorolac Total	Other NSAID Events	Other NSAID Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Barton 2002	5	41	4	38	46.0%	1.16 [0.34 , 4.00]
Christensen 2011	0	47	0	51		Not estimable
Gan 2012	2	82	4	87	43.0%	0.53 [0.10 , 2.82]
Mehlisch 2003	0	50	0	51		Not estimable
Rasmussen 2002	1	42	1	42	11.1%	1.00 [0.06 , 15.47]
Total (95% CI)		**262**		**269**	**100.0%**	**0.87 [0.35 , 2.19]**
Total events:	8		9			

Heterogeneity: Chi² = 0.55, df = 2 (P = 0.76); I² = 0%
Test for overall effect: Z = 0.29 (P = 0.77)
Test for subgroup differences: Not applicable



Analysis 2.5. Comparison 2: Ketorolac versus other NSAID, Outcome 5: Number of participants withdrawing due to lack of efficacy

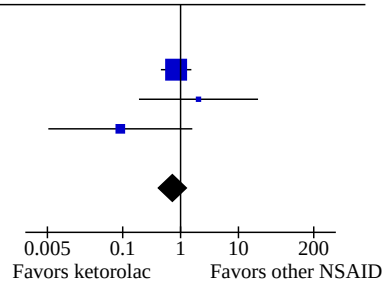
Study or Subgroup	Ketorolac Events	Ketorolac Total	Other NSAID Events	Other NSAID Total	Risk Ratio M-H, Fixed, 95% CI
Bikhazi 2004	0	42	0	41	Not estimable
Gan 2012	6	82	8	87	0.80 [0.29 , 2.19]
Rasmussen 2002	0	42	0	42	Not estimable



Analysis 2.6. Comparison 2: Ketorolac versus other NSAID, Outcome 6: Number of participants withdrawing for any cause

Study or Subgroup	Ketorolac Events	Ketorolac Total	Other NSAID Events	Other NSAID Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bikhazi 2004	0	42	0	41		Not estimable
Gan 2012	15	82	19	87	74.0%	0.84 [0.46 , 1.54]
Mehlisch 2003	2	50	1	51	4.0%	2.04 [0.19 , 21.79]
Rasmussen 2002	0	42	5	42	22.1%	0.09 [0.01 , 1.59]
Total (95% CI)		**216**		**221**	**100.0%**	**0.72 [0.41 , 1.26]**
Total events:	17		25			

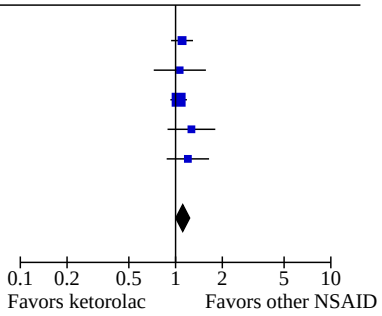
Heterogeneity: Chi² = 2.99, df = 2 (P = 0.22); I² = 33%
Test for overall effect: Z = 1.16 (P = 0.25)
Test for subgroup differences: Not applicable



Analysis 2.7. Comparison 2: Ketorolac versus other NSAID, Outcome 7: Number of participants reporting any adverse event

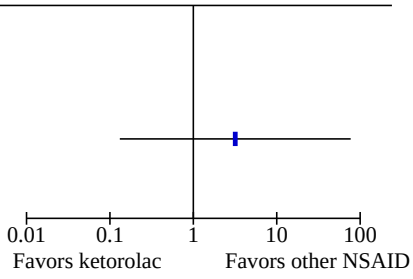
Study or Subgroup	Ketorolac Events	Ketorolac Total	Other NSAID Events	Other NSAID Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Barton 2002	38	41	32	38	18.9%	1.10 [0.94 , 1.29]
Bikhazi 2004	24	42	22	41	12.6%	1.06 [0.72 , 1.57]
Gan 2012	72	82	73	87	40.2%	1.05 [0.93 , 1.18]
Mehlisch 2003	31	50	25	51	14.1%	1.26 [0.89 , 1.80]
Rasmussen 2002	30	42	25	42	14.2%	1.20 [0.88 , 1.64]
Total (95% CI)		**257**		**259**	**100.0%**	**1.11 [1.00 , 1.23]**
Total events:	195		177			

Heterogeneity: Chi² = 1.73, df = 4 (P = 0.78); I² = 0%
Test for overall effect: Z = 2.02 (P = 0.04)
Test for subgroup differences: Not applicable



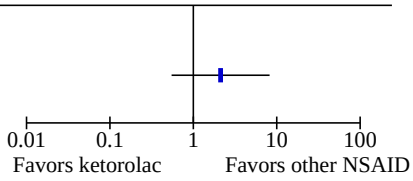
Analysis 2.8. Comparison 2: Ketorolac versus other NSAID, Outcome 8: Number of participants reporting a serious adverse event

