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Oral non-steroidal anti-inflammatory drugs (single dose) for perineal pain in the early postpartum period (Review)

Wuytack F, Smith V, Cleary BJ

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[Intervention Review]

Oral non-steroidal anti-inflammatory drugs (single dose) for perineal pain in the early postpartum period

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ABSTRACT

Background

Many women experience perineal pain after childbirth, especially after having sustained perineal trauma. Perineal pain-management strategies are an important part of postnatal care. Non-steroidal anti-inflammatory drugs (NSAIDs) are a commonly-used type of medication in the management of postpartum pain, and their effectiveness and safety should be assessed. This is an update of a review first published in 2016.

Objectives

To determine the effectiveness of a single dose of an oral NSAID for relief of acute perineal pain in the early postpartum period.

Search methods

For this update, we searched the Cochrane Pregnancy and Childbirth Group's Trials Register, ClinicalTrials.gov, the WHO International Clinical Trials Registry Platform (ICTRP) (9 December 2019), OpenSIGLE and ProQuest Dissertations and Theses (28 February 2020), and reference lists of retrieved studies.

Selection criteria

Randomised controlled trials (RCTs) assessing a single dose of a NSAID versus a single dose of placebo, paracetamol or another NSAID for women with perineal pain in the early postpartum period. We excluded quasi-RCTs and cross-over trials. We included papers in abstract format only if they had sufficient information to determine that they met the review's prespecified inclusion criteria.

Data collection and analysis

Two review authors (FW and VS) independently assessed all identified papers for inclusion and risks of bias, resolving any discrepancies through discussion. Two review authors independently conducted data extraction, including calculations of pain relief scores, and checked it for accuracy. We assessed the certainty of the evidence using the GRADE approach.

Main results

We included 35 studies examining 16 different NSAIDs and involving 5136 women (none were breastfeeding). Studies were published between 1967 and 2013. Risk of bias due to random sequence generation, allocation concealment and blinding of outcome assessors was generally unclearly to poorly reported, but participants and caregivers were blinded, and outcome data were generally complete. We downgraded the certainty of evidence due to risk of bias, suspected publication bias, and imprecision for small numbers of participants.

NSAID versus placebo

Compared to women who receive a placebo, more women who receive a single-dose NSAID may achieve **adequate pain relief** at four hours (risk ratio (RR) 1.91, 95% confidence interval (CI) 1.64 to 2.23; 10 studies, 1573 women; low-certainty evidence) and at six hours (RR 1.92, 95% CI 1.69 to 2.17; 17 studies, 2079 women; very low-certainty evidence), although we are less certain about the effects at six hours. At four hours after administration, women who receive a NSAID are probably less likely to **need additional analgesia** compared to women who receive placebo (RR 0.39, 95% CI 0.26 to 0.58; 4 studies, 486 women; moderate-certainty evidence) and may be less likely to **need additional analgesia** at six hours after initial administration, although the evidence was less certain at six hours (RR 0.32, 95% CI 0.26 to 0.40; 10 studies, 1012 women; very low-certainty evidence).

One study reported that no adverse events were observed at four hours post-administration (90 women). There may be little or no difference in maternal adverse effects between NSAIDs and placebo at six hours post-administration (RR 1.38, 95% CI 0.71 to 2.70; 13 studies, 1388 women; low-certainty evidence). Fourteen **maternal adverse effects** were reported in the NSAID group (drowsiness (5), abdominal discomfort (2), weakness (1), dizziness (2), headache (2), moderate epigastralgia (1), not specified (1)) and eight in the placebo group (drowsiness (2), light-headedness (1), nausea (1), backache (1), dizziness (1), epigastric pain (1), not specified (1)), although not all studies assessed adverse effects. **Neonatal adverse effects** were not assessed in any of the studies.

NSAID versus paracetamol

NSAIDs may lead to more women achieving **adequate pain relief** at four hours, compared with paracetamol (RR 1.54, 95% CI 1.07 to 2.22; 3 studies, 342 women; low-certainty evidence). We are uncertain if there is any difference in adequate pain relief between NSAIDs and paracetamol at six hours post-administration (RR 1.82, 95% CI 0.61 to 5.47; 2 studies, 99 women; very low-certainty evidence) or in the **need for additional analgesia** at four hours (RR 0.55, 95% CI 0.27 to 1.13; 1 study, 73 women; very low-certainty evidence). NSAIDs may reduce the risk of requiring additional analgesia at six hours compared with paracetamol (RR 0.28, 95% CI 0.12 to 0.67; 1 study, 59 women; low-certainty evidence).

One study reported that no **maternal adverse effects** were observed at four hours post-administration (210 women). Six hours post-administration, we are uncertain if there is any difference between groups in the number of maternal adverse effects (RR 0.74, 95% CI 0.27 to 2.08; 3 studies, 300 women; very low-certainty evidence), with one case of pruritis in the NSAID group and one case of sleepiness in the paracetamol group. **Neonatal adverse effects** were not assessed in any of the included studies.

Comparisons of different NSAIDs or doses did not demonstrate any differences in effectiveness for any primary outcome measures; however, few data were available on some NSAIDs.

None of the included studies reported on any of this review's secondary outcomes.

Authors' conclusions

In women who are not breastfeeding and who sustained perineal trauma, NSAIDs (compared to placebo or paracetamol) may provide greater pain relief for acute postpartum perineal pain and fewer women need additional analgesia, but uncertainty remains, as the evidence is rated as low- or very low-certainty. The risk of bias was unclear for many studies, adverse effects were often not assessed and breastfeeding women were not included. While this review provides some indication of the likely effect, there is uncertainty in our conclusions. The main reasons for downgrading were the inclusion of studies at high risk of bias and inconsistency in the findings of individual studies.

Future studies could examine NSAIDs' adverse effects, including neonatal effects and the compatibility of NSAIDs with breastfeeding, and could assess other secondary outcomes. Future research could consider women with and without perineal trauma, including perineal tears. High-quality studies could be conducted to further assess the efficacy of NSAIDs versus paracetamol and the efficacy of multimodal treatments.

PLAIN LANGUAGE SUMMARY

Anti-inflammatory drugs for relief of perineal pain after childbirth

What is the issue?

Following childbirth, many women experience pain in the perineum, an area between the anus and vagina. This Cochrane Review asked if this pain can be reduced by one dose of a non-steroidal anti-inflammatory drug (NSAID), such as aspirin or ibuprofen.

Why is this important?

The pain some women experience in the perineum after childbirth can be particularly acute if the perineum tears during the birth, or needs to be cut (known as an episiotomy). Even a woman without tearing or surgery often experiences discomfort in her perineum, which can affect her mobility as well as her ability to care for her baby. This review is part of a series of reviews on the effectiveness of different drugs for pain relief for perineal pain immediately after birth. We are looking specifically at NSAIDs, such as aspirin and ibuprofen.

What evidence did we find?

We found 35 studies with 5136 women that examined 16 different NSAIDs (aspirin, ibuprofen, etc.). We included studies up to 9 December 2019. The studies we found only included women who had trauma of the perineum and who were not breastfeeding. Studies were conducted between 1967 and 2013 and had few women in them.

The studies showed that a single dose of a NSAID may provide greater pain relief at four hours (low-certainty evidence) after taking the drug when compared to a placebo (dummy pill) or no treatment in non-breastfeeding women who had sustained perineal trauma during childbirth. We are uncertain if there is any difference between NSAID and placebo in achieving **adequate pain relief** at six hours.

Women who received a single dose of NSAID are probably less likely to need additional pain relief at four hours (moderate-certainty evidence) after taking the drug compared to women who received placebo or no treatment. We are uncertain if there is any difference between NSAIDs and placebo for women needing additional pain relief at six hours (very low-certainty evidence). Not all of the studies assessed adverse effects of the drugs, but some studies reported maternal adverse effects such as drowsiness, headache, weakness, nausea, gastric discomfort. The evidence is very uncertain about the difference in maternal adverse effects between NSAIDs and placebo at six hours after administration (very low-certainty evidence). One small study (90 women) reported that there were no maternal adverse effects at four hours after administration. None of the studies measured possible adverse effects on the baby.

A NSAID may also be better than paracetamol in providing pain relief at four hours after administration. We are uncertain if there is any difference between NSAID and paracetamol in achieving **adequate pain relief** at six hours or in the number of women who need additional pain relief at four hours after administration. Women who receive NSAID may be less likely to need additional pain relief at six hours compared to women who received paracetamol. One study reported that no **maternal adverse effects** were observed at four hours (210 women). Three small studies reported maternal adverse effects at six hours after administration but we are uncertain if there is any difference between the groups. Adverse effects on the baby were not reported in any of the included studies and all studies excluded women who were breastfeeding.

Comparisons of different NSAIDs and different doses of the same NSAID did not demonstrate any clear differences in their effectiveness on any of the main outcomes measured in this review. However, little information was available for some NSAIDs.

None of the included studies reported on any of this review's secondary outcomes, including: extended hospital stay or readmission to hospital for perineal pain; breastfeeding; perineal pain at six weeks after having the baby; women's views, postpartum depression or measures of disability due to perineal pain.

What does this mean?

For women who are not breastfeeding, a single dose of a NSAID may be better than placebo or paracetamol for perineal pain at four hours. No serious side effects were reported, but not all studies examined these. For women who breastfeed, there are no data and these women should seek help, as some NSAIDs are not recommended for women who breastfeed.

SUMMARY OF FINDINGS

Summary of findings 1. NSAID compared with placebo for perineal pain in the early postpartum period

NSAID compared with placebo for perineal pain in the early postpartum period

Patient or population: women with perineal pain in the early postpartum period
Settings: maternity hospitals in the USA, UK, Belgium, Spain, France, Italy, Venezuela, India, Malaysia, Thailand, and Iran
Intervention: NSAID
Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	NSAID				
Adequate pain relief (4 hours after administration)	284 per 1000	543 per 1000 (466 to 634)	RR 1.91 (1.64 to 2.23)	1573 (10 studies)	⊕⊕⊝⊝ low[a,b]	-
Adequate pain relief (6 hours after administration)	321 per 1000	615 per 1000 (542 to 696)	RR 1.92 (1.69 to 2.17)	2079 (17 studies)	⊕⊝⊝⊝ very low[b,c]	-
Need for additional analgesia (4 hours after administration)	305 per 1000	119 per 1000 (79 to 177)	RR 0.39 (0.26 to 0.58)	486 (4 studies)	⊕⊕⊕⊝ moderate[d]	-
Need for additional analgesia (6 hours after administration)	438 per 1000	140 per 1000 (114 to 175)	RR 0.32 (0.26 to 0.40)	1012 (10 studies)	⊕⊝⊝⊝ very low[b,c]	-
Maternal drug adverse effects (4 hours after administration)	See comment		Not estimable	90 (1 RCT)	One small study (90 women) reported no maternal drug adverse events in either the intervention or control group	
Maternal drug adverse effects (6 hours after administration)	22 per 1000	31 per 1000 (16 to 60)	RR 1.38 (0.71 to 2.70)	1388 (13 studies)	⊕⊕⊝⊝ low[a,e]	-
Neonatal drug adverse effects	Not reported					

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

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

[a]Downgraded one level for serious risk of bias: two studies included in this outcome had instances of high risk of bias. The remaining studies had a mix of low and unclear risk of bias.
[b]Downgraded one level based on visual inspection of funnel plot which indicates likely publication bias.
[c]Downgraded two levels for serious risk of bias: four studies included in this outcome had instances of high risk of bias. The remaining studies had a mix of low and unclear risk of bias.
[d]Downgraded one level for serious risk of bias: one study included in this outcome had instances of high risk of bias. The remaining studies had a mix of low and unclear risk of bias.
[e]Downgraded one level for imprecision (few events); 95% CI around the pooled estimate includes no effect.