Study or Subgroup	Ketorolac Events	Ketorolac Total	Other NSAID Events	Other NSAID Total	Risk Ratio M-H, Fixed, 95% CI
Barton 2002	0	41	0	38	Not estimable
Bikhazi 2004	0	42	0	41	Not estimable
Christensen 2011	0	47	0	51	Not estimable
Gan 2012	1	82	0	87	3.18 [0.13 , 76.99]
Mehlisch 2003	0	50	0	51	Not estimable



Analysis 2.9. Comparison 2: Ketorolac versus other NSAID, Outcome 9: Number of participants experiencing thrombophlebitis

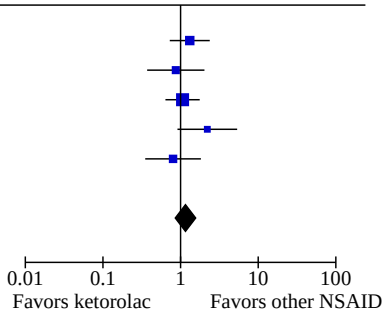
Study or Subgroup	Ketorolac Events	Ketorolac Total	Other NSAID Events	Other NSAID Total	Risk Ratio M-H, Fixed, 95% CI
Christensen 2011	0	47	0	51	Not estimable
Gan 2012	6	82	3	87	2.12 [0.55 , 8.21]



Analysis 2.10. Comparison 2: Ketorolac versus other NSAID, Outcome 10: Number of participants reporting nausea

Study or Subgroup	Ketorolac Events	Ketorolac Total	Other NSAID Events	Other NSAID Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Barton 2002	17	41	12	38	21.2%	1.31 [0.73 , 2.38]
Bikhazi 2004	8	42	9	41	15.5%	0.87 [0.37 , 2.03]
Gan 2012	22	82	22	87	36.3%	1.06 [0.64 , 1.76]
Mehlisch 2003	13	50	6	51	10.1%	2.21 [0.91 , 5.36]
Rasmussen 2002	8	42	10	42	17.0%	0.80 [0.35 , 1.83]
Total (95% CI)		**257**		**259**	**100.0%**	**1.16 [0.86 , 1.56]**
Total events:	68		59			

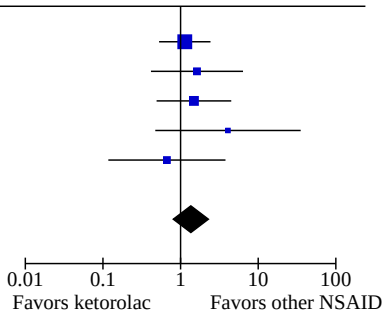
Heterogeneity: Chi² = 3.55, df = 4 (P = 0.47); I² = 0%
Test for overall effect: Z = 0.94 (P = 0.35)
Test for subgroup differences: Not applicable



Analysis 2.11. Comparison 2: Ketorolac versus other NSAID, Outcome 11: Number of participants experiencing vomiting

Study or Subgroup	Ketorolac Events	Ketorolac Total	Other NSAID Events	Other NSAID Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Barton 2002	11	41	9	38	44.0%	1.13 [0.53 , 2.43]
Bikhazi 2004	5	42	3	41	14.3%	1.63 [0.42 , 6.37]
Gan 2012	7	82	5	87	22.9%	1.49 [0.49 , 4.49]
Mehlisch 2003	4	50	1	51	4.7%	4.08 [0.47 , 35.25]
Rasmussen 2002	2	42	3	42	14.1%	0.67 [0.12 , 3.79]
Total (95% CI)		**257**		**259**	**100.0%**	**1.36 [0.81 , 2.28]**
Total events:	29		21			

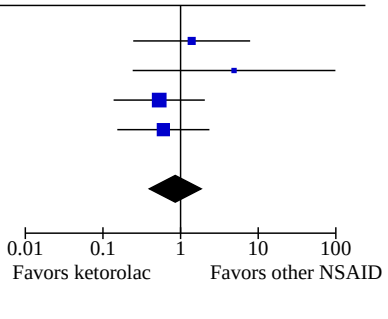
Heterogeneity: Chi² = 1.95, df = 4 (P = 0.74); I² = 0%
Test for overall effect: Z = 1.15 (P = 0.25)
Test for subgroup differences: Not applicable



Analysis 2.12. Comparison 2: Ketorolac versus other NSAID, Outcome 12: Number of participants reporting pruritus

Study or Subgroup	Ketorolac Events	Ketorolac Total	Other NSAID Events	Other NSAID Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Barton 2002	3	41	2	38	15.5%	1.39 [0.25 , 7.87]
Bikhazi 2004	2	42	0	41	3.8%	4.88 [0.24 , 98.73]
Gan 2012	3	82	6	87	43.4%	0.53 [0.14 , 2.05]
Rasmussen 2002	3	42	5	42	37.3%	0.60 [0.15 , 2.35]
Total (95% CI)		**207**		**208**	**100.0%**	**0.85 [0.40 , 1.84]**
Total events:	11		13			

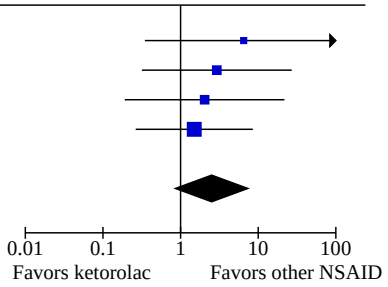
Heterogeneity: Chi² = 2.33, df = 3 (P = 0.51); I² = 0%
Test for overall effect: Z = 0.40 (P = 0.69)
Test for subgroup differences: Not applicable



Analysis 2.13. Comparison 2: Ketorolac versus other NSAID, Outcome 13: Number of participants experiencing sedation

Study or Subgroup	Ketorolac Events	Ketorolac Total	Other NSAID Events	Other NSAID Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Barton 2002	3	41	0	38	11.5%	6.50 [0.35 , 121.85]
Bikhazi 2004	3	42	1	41	22.4%	2.93 [0.32 , 27.02]
Mehlisch 2003	2	50	1	51	21.9%	2.04 [0.19 , 21.79]
Rasmussen 2002	3	42	2	42	44.2%	1.50 [0.26 , 8.52]
Total (95% CI)		**175**		**172**	**100.0%**	**2.51 [0.86 , 7.35]**
Total events:	11		4			

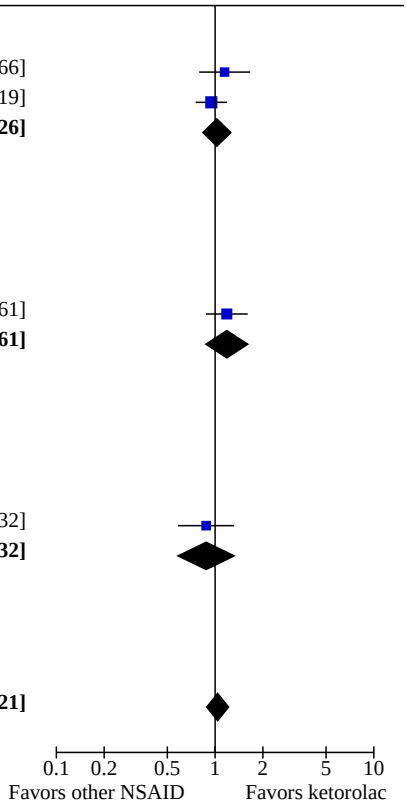
Heterogeneity: Chi² = 0.79, df = 3 (P = 0.85); I² = 0%
Test for overall effect: Z = 1.68 (P = 0.09)
Test for subgroup differences: Not applicable



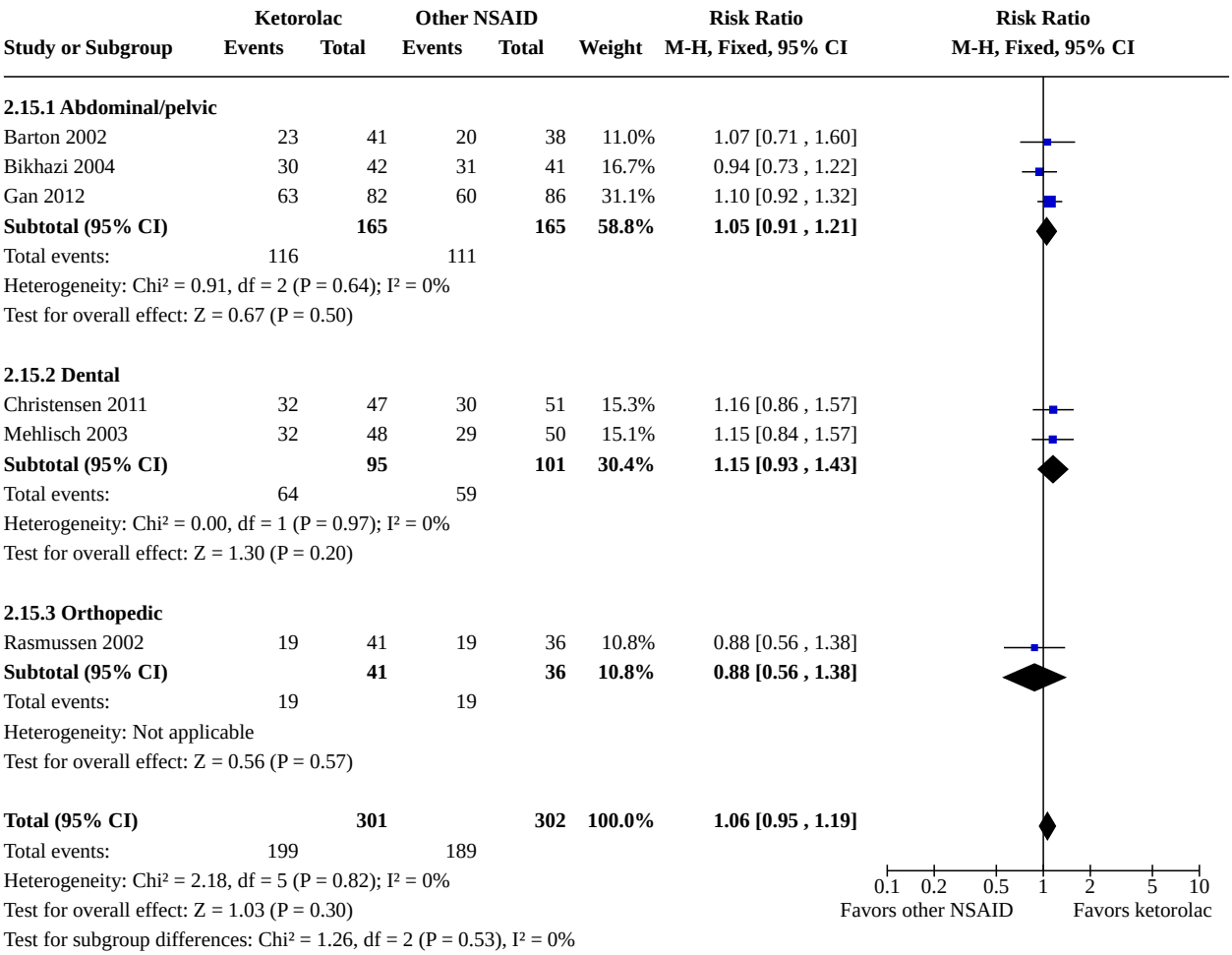
Analysis 2.14. Comparison 2: Ketorolac versus other NSAID, Outcome 14: Number of participants with at least 50% pain relief at 4 hours: subgroup analysis