Summary of findings 2. NSAID (single administration, any dose) compared to paracetamol for perineal pain in the early postpartum period

NSAID (single administration, any dose) compared to paracetamol for perineal pain in the early postpartum period

Patient or population: women with perineal pain in the early postpartum period
Setting: maternity hospitals in Italy, Spain, USA, France and Thailand
Intervention: NSAID (single administration, any dose)
Comparison: paracetamol

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with paracetamol	Risk with NSAID (single administration, any dose)				
Adequate pain relief (4 hours after administration)	Study population		RR 1.54 (1.07 to 2.22)	342 (3 RCTs)	⊕⊕⊖⊖ low[a,b]	-
	205 per 1000	315 per 1000 (219 to 454)				
Adequate pain relief (6 hours after administration)	Study population		RR 1.82 (0.61 to 5.47)	99 (2 RCTs)	⊕⊖⊖⊖ very low[a,c]	-
	200 per 1000	364 per 1000 (122 to 1000)				
Need for additional analgesia (4 hours after administration)	Study population		RR 0.55 (0.27 to 1.13)	73 (1 RCT)	⊕⊖⊖⊖ very low[a,c]	-
	405 per 1000	223 per 1000				

		(109 to 458)				
Need for additional analgesia (6 hours after administration)	Study population		RR 0.28 (0.12 to 0.67)	59 (1 RCT)	⊕⊕⊖⊖ low[a,b]	-
	571 per 1000	160 per 1000 (69 to 383)				
Maternal drug adverse effects (4 hours after administration)	See comment		not estimable	210 (1 RCT)	1 study (210 women) reported no maternal drug adverse events in either the intervention or control group	
Maternal drug adverse effects (6 hours after administration)	Study population		RR 0.74 (0.27 to 2.08)	300 (3 RCTs)	⊕⊖⊖⊖ very low[a,c]	-
	53 per 1000	39 per 1000 (14 to 111)				
Neonatal drug adverse effects - not reported	-	-	-	-	--	-

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).
CI: Confidence interval; **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 the 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 one level for serious risk of bias: unclear risk of selection bias.
[b]Downgraded one level for imprecision: few participants.
[c]Downgraded two levels for imprecision: few participants and wide 95% confidence interval consistent with possible benefit and possible harm.

BACKGROUND

Description of the condition

The perineum in women is a diamond-shaped area between the vagina and the anus (Chou 2009). Pain in this area is particularly common following childbirth. A study conducted in the UK found that 92% of all women, with or without perineal trauma, reported perineal pain in the first day after birth, although this resolved for 88% of women at two months postpartum (Andrews 2008). Macarthur 2004, in a prospective cohort study involving 447 women in Canada, reported an incidence of perineal pain in the first day after birth of 75% in women with an intact perineum. This shows that perineal pain is not limited to women who sustain perineal trauma. However, women who have perineal trauma, which is approximately 70% of women giving birth, more commonly experience perineal pain (Laws 2009), report more severe pain and are more likely to use analgesic medicines (Leeman 2009). Spontaneous trauma to the perineum during childbirth has a four-degree classification system depending on the tissues affected, varying from tearing of only the skin, subcutaneous tissue and/or vaginal mucosa in a first-degree tear, to tearing of the deep and superficial perineal muscles and anal sphincter in a third-degree tear. In a fourth-degree tear, the ano-rectal epithelium is also disrupted (Kettle 2004). Episiotomy is another type of trauma to the perineum and involves a surgical incision of the perineum to increase the diameter of the vulval outlet (Kettle 2004). In Macarthur 2004, perineal pain was experienced by 95% (210/220) of women with first-/second-degree tears, 97% (94/96) of those who had undergone episiotomies, and 100% (46/46) of women with third-/fourth-degree tears, but by six weeks postpartum, the frequency of perineal pain was not different between trauma groups. Preventing perineal trauma, as far as is possible, is thus vital for minimising the experience of perineal pain. A Cochrane Review evaluating perineal techniques to avoid perineal trauma during childbirth (Aasheim 2017) found that the use of warm compresses reduces third- and fourth-degree tears. However, perineal trauma is not fully preventable and women without perineal trauma also frequently experience perineal pain (Andrews 2008; Macarthur 2004). Consequently, pain-management strategies for perineal pain are an important part of postpartum care, particularly as perineal pain can interfere with a woman's mobility, affect her ability to care for her baby (East 2012a), and, if the pain persists, may be associated with urinary/faecal incontinence and dyspareunia (Andrews 2008; Thompson 2002).

Most women experience short-term perineal pain following childbirth, but between 6% to 30% of women continue to report perineal pain at one year postpartum (Schytt 2007; Williams 2007). Definitions of acute and chronic pain vary in the literature, but chronic pain is often described as pain present for more than 12 weeks (Airaksinen 2006). Pain of up to 12 weeks duration is generally considered acute pain, although pain lasting between six and 12 weeks has been further classified as sub-acute (Van Tulder 2006). More recently, rather than defining pain according to set time-frames of duration, chronic pain has been defined as pain that persists longer than the usual course (Loeser 2011). Acute pain presenting in the early postpartum period should be differentiated from chronic perineal pain in this context (Chou 2009), because of different pathophysiological processes that occur when acute pain becomes chronic (Voscopoulus 2010). The term 'early postpartum period' is equally challenging to define and varies in time-frame durations in the literature. Early postpartum period has previously been defined as a time period of between three and 12 weeks after a baby's birth (Moodley 2003; Nicklas 2013; O'Brien 2003), a time period of one week's duration (Abou Saleh 1997), a time period of up to six months postpartum (Goodman 2003; Teich 2014), or without any specified time limit. In this review, for consistency with previous Cochrane Reviews examining interventions for early postpartum perineal pain (Chou 2009; Chou 2013), we consider the first four weeks after the birth to be the 'early postpartum period'. When women experience postpartum perineal pain in this period, it can thus be considered acute pain.

Several methods of pharmacological and non-pharmacological pain relief are currently being used in managing acute postpartum perineal pain. These include cooling treatments, topical anaesthetics, analgesics and non-steroidal anti-inflammatory drugs (NSAIDs). Previous Cochrane Reviews evaluating the effectiveness of several treatment strategies for acute perineal pain postpartum concluded that rectal NSAID suppositories are associated with less pain up to 24 hours postpartum compared to placebo (Hedayati 2003) and paracetamol provides more pain relief to women compared to placebo (Chou 2013). In addition, there is non-compelling evidence for the use of topical anaesthesia (Hedayati 2005), limited evidence for the use of local cooling treatments (East 2012b), and a lack of evidence to support the use of therapeutic ultrasound (Hay-Smith 1998).

In this review we focus on oral NSAIDs (single-dose) for alleviating perineal pain in the early postpartum period, that is, during the first four weeks after birth.

Description of the intervention

NSAIDs are a group of medicines that have been used for centuries for their analgesic, anti-pyretic and anti-inflammatory properties. Salicin was first extracted from willow bark in 1829 by Leroux (Brunton 2011), and the derivative aspirin was produced in 1899 (Rao 2008). In the 20th century, many NSAIDs were developed, but it was not until the 1970s that a mechanism of action was identified (Rainsford 2007; Vane 1971), and our understanding of their effects as well as their use in the treatment and management of various conditions continue to evolve. NSAIDs are mainly categorised according to their inhibitory effects on two isoforms of cyclo-oxygenase (COX1 and COX2), as described below.

Various routes for NSAID administration are available, including intra-muscular injection, intravenously, per rectum, topically and orally (Tramèr 1998). This review examines the effectiveness of NSAIDs taken orally. More specifically, this review evaluates the effectiveness of a single oral dose of a NSAID, defining a single dose as a dose taken at one time rather than dosage regimens that would involve more than one dose of a given NSAID over time (Howard 2013). The speed at which an oral NSAID is absorbed into the bloodstream varies for different NSAIDs. For example, for ibuprofen, peak plasma concentrations are observed 15 to 30 minutes after ingesting the drug, with a half-life in the plasma of approximately two hours (Davies 1998). This is an example of a fast-acting NSAID, whereas slow-acting NSAIDs such as naproxen show later peak plasma concentrations and have a longer half-life (Vree 1993). The recommended dosage at which NSAIDs are administered also depends on the individual NSAID, as well as the route of administration and the reason for taking the drug. For acute pain, for instance, a single oral dose of 400 mg of ibuprofen is

generally taken, which can be repeated every four to six hours up to a maximum daily dose of 2400 mg. Naproxen, as another example, has a maximum daily dose of 1250 mg and is given orally for acute pain in an initial dose of 500 mg followed by 250 mg doses every six to eight hours afterwards, as required (BNF 2014).

The most common adverse effects of NSAIDs include abdominal pain, nausea, dyspepsia, headache, pruritis, urticaria and other skin rashes. Rarely, NSAIDs can lead to perforation of gastric ulcers and gastrointestinal bleeding, hypersensitivity reactions, bronchospasm, haematopoietic disorders, hypertension, cardiac failure and renal failure. Adverse effects are more likely in elderly people and may be minimised by using the lowest effective dose for the shortest duration necessary (Irish Pharmaceutical Healthcare Association 2014).

How the intervention might work

During childbirth, due to pressure on or trauma of the perineum, a local inflammatory response occurs causing perineal pain. NSAIDs may improve perineal pain through their anti-inflammatory action. Moreover, they have a known analgesic effect, particularly for pain that is associated with tissue trauma/injury and inflammation (Rao 2008). This review focuses on the effectiveness of a single dose of a NSAID in relieving perineal pain, which, if effective, will mainly be due to its early analgesic properties as its anti-inflammatory effect will be minimal at this dosage. NSAIDs are believed to act peripherally by inhibiting COX enzymes that catalyse the conversion of arachidonic acid into prostaglandin (PG) (Rao 2008). There are two main isoforms of COX: COX1 and COX2. COX1 is normally present in most tissues and cells and is not related to inflammation, whereas COX2 is induced by inflammatory mediators and is only found in tissues in the presence of inflammation. In addition, COX2 catalyses the production of pro-inflammatory prostaglandin G_2 (Seibert 1994; Smith 1998). Selective COX2 inhibitors were developed to diminish the side effects of non-selective NSAIDs that result from COX1 inhibition, particularly the inhibition of gastro-protective prostaglandin synthesis. However, selective COX2 NSAIDs exhibit cardiovascular adverse effects (Solomon 2004).

Pain experienced in the perineal area is transmitted through the pudendal nerve to the spinal segments S2 to S4. NSAIDs thus act peripherally by inhibiting pro-inflammatory prostaglandin production and by subsequently reducing inflammation in the perineal area and decreasing pudendal pain nerve fibres excitation.

This review examines the effectiveness of a single dose of any NSAID for the management of perineal pain in the early postpartum period.

Why it is important to do this review

Postpartum perineal pain is a very common post-childbirth complaint. It can have negative consequences for mother and child, including disability in daily functioning for the mother; for example, it can interfere in her taking care of her infant and in breastfeeding. Early pain management is thus relevant to provide relief and prevent chronicity.

NSAIDs are commonly used in the management of postpartum pain (Leeman 2009). It is therefore important to consider their effectiveness and safety, including their safety for the neonate in breastfeeding mothers. The use of NSAID rectal suppositories has been examined in a previous Cochrane Review (Hedayati 2003). Adding to the evidence from previous Cochrane Reviews evaluating alternative management strategies for postpartum perineal pain, this systematic review evaluates and synthesises studies examining the effectiveness of NSAIDs that are administered orally and in a single dose.

OBJECTIVES

To determine the effectiveness of a single dose of an oral non-steroidal anti-inflammatory drug (NSAID) for relief of acute perineal pain in the early postpartum period.