Study or Subgroup	Ketorolac Events	Ketorolac Total	Other NSAID Events	Other NSAID Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.14.1 Abdominal/pelvic						
Barton 2002	26	41	21	38	20.6%	1.15 [0.79 , 1.66]
Bikhazi 2004	32	42	33	41	31.5%	0.95 [0.75 , 1.19]
Subtotal (95% CI)		**83**		**79**	**52.1%**	**1.03 [0.84 , 1.26]**
Total events:	58		54			
Heterogeneity: Chi² = 0.84, df = 1 (P = 0.36); I² = 0%						
Test for overall effect: Z = 0.25 (P = 0.80)						
2.14.2 Dental						
Mehlisch 2003	33	48	29	50	26.8%	1.19 [0.88 , 1.61]
Subtotal (95% CI)		**48**		**50**	**26.8%**	**1.19 [0.88 , 1.61]**
Total events:	33		29			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.10 (P = 0.27)						
2.14.3 Orthopedic						
Rasmussen 2002	21	41	21	36	21.1%	0.88 [0.58 , 1.32]
Subtotal (95% CI)		**41**		**36**	**21.1%**	**0.88 [0.58 , 1.32]**
Total events:	21		21			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.63 (P = 0.53)						
Total (95% CI)		**172**		**165**	**100.0%**	**1.04 [0.89 , 1.21]**
Total events:	112		104			

Heterogeneity: Chi² = 2.30, df = 3 (P = 0.51); I² = 0%
Test for overall effect: Z = 0.46 (P = 0.65)
Test for subgroup differences: Chi² = 1.40, df = 2 (P = 0.50), I² = 0%



Analysis 2.15. Comparison 2: Ketorolac versus other NSAID, Outcome 15: Number of participants with at least 50% pain relief at 6 hours: subgroup analysis



Comparison 3. Ketorolac versus opioid

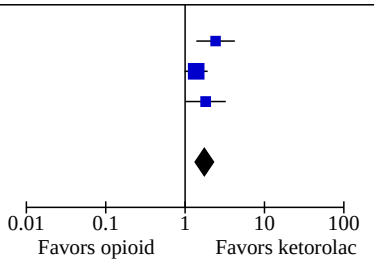
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Number of participants with at least 50% pain relief at 4 hours	3	243	Risk Ratio (M-H, Fixed, 95% CI)	1.75 [1.34, 2.28]
3.2 Number of participants with at least 50% pain relief at 6 hours	3	243	Risk Ratio (M-H, Fixed, 95% CI)	1.90 [1.40, 2.56]
3.3 Number of participants using rescue medication over 4 to 6 hours post interventions	2	163	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.25, 2.04]
3.4 Number of participants withdrawing due to adverse events	2	167	Risk Ratio (M-H, Fixed, 95% CI)	1.47 [0.47, 4.64]
3.5 Number of participants withdrawing due to lack of efficacy	2		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.6 Number of participants withdrawing for any cause	2	166	Risk Ratio (M-H, Fixed, 95% CI)	0.20 [0.02, 1.65]
3.7 Number of participants reporting any adverse event	3	249	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.67, 1.18]
3.8 Number of participants reporting a serious adverse event	2		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.9 Number of participants reporting nausea	4	369	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.55, 1.17]
3.10 Number of participants experiencing vomiting	4	369	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.48, 1.44]
3.11 Number of participants reporting pruritus	3	249	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.30, 1.74]
3.12 Number of participants experiencing sedation	3	249	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.31, 1.55]

Analysis 3.1. Comparison 3: Ketorolac versus opioid, Outcome 1: Number of participants with at least 50% pain relief at 4 hours

Study or Subgroup	Ketorolac Events	Ketorolac Total	Opioid Events	Opioid Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Barton 2002	26	41	11	42	24.6%	2.42 [1.39 , 4.23]
Bikhazi 2004	32	42	21	38	49.9%	1.38 [0.99 , 1.92]
Rasmussen 2002	21	41	11	39	25.5%	1.82 [1.01 , 3.25]
Total (95% CI)		**124**		**119**	**100.0%**	**1.75 [1.34 , 2.28]**
Total events:	79		43			

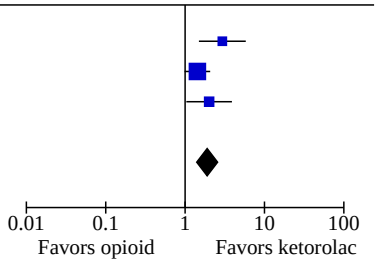
Heterogeneity: Chi² = 3.28, df = 2 (P = 0.19); I² = 39%
Test for overall effect: Z = 4.11 (P < 0.0001)
Test for subgroup differences: Not applicable



Analysis 3.2. Comparison 3: Ketorolac versus opioid, Outcome 2: Number of participants with at least 50% pain relief at 6 hours

Study or Subgroup	Ketorolac Events	Ketorolac Total	Opioid Events	Opioid Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Barton 2002	23	41	8	42	21.3%	2.95 [1.49 , 5.81]
Bikhazi 2004	30	42	19	38	53.8%	1.43 [0.99 , 2.07]
Rasmussen 2002	19	41	9	39	24.9%	2.01 [1.04 , 3.89]
Total (95% CI)		**124**		**119**	**100.0%**	**1.90 [1.40 , 2.56]**
Total events:	72		36			

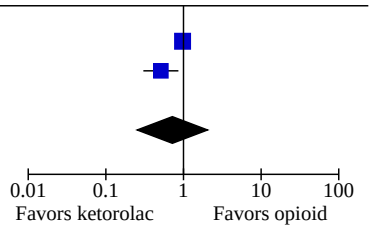
Heterogeneity: Chi² = 3.88, df = 2 (P = 0.14); I² = 48%
Test for overall effect: Z = 4.15 (P < 0.0001)
Test for subgroup differences: Not applicable



Analysis 3.3. Comparison 3: Ketorolac versus opioid, Outcome 3: Number of participants using rescue medication over 4 to 6 hours post interventions

Study or Subgroup	Ketorolac Events	Ketorolac Total	Opioid Events	Opioid Total	Weight	Risk Ratio M-H, Random, 95% CI
Barton 2002	38	41	40	42	53.0%	0.97 [0.87 , 1.09]
Bikhazi 2004	13	42	23	38	47.0%	0.51 [0.30 , 0.86]
Total (95% CI)		**83**		**80**	**100.0%**	**0.72 [0.25 , 2.04]**
Total events:	51		63			

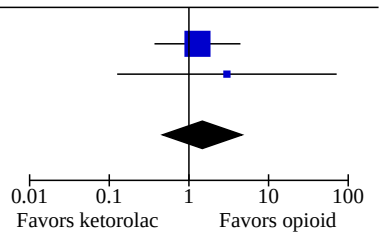
Heterogeneity: Tau² = 0.53; Chi² = 15.45, df = 1 (P < 0.0001); I² = 94%
Test for overall effect: Z = 0.62 (P = 0.53)
Test for subgroup differences: Not applicable



Analysis 3.4. Comparison 3: Ketorolac versus opioid, Outcome 4: Number of participants withdrawing due to adverse events

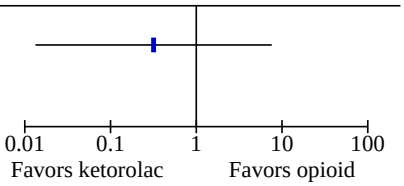
Study or Subgroup	Ketorolac Events	Ketorolac Total	Opioid Events	Opioid Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Barton 2002	5	41	4	42	88.8%	1.28 [0.37 , 4.44]
Rasmussen 2002	1	42	0	42	11.2%	3.00 [0.13 , 71.61]
Total (95% CI)		**83**		**84**	**100.0%**	**1.47 [0.47 , 4.64]**
Total events:	6		4			

Heterogeneity: Chi² = 0.24, df = 1 (P = 0.62); I² = 0%
Test for overall effect: Z = 0.66 (P = 0.51)
Test for subgroup differences: Not applicable



Analysis 3.5. Comparison 3: Ketorolac versus opioid, Outcome 5: Number of participants withdrawing due to lack of efficacy

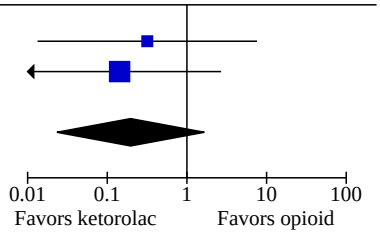
Study or Subgroup	Ketorolac Events	Ketorolac Total	Opioid Events	Opioid Total	Risk Ratio M-H, Fixed, 95% CI
Bikhazi 2004	0	42	1	40	0.32 [0.01 , 7.58]
Rasmussen 2002	0	42	0	42	Not estimable