METHODS

Criteria for considering studies for this review

Types of studies

We include only randomised controlled trials (RCTs), comparing a non-steroidal anti-inflammatory drug (NSAID) with another NSAID, aspirin, paracetamol or placebo/no-drug treatment. We exclude quasi-RCTs and cross-over trials. We included papers in abstract format only if they had sufficient information to determine that they met the review's prespecified inclusion criteria. If they did not include this information, we excluded them, but first contacted authors to request the full-text version.

Types of participants

All women who had acute perineal pain or who had been treated for acute perineal pain in the early postpartum period, i.e. the first four weeks after giving birth or as defined by the authors of the studies.

Types of interventions

- Single dose of a NSAID compared with placebo/no drug treatment
- Single dose of a NSAID compared with a single dose of paracetamol
- Single dose of a NSAID compared with a single dose of another NSAID/aspirin

We excluded studies examining NSAIDs administered as suppositories as these have been examined in another Cochrane Review (Hedayati 2003). Our review only includes studies examining the effectiveness of NSAIDs administered orally (single-dose). Studies that evaluated more than one dose of NSAIDs were included in the review if data on the effectiveness of a single dose were collected and reported separately.

Types of outcome measures

Primary outcomes

- Adequate pain relief as reported by the woman, or by determination of greater than 50% relief of pain (either as stated by the woman or as calculated using a formula)*
- Need for additional analgesia for relief of perineal pain
- Maternal drug adverse effects, e.g. nausea, vomiting, sedation, constipation, diarrhoea, drowsiness, sleepiness, psychological impact
- Neonatal drug adverse effects, e.g. nausea, vomiting, sedation, constipation, diarrhoea, drowsiness, sleepiness, psychological impact

* Assessment of 50% pain relief via Total Pain Relief (TOTPAR) and Summed Pain Intensity Difference (SPID) scores (see 'Assessment of pain' section)

Secondary outcomes

- Prolonged hospitalisation due to perineal pain (days)
- Rehospitalisation due to perineal pain
- Fully breastfeeding at discharge
- Mixed feeding at discharge
- Fully breastfeeding at six weeks
- Mixed feeding at six weeks
- Perineal pain at six weeks
- Maternal views (using a validated questionnaire), for example, women's satisfaction with the intervention
- Maternal postpartum depression, measured using a validated depression scale, for example the Edinburgh Postnatal Depression (EPD) scale
- Instrumental measures of disability due to perineal pain/activities of daily living (ADLs)/quality of life (QoL), for example, 15D Health-Related Quality of Life (HRQoL) instrument

Search methods for identification of studies

The following Methods section of this review is based on a standard template used by Cochrane Pregnancy and Childbirth.

Electronic searches

For this update, we searched Cochrane Pregnancy and Childbirth's Trials Register by contacting their Information Specialist (9 December 2019).

The Register is a database containing over 25,000 reports of controlled trials in the field of pregnancy and childbirth. It represents over 30 years of searching. For full current search methods used to populate Pregnancy and Childbirth's Trials Register including the detailed search strategies for CENTRAL, MEDLINE, Embase and CINAHL; the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service, please follow this link.

Briefly, Cochrane Pregnancy and Childbirth's Trials Register is maintained by their Information Specialist and contains trials identified from:

- monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
- weekly searches of MEDLINE (Ovid);
- weekly searches of Embase (Ovid);
- monthly searches of CINAHL (EBSCO);
- handsearches of 30 journals and the proceedings of major conferences;
- weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.

Search results are screened by two people and the full text of all relevant trial reports identified through the searching activities described above is reviewed. Based on the intervention described, each trial report is assigned a number that corresponds to a specific Pregnancy and Childbirth review topic (or topics), and is then added to the Register. The Information Specialist searches the Register for each review using this topic number rather than keywords. This results in a more specific search set that has been fully accounted for in the relevant review sections (Included studies; Excluded studies).

In addition, we searched ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform (ICTRP) for unpublished, planned and ongoing trial reports (9 December 2019) using the search methods detailed in Appendix 1.

We also searched the OpenSIGLE database to identify grey literature and the ProQuest Dissertations and Theses to retrieve dissertation theses related to our topic of interest (28 February 2020) (see: Appendix 1 for search methods used).

Searching other resources

We reviewed the reference lists of all selected papers to identify any additional potentially eligible studies not captured by the electronic searches. We also contacted experts in the field of pain relief and maternity care, and, where appropriate, authors of studies published in abstract format only, to identify any unpublished studies.

We did not apply any language or date restrictions.

Data collection and analysis

Assessment of pain

The number of women achieving adequate pain relief was defined as one of the following.

- The number of women reporting 'good' or 'excellent' pain relief when asked about their level of pain relief four to six hours after receiving their allocated treatment (the data were extracted as dichotomous data).
- The number of women who reported 50% pain relief or greater.
- The number of women who achieved 50% pain relief or greater, as calculated by using derived pain relief scores (TOTPAR (total pain relief) or SPID (summed pain intensity differences)) over four to six hours.

TOTPAR or SPID (or both) were calculated provided sufficient data were present. Examples of possible pain measures included the five-point pain relief (PR) scale with standard or comparable wording (none, slight, moderate, good, complete), the four-point pain intensity (PI) scale (none, mild, moderate, severe), or the visual analogue scale (VAS) or both for pain relief or pain intensity. From these categorical scales, it was possible to convert results into dichotomous data (the proportion of women achieving at least 50% or greater, max TOTPAR) using standard formulae (Moore 1996; Moore 1997b). Conversion of data in this way allowed the use of these data in a meta-analysis (Moore 1997a; Moore 1997b). We used the following equations to estimate the proportions of women achieving at least 50% of maximum TOTPAR:

Proportion with greater than 50% maxTOTPAR = (1.33 x mean %maxTOTPAR – 11.5)

With %maxTOTPAR = mean TOTPAR x 100/(maximum score x number of hours)

(Cooper 1991; Moore 1997b)

Proportion with greater than 50% maxTOTPAR = (1.36 x mean %maxSPID – 2.3)

With %maxSPID = mean SPID x 100/(maximum score x number of hours)

(Cooper 1991; Moore 1997a)

We then calculated the number of women achieving at least 50% maxTOTPAR by multiplying the proportions of women with at least 50% maxTOTPAR by the total number of women in the treatment groups. We then used the number of women with at least 50% maxTOTPAR to calculate the relative benefit and the number needed to treat for an additional beneficial outcome. Where studies used more than one method of calculating adequate pain relief, we preferred for analyses and reporting purposes (in order of decreasing preference) as follows: i) the proportion with at least 50% maxTOTPAR calculated using SPID; ii) the proportion with at least 50% maxTOTPAR calculated using TOTPAR; and iii) the number of women reporting 'good' or 'excellent' pain relief/ number of women reporting at least 50% pain relief. We also assessed the number of women who remedicated in the period of four to eight hours, as well as the median time to remedication, if the information was available.

Selection of studies

Two review authors (FW and VS) independently assessed for inclusion all of the potential studies identified by the search strategy. We resolved any disagreement through discussion or, if necessary, we would have consulted a third person, but this was not required. We included studies presented only as abstracts if they had sufficient information to confirm that they met the review's prespecified inclusion criteria.

We created a study flow diagram to map out the number of records identified, included and excluded (Figure 1).

Data extraction and management

We designed a form to extract data based on the Cochrane Pregnancy and Childbirth Group's data extraction template form. For eligible studies, two review authors (FW and VS) extracted the data independently using the agreed form. We resolved discrepancies through discussion or, if necessary, we would have consulted a third person, but this was not required. We entered data into Review Manager 5 software (RevMan 2020), and FW and VS independently checked these data for accuracy.

Where information about any of the above was unclear, we attempted to contact authors of the original reports to provide further details.

Assessment of risk of bias in included studies

Two review authors (FW and VS) independently assessed risks of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We resolved any disagreement by discussion or, if necessary, we would have involved a third assessor, but this was not required.

(1) Random sequence generation (checking for possible selection bias)

We describe for each included study the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.

We assessed the method as:

- low risk of bias (any truly random process, e.g. random-number table, computer random-number generator);
- high risk of bias (any non-random process, e.g. odd or even date of birth, hospital or clinic record number);
- unclear risk of bias.

(2) Allocation concealment (checking for possible selection bias)

We describe for each included study the methods used to conceal allocation to interventions prior to assignment, and assessed 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 randomisation, consecutively-numbered sealed opaque envelopes);
- high risk of bias (open random allocation, unsealed or non-opaque envelopes, alternation, date of birth);
- unclear risk of bias.

(3.1) Blinding of participants and personnel (checking for possible performance bias)

We describe for each included study the methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. We considered that studies were at low risk of bias if they were blinded, or if we judged that a lack of blinding would be unlikely to affect results. We assessed blinding separately for different outcomes or classes of outcomes.

We assessed the methods as:

- low, high or unclear risk of bias for participants;
- low, high or unclear risk of bias for personnel.

(3.2) Blinding of outcome assessment (checking for possible detection bias)

We describe for each included study the methods used, if any, to blind outcome assessors from knowledge of which intervention a participant received. We assessed blinding separately for different outcomes or classes of outcomes.

We assessed the methods used to blind outcome assessment as:

- low, high or unclear risk of bias.

(4) Incomplete outcome data (checking for possible attrition bias due to the amount, nature and handling of incomplete outcome data)

We describe for each included study, and for each outcome, the completeness of data including attrition and exclusions from the analysis. We state whether attrition and exclusions were reported and the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or

exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information was reported, or could be supplied by the trial authors, we re-included missing data in the relevant analyses.

We assessed the methods as:

- low risk of bias (e.g. no missing outcome data, missing outcome data balanced across groups);
- high risk of bias (e.g. numbers or reasons for missing data imbalanced across groups, 'as treated' analysis done with substantial departure of intervention received from that assigned at randomisation);
- unclear risk of bias.

(5) Selective reporting (checking for reporting bias)

We describe for each included study how we investigated the possibility of selective outcome reporting bias and what we found.

We assessed the methods as:

- low risk of bias (where it is clear that all of the study's prespecified outcomes and all expected outcomes of interest to the review have been reported);
- high risk of bias (where not all the study's prespecified outcomes have been reported; one or more reported primary outcomes were not prespecified; outcomes of interest are reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported);
- unclear risk of bias.

(6) Other bias (checking for bias due to problems not covered by (1) to (5) above)

We describe for each included study any important concerns we had about other possible sources of bias.

We assessed whether each study was free of other problems that could put it at risk of bias:

- low risk of other bias;
- high risk of other bias;
- unclear whether there is risk of other bias.

(7) Overall risk of bias

We made explicit judgements about whether studies were at high risk of bias, according to the criteria described in the *Handbook* (Higgins 2011). With reference to (1) to (6) above, we assessed the likely magnitude and direction of the bias and whether we considered it was likely to impact on the findings. We intended to explore the impact of the level of bias in sensitivity analyses - *see* Sensitivity analysis.

Measures of treatment effect

We carried out statistical analyses using the Review Manager 5 software (RevMan 2020).

Dichotomous data

For dichotomous data, we presented the results as the summary risk ratio (RR) with a 95% confidence interval (CI).

Continuous data

For continuous data, we planned to use the mean difference (MD) if outcomes were measured in the same way between trials. We also planned to use the standardised mean difference (SMD) to combine trials that measured the same outcome, but used different methods; however, these were not required as there were no continuous data in the included studies.

Unit of analysis issues

Cluster-randomised trials

We did not identify any cluster-randomised trials on the topic. However, if we had found any, we would have included them using the guidance in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2020).

Multi-arm trials

For multi-armed trials, only the comparisons of intervention arms that were relevant to this review were included. For example, if a study compared ibuprofen, codeine and placebo, we included only the ibuprofen versus placebo comparison.

If comparisons shared intervention or control groups then we divided the number of participants approximately evenly among the comparisons (Deeks 2020). For example, in the studies with two (or more) intervention groups and one control group we divided the number of participants and the number of events in the control group by half (or more where there were more intervention groups).

Dealing with missing data

For the included studies, we noted levels of attrition. We attempted to contact study authors to ask them to provide missing outcome data. Where this was not possible, we planned to explore the impact of including such studies in the overall assessment of results using a sensitivity analysis, but this was not required.

For all outcomes, we carried out analyses, as far as possible, on an intention-to-treat basis, i.e. we attempted to include all participants randomised to each group in the analyses, and all participants were analysed in the group to which they were allocated, regardless of whether or not they received the allocated intervention. The denominator for each outcome in each trial is the number randomised minus any participants whose outcomes were known to be missing.

Assessment of heterogeneity

We assessed statistical heterogeneity in each meta-analysis using the Tau^2, I^2 and Chi^2 statistics. We regarded heterogeneity as substantial if an I^2 was greater than 30% and either a Tau^2 was greater than zero, or there was a low P value (< 0.10) in the Chi^2 test for heterogeneity.

Assessment of reporting biases

Where there were 10 or more studies in a meta-analysis we investigated reporting biases (such as publication bias) using funnel plots. We assessed funnel plot asymmetry visually.

Where we suspected reporting bias, (see 'Selective reporting bias' above), we attempted to contact study authors to ask them to provide missing outcome data. Where this was not possible, we

planned to explore the impact of including such studies in the overall assessment of results using a sensitivity analysis, but this was not required.

Data synthesis

We carried out statistical analysis using the Review Manager 5 software (RevMan 2020). We used a fixed-effect meta-analysis for combining data where it was reasonable to assume that studies were estimating the same underlying treatment effect, i.e. where trials examined the same intervention, and the trials' populations and methods were judged sufficiently similar. If there was clinical heterogeneity sufficient to expect that the underlying treatment effects differed between trials, or if we detected substantial statistical heterogeneity, we used a random-effects meta-analysis to produce an overall summary, if an average treatment effect across trials was considered clinically meaningful. The random-effects summary was treated as the average of the range of possible treatment effects, and we discuss the clinical implications of treatment effects differing between trials. If the average treatment effect was not clinically meaningful, we did not combine trials.

If we used random-effects analyses, the results are presented as the average treatment effect with a 95% confidence interval, and the estimates of Tau^2 and I^2.

Subgroup analysis and investigation of heterogeneity

Where we identified substantial heterogeneity, we investigated it using subgroup analyses. We considered whether an overall summary was meaningful in the presence of heterogeneity, and if it was, we used a random-effects analysis to produce it.

We had planned to carry out the following subgroup analyses.

- Drugs compatible with breastfeeding versus those that are not compatible with breastfeeding because they have adverse effects on the infant.
- Primiparous versus multiparous women.
- Women with perineal trauma versus women who gave birth over an intact perineum.
- Women who used prior pain relief versus women who did not use prior pain relief.
- Different time-frames of when the dose was taken after the birth.

We were unable to carry out the planned subgroup analyses due to the absence of relevant data in the included studies.

We planned to use the following outcomes in subgroup analyses.

- Adequate pain relief as reported by the woman, or by determination of 50% or greater relief of pain (either as stated by the woman or as calculated using a formula).*
- Need for additional analgesia for relief of perineal pain.
- Maternal drug adverse effects, e.g. nausea, vomiting, sedation, constipation, diarrhoea, drowsiness, sleepiness, psychological impact.

* Assessment of 50% pain relief via TOTPAR and SPID scores (see 'Assessment of pain' section).

We assessed subgroup differences by interaction tests available within RevMan (RevMan 2020). We report the results of subgroup analyses quoting the Chi^2 statistic and P value, and the interaction test I^2 value.

We had also planned to use the outcome 'Neonatal drug adverse effects' in subgroup analyses, but this outcome was not measured in any of the included studies.

Sensitivity analysis

Where appropriate, we carried out planned sensitivity analysis to explore the effect of risks of bias for important outcomes in the review. We carried out sensitivity analysis for the primary outcomes, where appropriate, by excluding those studies judged to be at a high risk of bias for any of the following 'Risk of bias' domains: random sequence generation, allocation concealment, blinding of participants and personnel, and incomplete outcome data, reporting bias or other bias.

We also planned to conduct sensitivity analysis to explore the impact of including studies with high levels of missing data, but we did not have sufficient numbers of studies.

Summary of findings and assessment of the certainty of the evidence

We assessed the certainty of the evidence using the GRADE approach, as outlined in the GRADE handbook in order to assess the certainty of the body of evidence relating to the following outcomes for the main comparison (any NSAID versus placebo).

- Adequate pain relief as reported by the woman, or by determination of 50% or greater relief of pain.
- Need for additional analgesia for relief of perineal pain.
- Maternal drug adverse effects.
- Neonatal drug adverse effects.

We used GRADEpro Guideline Development Tool to import data from Review Manager 5 (RevMan 2020) in order to create a 'Summary of findings' table. We produced a summary of the intervention effect and a measure of certainty for each of the above outcomes using the GRADE approach. 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 evidence can be downgraded from 'high certainty' by one level for serious (or by two levels for very serious) limitations, depending on assessments for risk of bias, indirectness of evidence, serious inconsistency, imprecision of effect estimates or potential publication bias.

RESULTS

Description of studies

Results of the search

See: Figure 1.

Figure 1. Study flow diagram.

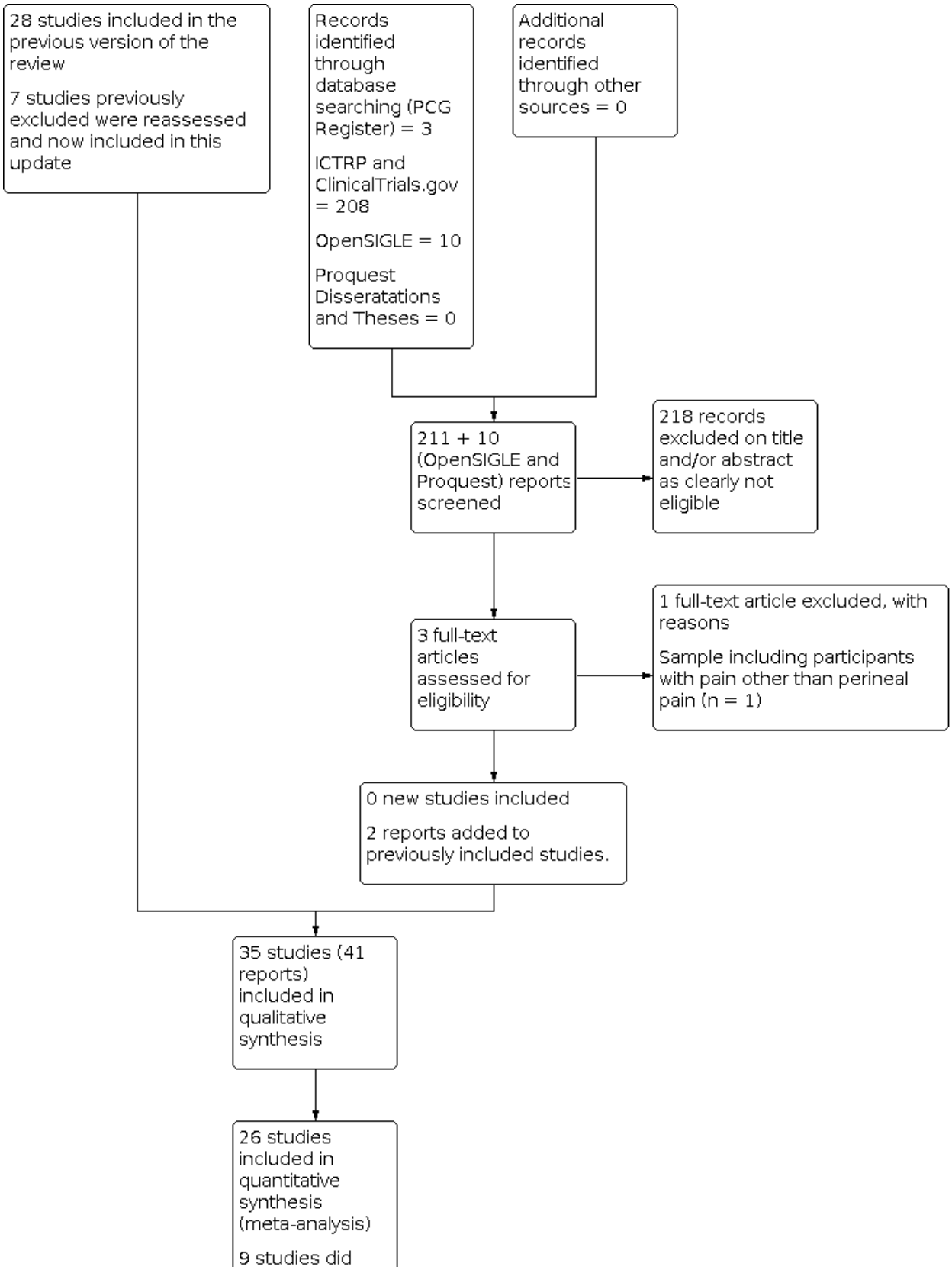
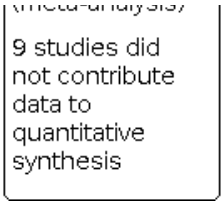


Figure 1. (Continued)



We retrieved 221 records (3 CPC Register, 208 from ICTRP and ClnicalTrials.gov (none of these 208 were eligible), 10 from OpenSIGLE (none of these were eligible) and zero from Proquest). We added one report each to two previously included studies (De Vroey 1978; London 1983), and excluded one new trial report (Lataste 1981). Seven studies previously excluded have been included in this update.

Included studies

Design and setting

We include 35 studies (41 reports), of which two studies were reported in one publication (Laska 1981a; Laska 1981b). Twenty-nine studies were multi-arm studies; in such cases we only extracted the data for any non-steroidal anti-inflammatory drug (NSAIDs) compared with placebo, paracetamol or another NSAID. These studies are described in the Characteristics of included studies section. The effectiveness of paracetamol versus placebo has been examined in a previous Cochrane Review (Chou 2013) and the effectiveness of NSAIDs compared with other non-NSAID drugs will be assessed in future reviews based on the generic protocol (Chou 2009).

Included studies were published between 1967 and 2013; one study was published in the 1960s, five in the 1970s, 22 in the 1980s and four in the 1990s. Only three studies were published since 2000; two in 2008 and one in 2013. Of the 35 included studies, 16 were conducted in the USA and eight in other high-income countries (Canada, UK, Belgium, Spain, France, Italy). Six studies were conducted in Venezuela. The remaining five studies were conducted in other low- or middle-income countries (India, Malaysia, Thailand, Iran).

Four studies reported the exact dates when the study had taken place (1965 - 1966 Bloomfield 1967; 2006 Kamondetdecha 2008; 2005 Lim 2008; 2009 - 2010 Suhrabi 2013). Similarly, reporting of declarations of interest was rare; only one study reported on this (Suhrabi 2013). Seven of the 35 studies had declared funding sources (public funding: Bloomfield 1967; Bloomfield 1974; funding from pharmaceutical industry: Hebertson 1986; Jain 1985; Melzack 1983; Olson 1997; Schachtel 1989). One study specifically stated that no funding or support was received (Suhrabi 2013).

Participants and sample sizes

A total of 5845 women were included in this review, of which 709 women received other drugs not included in this review and were subsequently excluded from the analysis. Of the 4837 women included in the analyses, 3145 received a NSAID and 1692 received placebo or paracetamol. Thirty-four of the 35 studies examined the effectiveness of NSAIDs for relief of post-episiotomy pain. One study (Lim 2008) only included women with any perineal trauma requiring repair but excluded third- or higher-degree tears. All trials excluded women who were breastfeeding and none of the included trials reported neonatal adverse outcomes.