Analysis 3.6. Comparison 3: Ketorolac versus opioid, Outcome 6: Number of participants withdrawing for any cause

Study or Subgroup	Ketorolac Events	Ketorolac Total	Opioid Events	Opioid Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bikhazi 2004	0	42	1	40	30.5%	0.32 [0.01 , 7.58]
Rasmussen 2002	0	42	3	42	69.5%	0.14 [0.01 , 2.68]
Total (95% CI)		**84**		**82**	**100.0%**	**0.20 [0.02 , 1.65]**
Total events:	0		4			

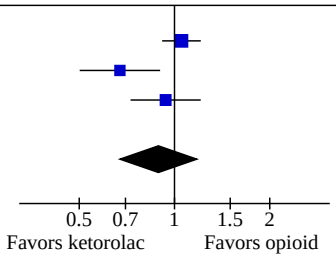
Heterogeneity: Chi² = 0.13, df = 1 (P = 0.71); I² = 0%
Test for overall effect: Z = 1.50 (P = 0.13)
Test for subgroup differences: Not applicable



Analysis 3.7. Comparison 3: Ketorolac versus opioid, Outcome 7: Number of participants reporting any adverse event

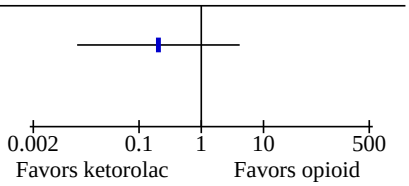
Study or Subgroup	Ketorolac Events	Ketorolac Total	Opioid Events	Opioid Total	Weight	Risk Ratio M-H, Random, 95% CI
Barton 2002	38	41	37	42	38.9%	1.05 [0.91 , 1.21]
Bikhazi 2004	24	42	34	40	29.3%	0.67 [0.50 , 0.90]
Rasmussen 2002	30	42	32	42	31.7%	0.94 [0.73 , 1.21]
Total (95% CI)		**125**		**124**	**100.0%**	**0.89 [0.67 , 1.18]**
Total events:	92		103			

Heterogeneity: Tau² = 0.05; Chi² = 9.21, df = 2 (P = 0.01); I² = 78%
Test for overall effect: Z = 0.82 (P = 0.41)
Test for subgroup differences: Not applicable



Analysis 3.8. Comparison 3: Ketorolac versus opioid, Outcome 8: Number of participants reporting a serious adverse event

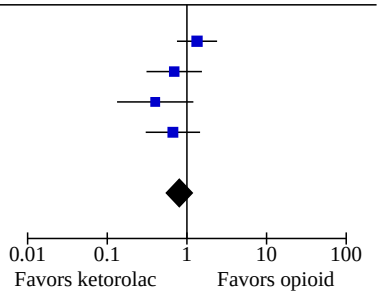
Study or Subgroup	Ketorolac Events	Ketorolac Total	Opioid Events	Opioid Total	Risk Ratio M-H, Fixed, 95% CI
Barton 2002	0	41	2	42	0.20 [0.01 , 4.14]
Bikhazi 2004	0	42	0	40	Not estimable



Analysis 3.9. Comparison 3: Ketorolac versus opioid, Outcome 9: Number of participants reporting nausea

Study or Subgroup	Ketorolac Events	Ketorolac Total	Opioid Events	Opioid Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Barton 2002	17	41	13	42	27.9%	1.34 [0.75 , 2.39]
Bikhazi 2004	8	42	11	40	24.4%	0.69 [0.31 , 1.54]
Gonzalez 1994	4	60	10	60	21.7%	0.40 [0.13 , 1.21]
Rasmussen 2002	8	42	12	42	26.0%	0.67 [0.30 , 1.46]
Total (95% CI)		**185**		**184**	**100.0%**	**0.80 [0.55 , 1.17]**
Total events:	37		46			

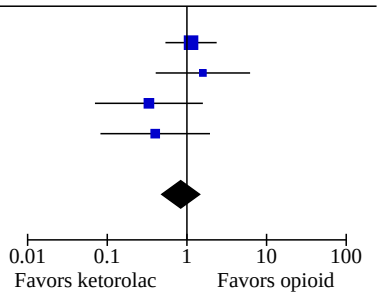
Heterogeneity: Chi² = 4.87, df = 3 (P = 0.18); I² = 38%
Test for overall effect: Z = 1.15 (P = 0.25)
Test for subgroup differences: Not applicable



Analysis 3.10. Comparison 3: Ketorolac versus opioid, Outcome 10: Number of participants experiencing vomiting