Interventions and comparisons

Sixteen different NSAIDs were examined in the studies included in this review. These were aspirin, ibuprofen, diclofenac, diflunisal, dipyrone, fenoprofen, fluproquazone, zomepirac, meclofenamate sodium, aceclofenac, ketoprofen, flurbiprofen, fendosal, piroxicam, tiaprofenic and celecoxib. Studies, or data from studies, reporting on indoprofen, zomepirac and fluproquazone were subsequently removed from the analyses, as these NSAIDs are currently withdrawn from the market due to causing the following adverse effects: fluproquazone for adverse effects on the liver (Kaplowitz 2013), indoprofen for reports of adverse reactions including reports of carcinogenicity in animal studies (Brayfield 2014), and zomepirac for being associated with fatal and near-fatal anaphylactoid reactions (Brayfield 2014).

Doses of the intervention drugs varied across studies, with the different doses of individual drugs compared in subgroup analyses. Drugs deemed to have equivalent doses, i.e. aspirin 500 mg to 650 mg and ibuprofen 300 mg to 400 mg, were combined for purposes of analyses.

Outcomes

For 26 of the 35 included studies, some measure of adequate pain relief could be extracted four to six hours after drug administration. Seven studies provided data on adequate pain relief four hours after taking the medication, nine studies reported this outcome measure at six hours, and seven studies reported adequate pain relief at both four hours and six hours. In addition, three studies (two publications) reported adequate pain relief outcomes at five hours after drug administration (Jain 1985; Laska 1981a; Laska 1981b). We included these data in the six-hours post-administration outcomes for analysis purposes. Twenty studies reported summed pain intensity differences (SPIDs). Eleven of these studies also reported total pain relief (TOTPAR), and five studies also reported adequate pain relief as a good/excellent rating or the number of women reporting at least 50% pain relief. The remaining six studies only reported adequate pain relief as good/excellent or the number of women with at least 50% pain relief. In 20 of the 26 studies that reported SPID, we calculated the number of women with adequate pain relief using the SPID measure as per protocol. In four of the 11 studies that provided both SPID and TOTPAR (Gleason 1987; Hebertson 1986; Jain 1988; Schachtel 1989), the SPID and TOTPAR calculations of the number of women with adequate pain relief did not match and the raw data for pain intensity or pain relief were not available. In these cases, we used the SPID data to calculate the number of women with adequate pain relief. The reasons for the discrepancy in the number of women with adequate pain relief when calculated using SPID versus TOTPAR are not entirely clear, but they may be due to calculation errors in the reports or

inaccurate time-weighting. The formula to calculate %max TOTPAR contains the number of hours over which pain relief was measured. Some studies for example, measured pain relief at half-hour and one-hour post-administration initially and then hourly thereafter up to six hours, providing a total of seven measurements of pain relief. To accurately apply these data to the formula, adjustments need to be made to account for the half-hour periods, or the %maxTOTPAR would otherwise be overestimated. We noted this absence of adjustment in a study that additionally provided the raw data and we were able to check the calculations. Also, in one of the five studies that reported adequate pain relief as good/excellent, or as the number of women with at least 50% pain relief in addition to SPID, there was a significant unexplained discrepancy between these two measures of adequate pain relief (Hopkinson 1980).

Fifteen studies reported on the need for additional analgesia, and 18 studies reported on any maternal drug adverse effects. None of the secondary outcomes prespecified in the review were reported in any of the included studies. Furthermore, for seven studies that met the review's inclusion criteria, data were not available for analyses because the outcomes were reported beyond the review's maximum six-hour time-frame (e.g. at eight hours and 12 hours) (Bloomfield 1970; Melzack 1983), data for the unique medication groups were not provided (Gruber 1979), outcome data were presented in graphs or in a format that could not be accurately extracted (Jain 1978; Okun 1982), and the numbers randomised to the intervention and placebo groups were not reported (Sunshine 1987b; Trop 1983).

Excluded studies

Fifty-eight of the 96 identified study reports did not meet the review's inclusion criteria and were excluded as follows: the intervention drug was not a NSAID or was administered by a route other than orally in 21 studies; two studies examined the effect of a NSAID in combination with another medication; the comparator was neither a placebo, paracetamol or an other NSAID in five studies; in 12 studies perineal pain was not reported separately for included women, but was reported collectively with other sources of pain or pain in other areas; 12 studies did not report on a single dose; and 4 studies were not RCTs. The remaining studies were excluded for the following reasons: one study (Cater 1985) was excluded because it only examined the NSAID zomepirac which was withdrawn voluntarily from the market by the manufacturer in 1983 because it was associated with fatal and near-fatal anaphylactoid reactions; and one study (Pedronetto 1975) was excluded because it only examined the NSAID indoprofen, which was withdrawn from markets in the 1980s due to reports of adverse reactions including reports of carcinogenicity in animal studies.

Risk of bias in included studies

There was generally poor reporting in the studies included in this review, particularly around methods of randomisation sequence generation, allocation concealment, and blinding of the outcome assessor, with 21 studies receiving unclear judgements for all three of these 'Risk of bias' criteria (see Figure 2 and Figure 3).

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

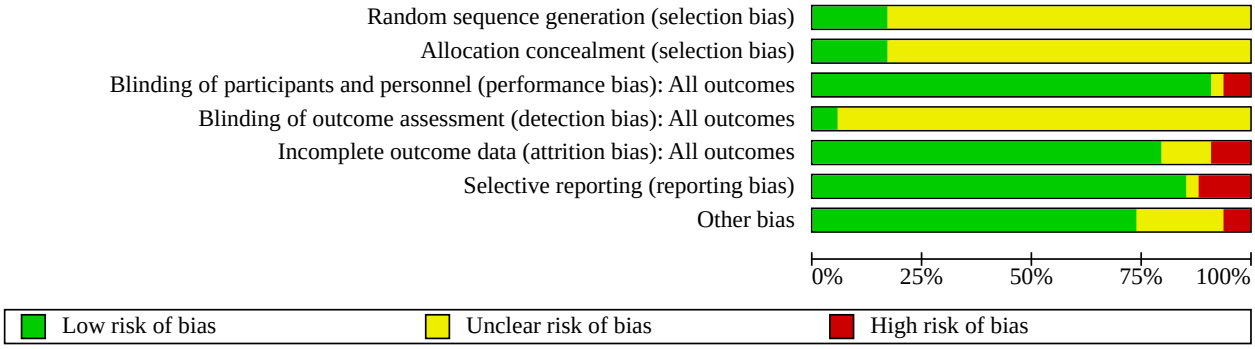


Figure 3. 'Risk of bias' summary: review authors' judgements on each risk of bias item for each included study.

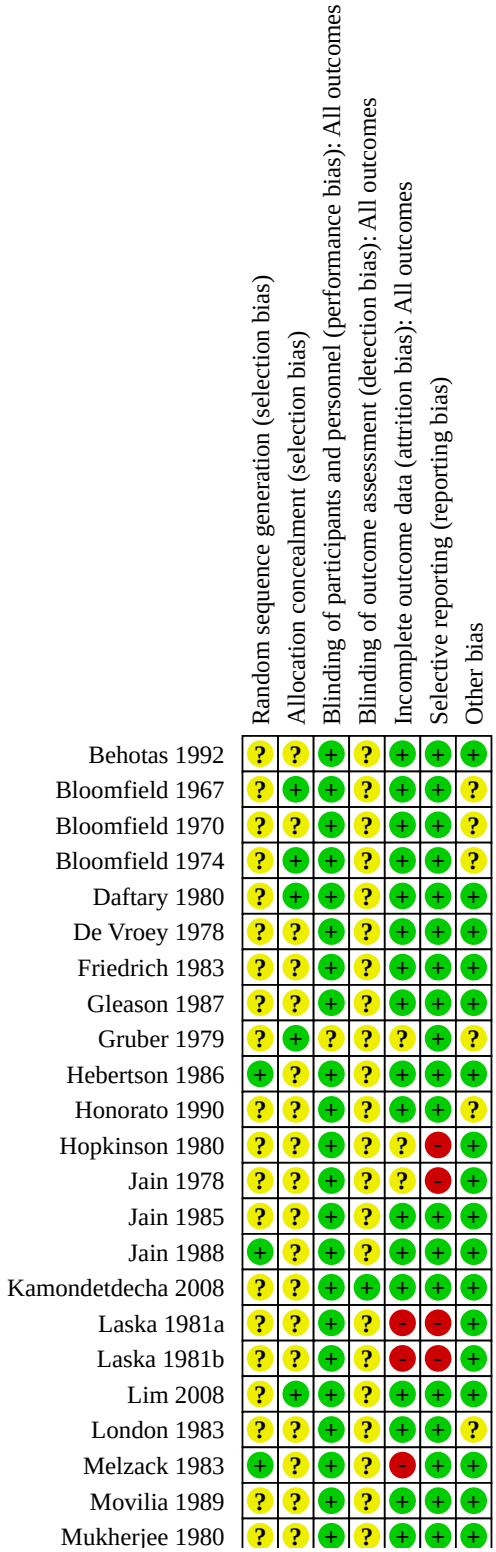
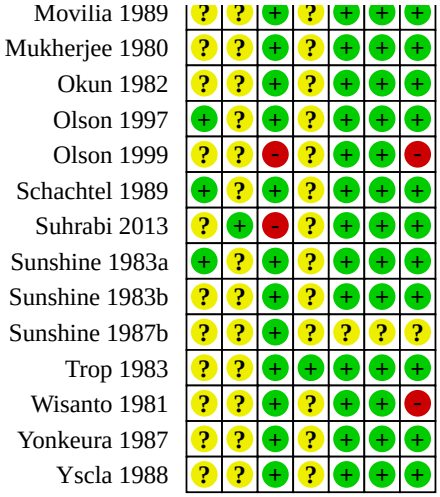


Figure 3. (Continued)



Allocation

Only six of the 35 studies described their sequence generation process. Five described using a computer-generated random sequence (Hebertson 1986; Jain 1988; Olson 1997; Schachtel 1989; Sunshine 1983a), and one described using random numbers but not the method (Melzack 1983).

Adequate allocation concealment was described in six studies (Bloomfield 1967; Bloomfield 1974; Daftary 1980; Gruber 1979; Lim 2008; Suhrabi 2013), but was unclear for all other included studies.

Blinding

Thirty-two of the 35 included studies were described as double-blind, defined as blinding of the participants as well as the personnel providing the treatment to the participants, reducing performance bias. Two studies were single-blind, with only the participants blinded to the treatment they received (Olson 1999; Suhrabi 2013). However, all but two studies (Kamondetdecha 2008; Trop 1983) did not clearly report whether or not the outcome assessor was blinded, making the extent of potential detection bias unclear.

Incomplete outcome data

We assessed three studies to have a high risk of attrition bias (Laska 1981a; Laska 1981b; Melzack 1983); in Laska 1981aand Laska 1981b information on withdrawals due to the need for rescue medication was not provided and in Melzack 1983 there was differential attrition.

We assessed four studies as being at unclear risk of attrition bias (Gruber 1979; Hopkinson 1980; Jain 1978; Sunshine 1987b). In Hopkinson 1980 there appeared to be missing data (possibly due to dropouts or withdrawals) at two-, three- and four-hour assessments without a clear statement of reasons for this in the study publication. In the other three unclear studies there was insufficient information in the trial report to assess the extent of incomplete outcome data.

We assessed all other studies to have a low risk of attrition bias because there was either low or non-differential attrition, or both.

Selective reporting

We rated the potential for reporting bias as low for most of the studies, but it is important to note that in the absence of trial protocols it is not truly possible to assess for reporting bias. We judged four studies (Hopkinson 1980; Jain 1978; Laska 1981a; Laska 1981b) as being at high risk of bias because they did not report one of the outcomes they had prespecified in the Methods sections of their papers.

Other potential sources of bias

For two studies there was an imbalance in some baseline characteristics, so we judged them as unclear (Bloomfield 1970; Bloomfield 1974). Two studies (Honorato 1990; London 1983) did not provide a clear statement on whether baseline characteristics were balanced or not and we judged these at unclear risk of bias. We judged Sunshine 1987b as unclear on 'Other bias' as there was insufficient information to accurately assess this criterion, and we judged Bloomfield 1967 as unclear because there could have been potential carry-over of effect of intrapartum analgesia.

One study that was stopped early due to administrative changes received a high risk of bias judgement (Olson 1999). Lastly, one study (Wisanto 1981) received a high risk of bias judgement for this criterion because the time-lag between episiotomy and drug intake was significantly ($P < 0.05$) shorter in the placebo group (8.08 hours ± 0.81) compared to the intervention group (10.21 hours ± 0.70). We found no other potential sources of bias in any of the other included studies.

Effects of interventions

See: **Summary of findings 1** NSAID compared with placebo for perineal pain in the early postpartum period; **Summary of findings 2** NSAID (single administration, any dose) compared to paracetamol for perineal pain in the early postpartum period

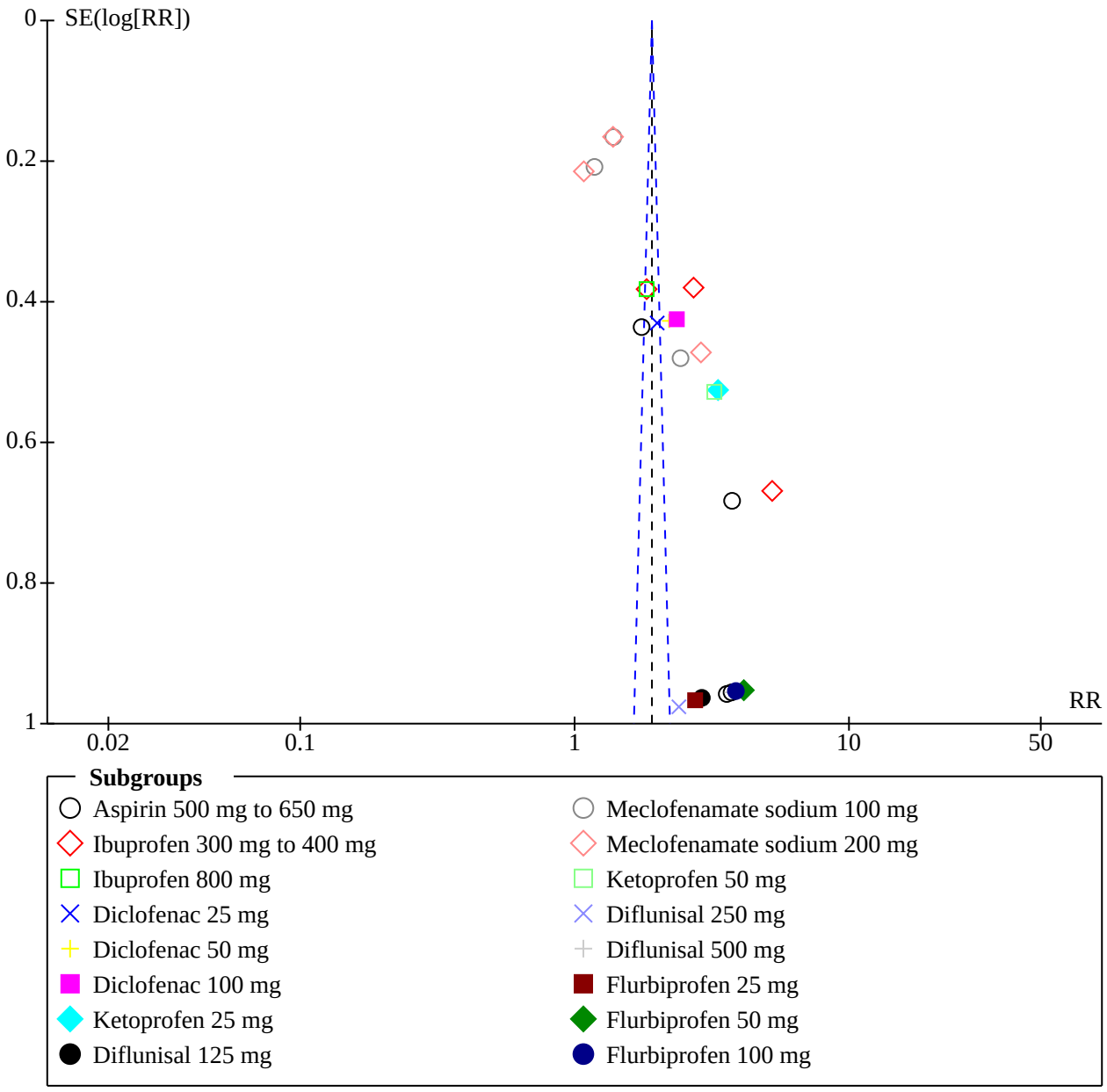
1. Any NSAID versus placebo

Primary outcomes

Adequate pain relief

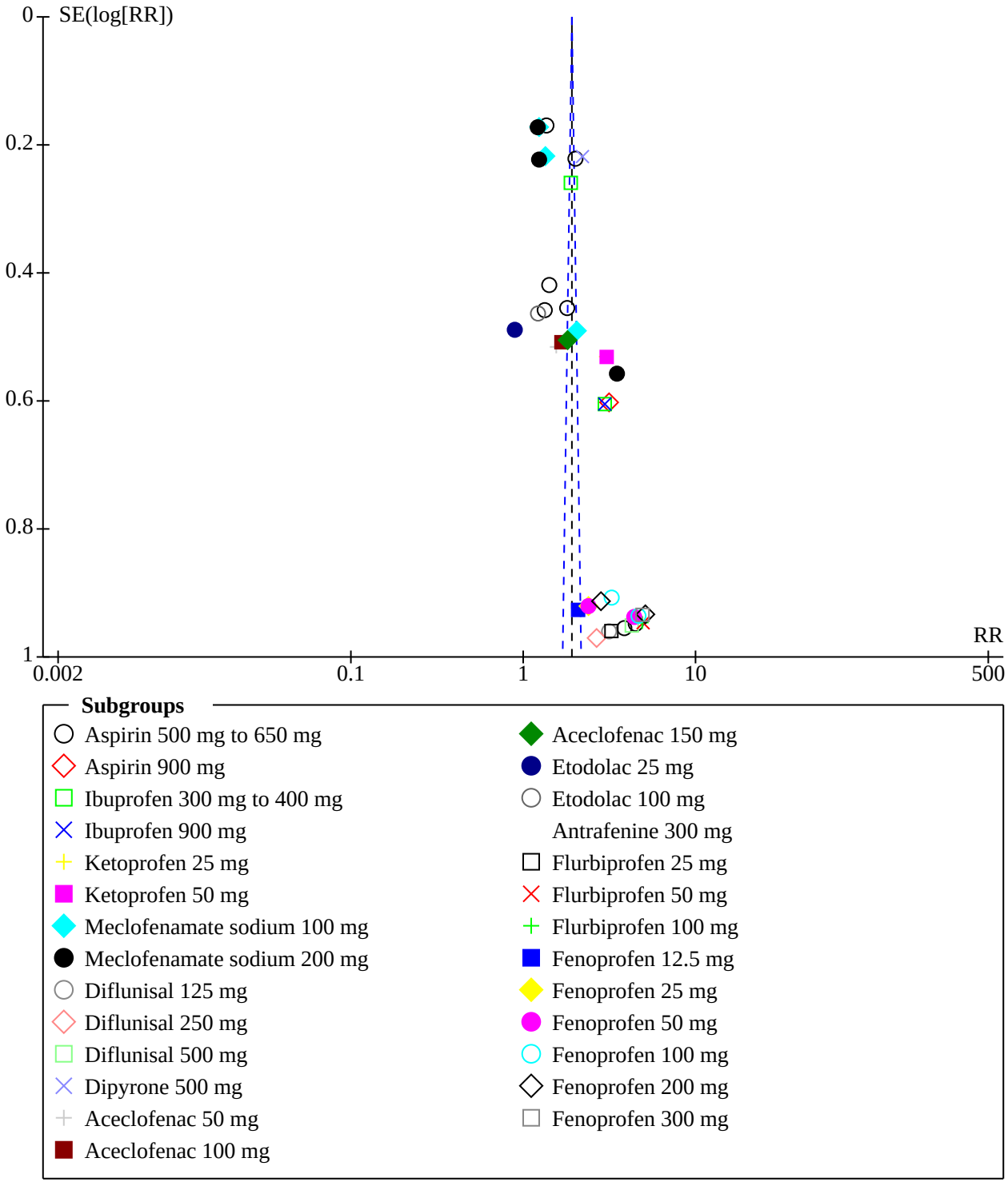
At four hours after drug administration, more women who receive a NSAID may experience adequate pain relief compared to women who receive placebo (risk ratio (RR) 1.91, 95% confidence interval (CI) 1.64 to 2.23; 10 studies, 1573 women; Analysis 1.1; low-certainty evidence; Summary of findings 1). Downgrading decisions were for risk of bias and possible publication bias (Figure 4).

Figure 4. Funnel plot of comparison: 1 NSAID (single administration, any dose) versus placebo, outcome: 1.1 Adequate pain relief (4 hours after administration).



At six hours after drug administration, more women may also experience adequate pain relief in the NSAID compared to the placebo group, although the certainty of evidence is very low (RR 1.92, 95% CI 1.69 to 2.17; 17 studies, 2079 women; Analysis 1.2; Summary of findings 1). The number needed to treat for an additional outcome of have adequate pain relief is four (95% CI 3 to 4) at four hours after drug administration and four (95% CI 3 to 5) at six hours post-administration. GRADE decisions for downgrading the certainty of the evidence for this outcome were based on risk of bias and possible publication bias (Figure 5).

Figure 5. Funnel plot of comparison: 1 NSAID (single administration, any dose) versus placebo, outcome: 1.2 Adequate pain relief (6 hours after administration).