Study or Subgroup	Ketorolac Events	Ketorolac Total	Opioid Events	Opioid Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Barton 2002	11	41	10	42	41.2%	1.13 [0.54 , 2.36]
Bikhazi 2004	5	42	3	40	12.8%	1.59 [0.41 , 6.21]
Gonzalez 1994	2	60	6	60	25.0%	0.33 [0.07 , 1.59]
Rasmussen 2002	2	42	5	42	20.9%	0.40 [0.08 , 1.95]
Total (95% CI)		**185**		**184**	**100.0%**	**0.84 [0.48 , 1.44]**
Total events:	20		24			

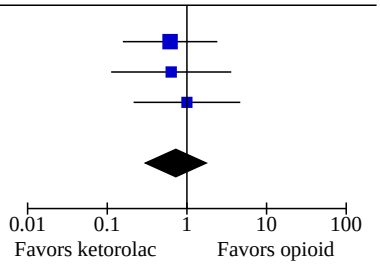
Heterogeneity: Chi² = 3.64, df = 3 (P = 0.30); I² = 18%
Test for overall effect: Z = 0.65 (P = 0.52)
Test for subgroup differences: Not applicable



Analysis 3.11. Comparison 3: Ketorolac versus opioid, Outcome 11: Number of participants reporting pruritus

Study or Subgroup	Ketorolac Events	Ketorolac Total	Opioid Events	Opioid Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Barton 2002	3	41	5	42	44.9%	0.61 [0.16 , 2.41]
Bikhazi 2004	2	42	3	40	27.9%	0.63 [0.11 , 3.60]
Rasmussen 2002	3	42	3	42	27.2%	1.00 [0.21 , 4.67]
Total (95% CI)		**125**		**124**	**100.0%**	**0.73 [0.30 , 1.74]**
Total events:	8		11			

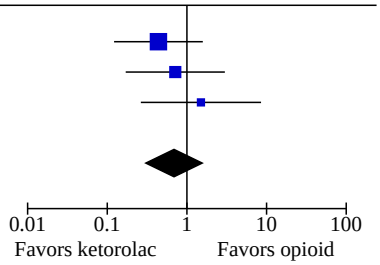
Heterogeneity: Chi² = 0.25, df = 2 (P = 0.88); I² = 0%
Test for overall effect: Z = 0.72 (P = 0.47)
Test for subgroup differences: Not applicable



Analysis 3.12. Comparison 3: Ketorolac versus opioid, Outcome 12: Number of participants experiencing sedation

Study or Subgroup	Ketorolac Events	Ketorolac Total	Opioid Events	Opioid Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Barton 2002	3	41	7	42	53.1%	0.44 [0.12 , 1.58]
Bikhazi 2004	3	42	4	40	31.5%	0.71 [0.17 , 2.99]
Rasmussen 2002	3	42	2	42	15.4%	1.50 [0.26 , 8.52]
Total (95% CI)		**125**		**124**	**100.0%**	**0.69 [0.31 , 1.55]**
Total events:	9		13			

Heterogeneity: Chi² = 1.25, df = 2 (P = 0.54); I² = 0%
Test for overall effect: Z = 0.90 (P = 0.37)
Test for subgroup differences: Not applicable



APPENDICES

Appendix 1. Glossary

Categorical rating scale: the most common are the four-category scale for pain intensity (none, mild, moderate, and severe) and the five-category scale for pain relief (none, slight, moderate, good or lots, and complete). For analysis, numbers are given to the verbal categories (for pain intensity, none = 0, mild = 1, moderate = 2, and severe = 3, and for relief, none = 0, slight = 1, moderate = 2, good or lots = 3, and complete = 4). Data from different participants are then combined to produce means (rarely medians) and measures of dispersion (usually standard errors of means). The validity of converting categories into numerical scores is checked by comparison with concurrent visual analogue scale (VAS) measurements. Good correlation is found, especially between pain relief scales using cross-modality matching techniques. Results are usually reported as continuous data, mean or median pain relief or intensity. Few studies present results as discrete data, giving the number of participants who report a certain level of pain intensity or relief at any given assessment point. The main advantages of the categorical scales are that they are quick and simple. The small number of descriptors may force the scorer to choose a particular category when none describes the pain satisfactorily.

Summed pain intensity difference (SPID): SPID is calculated as the sum of the differences between the pain scores and baseline pain score over a period of time. Differences between pain intensity values at the start and end of a measurement period are dealt with by the trapezoidal rule.

Total pain relief (TOTPAR): TOTPAR is calculated as the sum of pin relief scores over a period of time. If a participant had complete pain relief (as measured on a 5-point categorical scale) immediately after taking an analgesic, and maintained that level of pain relief for six hours, they would have a six-hour TOTPAR of the maximum of 24 (6 × 4). Differences between pain relief values at the start and end of a measurement period are dealt with by the trapezoidal rule. This is a simple method that approximately calculates the definite integral of the area under the pain relief curve by calculating the sum of the areas of several trapezoids that together closely approximate to the area under the curve.