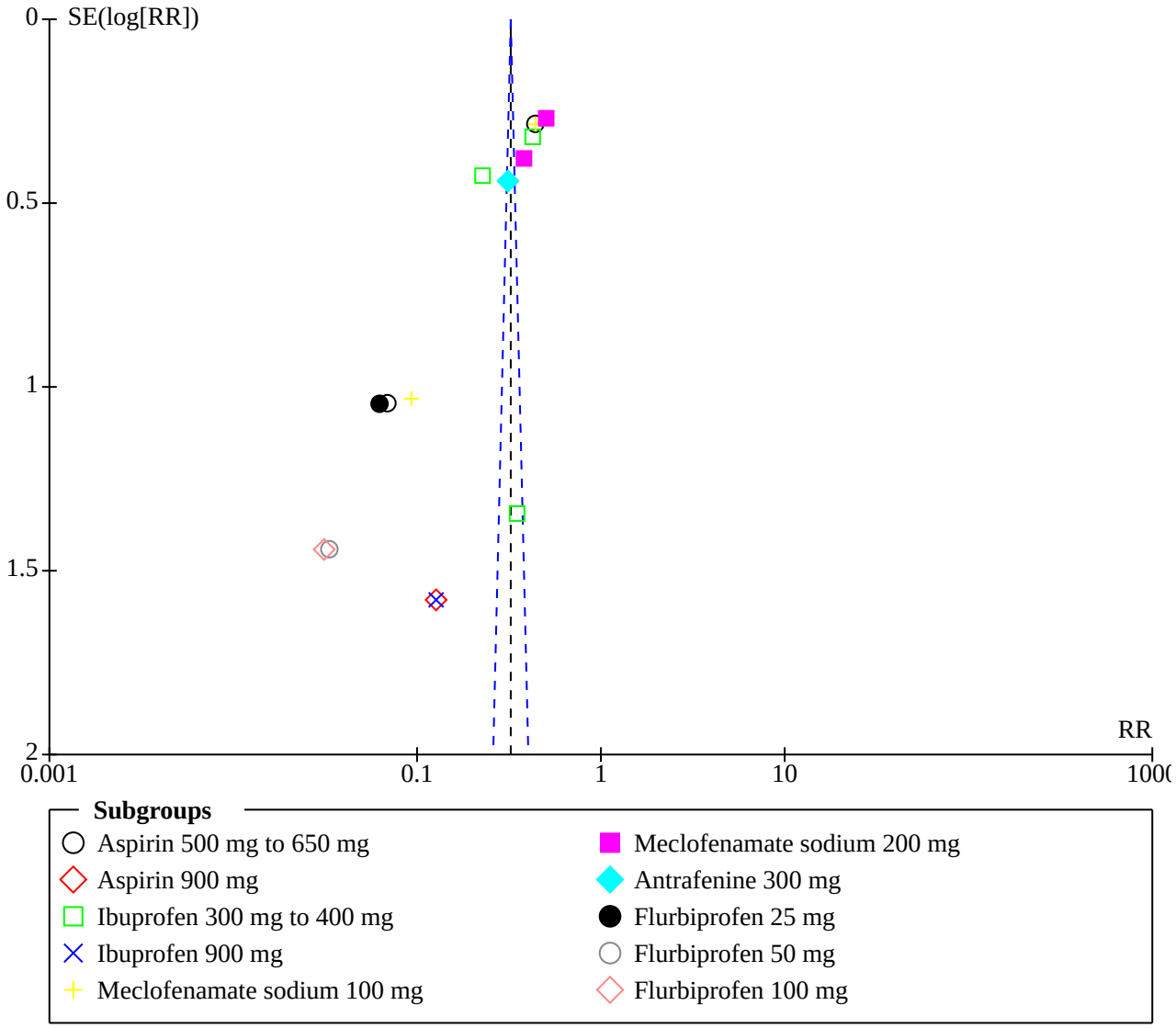
Sensitivity analysis removing studies at high risk of bias did not substantially change the effect estimate at either four hours' follow-up (RR 1.85, 95% CI 1.58 to 2.18) or at six hours (RR 1.74, 95% CI 1.53 to 1.97).

Additional analgesia

Women who received a NSAID are probably less likely to require additional analgesia at four hours (RR 0.39, 95% CI 0.26 to 0.58; 4 studies, 486 women; Analysis 1.3; moderate-certainty evidence; Summary of findings 1).

At six hours after initial administration women who received a NSAID may be less likely to require additional analgesia, although the evidence for this is very uncertain (RR 0.32, 95% CI 0.26 to 0.40; 10 studies, 1012 women; Analysis 1.4; very low-certainty evidence; Summary of findings 1). Downgrading was for risk of bias and possible publication bias (Figure 6).

Figure 6. Funnel plot of comparison: 1 NSAID (single administration, any dose) versus placebo, outcome: 1.4 Need for additional analgesia (6 hours after administration).



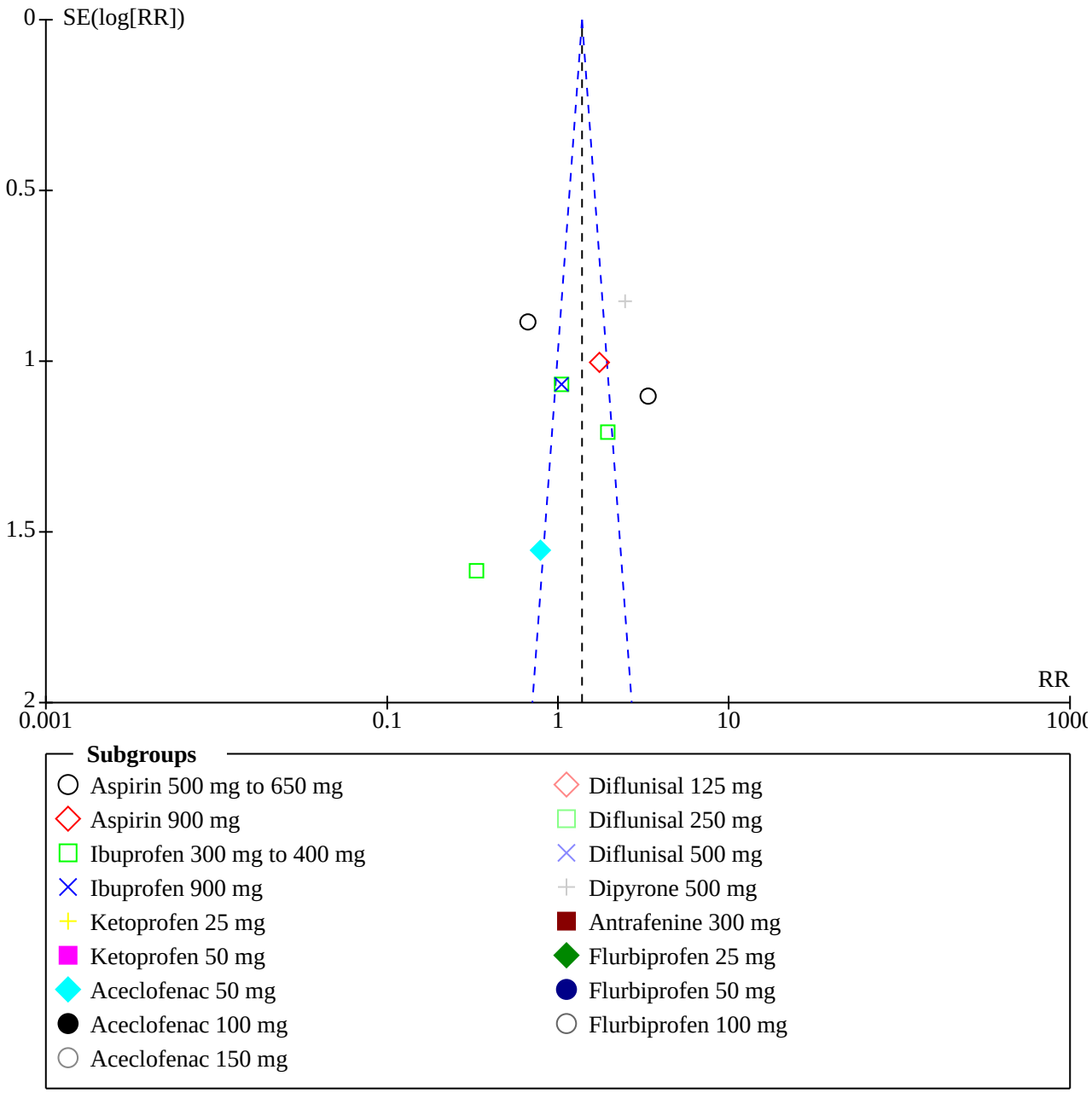
Sensitivity analysis removing studies at high risk of bias did not substantially change the effect estimate at either four hours' follow-up (RR 0.39, 95% CI 0.24 to 0.62) or at six hours (RR 0.32, 95% CI 0.26 to 0.41).

Maternal adverse effects

We could not estimate the RR for maternal drug adverse effects at four hours post-administration, as no adverse effects were observed in either the NSAID (60 women) or the placebo groups (30 women) in the one study (with two treatment arms) reporting at this follow-up time (Sunshine 1983b).

We are uncertain if there is any difference between NSAID and placebo in overall adverse effects at six hours post-administration because the certainty of the evidence is low and the 95% CI is consistent with both possible benefit and possible harm (RR 1.38, 95% CI 0.71 to 2.70; 13 studies, 1388 women; Analysis 1.5; Summary of findings 1). A visual inspection of the funnel plot for this outcome (Figure 7) did not suggest evidence of publication bias.

Figure 7. Funnel plot of comparison: 1 NSAID (single administration, any dose) versus placebo, outcome: 1.5 Maternal drug adverse effects (6 hours after administration).



Sensitivity analysis removing studies at high risk of bias did not change the effect estimate at six hours' follow-up, because the studies at high risk of bias did not contribute to the effect estimate, as they had no events in either arm.

At six hours after drug administration, six of the 17 comparisons (a NSAID versus placebo) across 13 studies reported adverse effects (Analysis 1.5). These were drowsiness (n = 5), abdominal discomfort (n = 2), weakness (n = 1), dizziness (n = 2), headache (n = 2), moderate epigastralgia (n = 1) for the NSAID groups, and drowsiness (n = 2), light-headedness (n = 1), nausea (n = 1), backache (n = 1), dizziness (n = 1) and epigastric pain (n = 1) for the placebo group. In two studies that reported adverse effects (Bloomfield 1967; Daftary 1980), the specific adverse effects were not stated.

Neonatal adverse effects

Neonatal drug adverse effects were not reported in any of the included studies.

Secondary outcomes

None of the studies assessed any of the review's prespecified secondary outcomes.

2. Any NSAID versus paracetamol

Primary outcomes

Adequate pain relief

At four hours after drug administration more women who receive any NSAID may experience adequate pain relief than women who received paracetamol (RR 1.54, 95% CI 1.07 to 2.22; 3 studies, 342 women; Analysis 2.1; low-certainty evidence; Summary of findings 2). Only two studies (Movilia 1989; Yscla 1988) examined a NSAID (aceclofenac 100 mg) versus paracetamol six hours after administration. At six hours we are uncertain if there is a difference between NSAID and paracetamol in the number of women with adequate pain relief, because the certainty of evidence is very low (RR 1.82, 95% CI 0.61 to 5.47; 2 studies, 99 women; $I^2 = 59\%$; Analysis 2.2; Summary of findings 2).

We did not conduct a sensitivity analysis, since there were no studies at high risk of bias included in this comparison.

Additional analgesia

One study (Schachtel 1989) assessed the need for additional analgesia four hours after NSAID (ibuprofen) administration compared with paracetamol (1000 mg). We are uncertain if there is any difference between the two drugs, because the certainty of evidence is very low (RR 0.55, 95% CI 0.27 to 1.13; 73 women; Analysis 2.3; Summary of findings 2).

Another study (Behotas 1992) examined the need for additional analgesia six hours after NSAID (ibuprofen) administration compared with paracetamol (1000 mg). Women who receive NSAID may be less likely to need any additional analgesia compared with women who receive paracetamol (RR 0.28, 95% CI 0.12 to 0.67; 59 women; Analysis 2.4;, low-certainty evidence; Summary of findings 2).

We did not conduct a sensitivity analysis, since there were no studies at high risk of bias included in this comparison.

Maternal adverse effects

No maternal adverse drugs adverse effects were reported in the one study (Kamondetdecha 2008; 210 women) that reported this outcome at four hours after drug administration. Six hours post-administration, two of three studies reported the following maternal drug adverse effects; pruritis (n = 1) for the NSAID group and sleepiness (n = 1) for the paracetamol group. We are uncertain if there is any difference in overall adverse effects between the groups (RR 0.74, 95% CI 0.27 to 2.08; 3 studies, 300 women; Analysis 2.5; very low-certainty evidence; Summary of findings 2).

We did not conduct a sensitivity analysis, since there were no studies at high risk of bias included in this comparison.

Neonatal adverse effects

Neonatal drug adverse effects were not reported in any of the included studies.