Visual analogue scale (VAS): for pain intensity, lines with left end labeled 'no pain' and right end labeled 'worst pain imaginable', and for pain relief lines with left end labeled 'no relief of pain' and right end labeled 'complete relief of pain', seem to overcome the limitation of forcing participant descriptors into particular categories. Participants mark the line at the point that corresponds to their pain or pain relief. The scores are obtained by measuring the distance between the 'no relief of pain' end and the participant's mark, usually in millimeters. The main advantages of VAS are that they are simple and quick to score, avoid imprecise descriptive terms, and provide many points from which to choose. More concentration and co-ordination are needed, which can be difficult postoperatively or with neurological disorders.

VAS TOTPAR and **VAS SPID** are visual analogue versions of TOTPAR and SPID.

See 'Measuring pain' in *Bandolier's Little Book of Pain* (Moore 2003).

Appendix 2. Search strategies

CENTRAL (Cochrane Library)

#1 MeSH descriptor: [Ketorolac] this term only

#2 (Ketorolac):ti,ab,kw (Word variations have been searched)

#3 (toradol):ti,ab,kw (Word variations have been searched)

#4 MeSH descriptor: [Ketorolac Tromethamine] this term only

#5 #1 or #2 or #3 or #4

#6 MeSH descriptor: [Pain, Postoperative] this term only

#7 ((pain* near/3 (post* or after))):ti,ab,kw (Word variations have been searched)

#8 #6 or #7

#9 #5 and #8

MEDLINE (OVID)

1. Ketorolac

2. ketorolac.tw.

3. toradol.tw.

4. Ketorolac Tromethamine/

5. or/1-4

6. Pain, Postoperative/

7. (pain* adj3 (post* or after)).tw.

8. 6 or 7

9. 5 and 8

10. randomized controlled trial.pt.

11. controlled clinical trial.pt.

12. randomized.ab.

13. placebo.ab.

14. drug therapy.fs.

15. randomly.ab.

16. trial.ab.

17. groups.ab.

18. 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17

19. exp animals/ not humans.sh.

20. 18 not 19

21. 9 and 20

Embase (OVID)

1 Ketorolac/

2 ketorolac.tw.

3 toradol.tw.

4 Ketorolac Trometamol/

5 or/1-4

6 Postoperative Pain/

7 (pain* adj3 (post* or after)).tw.

8 6 or 7

9 5 and 8

10 random$.tw.

11 factorial$.tw.

12 crossover$.tw.

13 cross over$.tw.

14 cross-over$.tw.

15 placebo$.tw.

16 (doubl$ adj blind$).tw.

17 (singl$ adj blind$).tw.

18 assign$.tw.

19 allocat$.tw.

20 volunteer$.tw.

21 Crossover Procedure/

22 double-blind procedure.tw.

23 Randomized Controlled Trial/

24 Single Blind Procedure/

25 or/10-24

26 (animal/ or nonhuman/) not human/

27 25 not 26

28 9 and 27

LILACS (Birme)

ketorolac or toradol [Words] and pain$ [Words] and (Pt randomized controlled trial OR Pt controlled clinical trial OR Mh randomized controlled trials OR Mh random allocation OR Mh double-blind method OR Mh single-blind method) AND NOT (Ct animal AND NOT (Ct human and Ct animal)) [Words]

HISTORY

Protocol first published: Issue 2, 2019

CONTRIBUTIONS OF AUTHORS

Draft the protocol	EM
Develop and run the search strategy	EM, MF PaPaS Information Specialist provided support.
Obtain copies of studies	EM, MF
Select which studies to include (two people)	EM, MF, RS
Extract data from studies (two people)	EM, MF, RS
Enter data into Review Manager 5	EM
Carry out the analysis	EM
Interpret the analysis	EM, MF, RS
Draft the final review	EM
Update the review	EM, MF, RS

DECLARATIONS OF INTEREST

EM: none known. EM is a pharmacist with a Master's degree in Pain Research, Education and Policy, and manages people with acute pain.

MF: none known.

RS: none known. RS is an anesthesiologist whose practice includes acute perioperative pain management.

SOURCES OF SUPPORT

Internal sources

- Saltonstall Fund for Pain Research, USA

  Funding for EM for development of protocol

External sources

- National Institute for Health Research (NIHR), UK

  Cochrane Infrastructure funding to the PaPaS CRG

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In our protocol we stated that "For meta-analyses with an I^2 score greater than 50%, we will reanalyze data using a random-effects model". Instead of presenting these as sensitivity analyses, we have now presented them in our primary analyses following discussion with the editorial team.

INDEX TERMS

Medical Subject Headings (MeSH)

Acute Pain [*drug therapy]; Analgesics, Opioid [administration & dosage] [adverse effects]; Anti-Inflammatory Agents, Non-Steroidal [*administration & dosage] [adverse effects]; Bias; Diclofenac [administration & dosage]; Injections, Intravenous; Isoxazoles [administration & dosage]; Ketorolac [*administration & dosage] [adverse effects]; Numbers Needed To Treat; Pain, Postoperative [*drug therapy]; Placebos [therapeutic use]; Randomized Controlled Trials as Topic; Time Factors

MeSH check words

Adult; Humans; Middle Aged; Young Adult