Secondary outcomes

None of the studies assessed any of the review's prespecified secondary outcomes.

3. NSAID versus another NSAID

Primary outcomes

Adequate pain relief

It is unclear if there is any difference in effectiveness between different NSAIDs in providing adequate pain relief at four hours after administration (Analysis 3.1) or six hours after administration (Analysis 3.2).

Even though comparisons between different NSAIDs did not show differences in benefit, the direction of effect was in favour of aspirin when compared to diflunisal, in favour of diclofenac when compared to aspirin, in favour of etodolac when compared to aspirin, in favour of dipyrone when compared to aspirin, in favour of ibuprofen when compared to aspirin at four hours but not at six hours, and in favour of flurbiprofen when compared to aspirin except at a lower dose (25 mg) (Analysis 3.1; Analysis 3.2).

Suhrabi 2013 was not included in the meta-analysis, as it did not report any of the review's prespecified outcome measures, but only reported pain intensity scores four hours post-administration on a 10-cm visual analogue scale. Using this measure of pain, no difference between celecoxib 100 mg (mean 2.57, standard deviation (SD) 1.4) and ibuprofen 400 mg (mean 2.7, SD 1.4) was found.

We did not conduct a sensitivity analysis, since there were no studies at high risk of bias included in this comparison.

Additional analgesia

It is unclear if there is any difference in the need for additional analgesia between the different NSAID groups at four hours after administration (Analysis 3.3) or at six at hours after administration (Analysis 3.4).

We did not conduct a sensitivity analysis, since there were no studies at high risk of bias included in this comparison.

Maternal adverse effects

There were no reports of maternal adverse effects at four hours after administration in either of the NSAID groups (aspirin: 62 women; other NSAID:103 women) (De Vroey 1978; Sunshine 1983b).

It is unclear if there is any difference between the different NSAID groups in the risk of maternal adverse effects at six hours after administration (Analysis 3.5).

We did not conduct a sensitivity analysis, since there were no studies at high risk of bias included in this comparison.

Neonatal adverse effects

Neonatal drug adverse effects were not reported in any of the included studies.

Secondary outcomes

None of the studies assessed any of the review's prespecified secondary outcomes.

4. NSAID versus a different dose of the same NSAID

Primary outcomes

Adequate pain relief

It is unclear if there is any difference between different doses of the same NSAID for achieving adequate pain relief at four hours after administration (Analysis 4.1) or at six hours after administration (Analysis 4.2). The different doses of the same NSAID that were investigated were equally effective, with the exception of fenoprofen 50 mg providing adequate pain relief to more women than fenoprofen 100 mg six hours after administration (Laska 1981a). All but one comparison showed little or no difference, but the direction of effect in the included studies was in favour of a lower dose of diflunisal (125 mg) compared to a higher dose (250 mg or 500 mg), in favour of a higher dose of diclofenac (50 mg or 100 mg) versus a lower dose (25 mg), in favour of flurbiprofen 50 mg or 100 mg versus 25 mg, in favour of aceclofenac 150 mg versus 50 mg or 100 mg, in favour of etodolac 100 mg versus 25 mg, in favour of a higher dose of fenoprofen (25 mg, 50 mg, 100 mg, 200 mg, 300 mg) versus a lower dose of fenoprofen (12.5 mg, 25 mg, 50 mg). In contrast, there was no or minimal direction of effect between ibuprofen 300 mg to 400 mg and ibuprofen 800 mg, meclofenamate sodium 100 mg and 200 mg, aceclofenac 50 mg and 100 mg, ketoprofen 25 mg and 50 mg, flurbiprofen 50 mg and 100 mg, fenoprofen 25 mg and 50 mg, and between fenoprofen 100 mg, 200 mg and 300 mg (Analysis 4.1; Analysis 4.2).

We did not conduct a sensitivity analysis, since there were no studies at high risk of bias included in this comparison.

Additional analgesia

It is unclear if there is any difference in the need for additional analgesia between groups examining different doses of the same NSAID at fours after administration (Analysis 4.3) or at six hours after administration Analysis 4.4).

We did not conduct a sensitivity analysis, since there were no studies at high risk of bias included in this comparison.

Maternal adverse effects

There were no reports of maternal adverse effects at four hours after administration in either of the NSAID groups (Hopkinson 1980; De Vroey 1978). It is unclear if there is any difference between the different doses of NSAID in the risk of maternal adverse effects at six hours after administration (Analysis 4.5).

DISCUSSION

Summary of main results

This review involved 5136 women with perineal pain in the early postpartum period, mostly following episiotomy, of whom 3145 received non-steroidal anti-inflammatory drugs (NSAIDs) and 1692 were given paracetamol or placebo. Aspirin 500 mg to 650 mg was the most studied NSAID/dose in the included studies (nine studies), followed by ibuprofen (six studies), while many other NSAIDs were only examined in a single study.

For women who sustained perineal trauma during childbirth, any NSAID may be more effective at providing adequate pain relief than placebo at four hours (low-certainty evidence) but we are less certain about the effects at six hours (very low-certainty evidence; Summary of findings 1). Women who received a NSAID are probably less likely to need additional analgesia at four-hour follow-up compared with placebo (moderate-certainty evidence), and may be less likely to need additional analgesia at six hours, although we are uncertain about this evidence (very low-certainty evidence; Summary of findings 1).

NSAIDs may be more effective than paracetamol four hours after administration (low-certainty evidence; Summary of findings 2), but we are uncertain about their relative effectiveness at six hours post-administration (very low-certainty evidence; Summary of findings 2). It may be that fewer women need additional analgesia at six hours after receiving a NSAID compared with paracetamol (low-certainty evidence; Summary of findings 2).

Maternal adverse effects were rare in both the NSAID group and the placebo or paracetamol groups. We are uncertain if there is any difference between NSAID and placebo (Summary of findings 1) or between NSAID and paracetamol (Summary of findings 2) in overall adverse effects at six hours post-administration.

In the studies that reported adverse effects, more than one adverse effect was reported in the aspirin, ibuprofen and dipyrone groups. Fewer adverse effects were reported for ibuprofen compared to aspirin. An equal number of adverse effects was reported at a lower dose of ibuprofen (300 mg to 400 mg) and a higher dose (800 mg), but their effectiveness in providing pain relief was also equivalent. Information on adverse effects of diclofenac, another commonly-used NSAID, was not reported in the included studies, but more women in the diclofenac group reported adequate pain relief than women in the aspirin group.

It is unclear if there is any difference in effectiveness between the different NSAIDS or the different doses of the same NSAID examined in the included studies. For example, ibuprofen 300 mg to 400 mg was equally as effective in relieving perineal pain in the early postpartum period as ibuprofen 800 mg to 900 mg at four and at six hours after drug administration.

Overall completeness and applicability of evidence

Only three of the 14 prespecified outcomes were examined in the included studies. The studies in this review did not examine the compatibility of NSAIDs with breastfeeding and did not report on neonatal adverse effects. In general, NSAIDs should be used with caution when breastfeeding, with paracetamol as the preferred choice of analgesic for breastfeeding women (BNF 2014). If a NSAID is required, of the NSAIDs that were examined in the studies included in this review, ibuprofen, fenoprofen, diclofenac sodium would be preferred when breastfeeding, while diflunisal, aceclofenac, aspirin, celecoxib, etodolac, flurbiprofen, ketoprofen, dipyrone, meclofenamate sodium should be avoided (BNF 2014; LacMed 2015). Although NSAIDs seem to provide better pain relief than placebo at four and six hours postpartum, there is no evidence available to evaluate the effect of NSAIDs on neonatal outcomes, since the studies in this review only included non-breastfeeding mothers. In addition, there are no data on outcomes such as disability and depression, that can be related to experiencing pain. Other prespecified outcomes that are important for women and service providers, including prolonged hospitalisation and rehospitalisation due to perineal pain, were also not examined in the included studies.

Quality of the evidence

Most of the included studies did not report details on how they generated the random sequence, whether allocation was concealed, and whether the outcome assessment was blinded. Only three studies were published after the year 2000, with most included studies conducted in the 1980s or earlier. Trial registries were only introduced in the past two decades; for example, ClinicalTrials.gov was launched in the year 2000. Moreover, the first CONSORT (Consolidated Standards of Reporting Trials) statement to improve reporting in clinical trials was only published in 1996 (Begg 1996). This may explain the lack of reporting of key methodological aspects in the studies included in this review.

We assessed the GRADE certainty of evidence for the main comparisons (NSAID versus placebo and NSAID versus paracetamol) for all primary outcomes at four- and six-hour follow-ups. The certainty of the evidence was downgraded for risks of bias, imprecision (due to low numbers of women and few events), and publication bias.

Asymmetry in the funnel plots (for the outcome of adequate pain relief) suggests that additional smaller studies comparing the use of a NSAID versus placebo may not have been published, which may lead to an overestimation of the intervention effect (Page 2020). In addition, one trial registration report identified in the search strategy included a letter from the authors confirming that their study would not be published (McCallum 1991). The funnel plots for additional analgesia and adverse effects at six hours post-administration were more symmetrical, but still did not show an equal spread across the triangle.

Potential biases in the review process

We reduced bias in the review process as far as possible by conducting a comprehensive literature search with no language or publication-status restrictions. We contacted study authors for missing data or to clarify information. Two review authors independently conducted study selection, data extraction and GRADE rating.

Agreements and disagreements with other studies or reviews

The results of this review are in agreement with a Cochrane Review assessing analgesia for relief of pain due to uterine cramping/involution after birth (Deussen 2020). This review found that NSAIDs were more effective than placebo in improving pain relief based on eleven studies including 946 women, but adverse effects reported were similar in the placebo and control groups.

AUTHORS' CONCLUSIONS

Implications for practice

The findings of this review need to be interpreted in the context of the certainty of the evidence and risks of bias of the included studies, which was unclear for many because of a lack of reporting on the random sequence generation, allocation concealment and blinding of the outcome assessment.

NSAIDs may be effective analgesics for women with perineal pain postpartum. The different NSAIDs (examined in the included studies) are all effective compared to placebo, and no particular NSAIDs were more effective than others; the choice of NSAIDs may thus be guided by its compatibility with breastfeeding, which was not examined in this review, as all trials excluded women who were breastfeeding.

This review only examined the effectiveness of a single-dose non-steroidal anti-inflammatory drug (NSAID), while in practice more than one dose is often given and women might receive a combination of paracetamol and a NSAID. The findings seem to support the practice of 'stepping up the pain ladder' to a NSAID if paracetamol does not provide sufficient pain relief, or providing multimodal pain relief (Berry 2001), combining paracetamol and a NSAID. The dosages that were compared in the included studies did not seem to impact on the effectiveness of a NSAID. Although NSAIDs may be more effective than paracetamol, the evidence is sparse and inconclusive. Other analgesia may also further be considered, but this is beyond the remit of this review and will be examined in further reviews in this series of reviews on pain relief for perineal pain in the early postpartum period.

Although there is limited evidence, maternal adverse effects seem rare.

None of the included studies reported on neonatal adverse effects or any data for the secondary outcomes of this review, including prolonged hospitalisation or rehospitalisation due to perineal pain, fully breastfeeding or mixed feeding at discharge and at six weeks, maternal views, postpartum depression, and disability

Implications for research

Future studies may examine NSAIDs' adverse-effects profile, including neonatal adverse effects and the compatibility of NSAIDs with breastfeeding, and may assess other important secondary outcomes of this review, including (re-)hospitalisation, maternal disability and maternal views. Moreover, studies mostly included women who had episiotomies. Future research needs to be extended to women with and without perineal trauma, including perineal tears. Finally, the small size of the studies and poor reporting limit the strength of the results of this review. Methodologically high-quality studies should be conducted to further assess the efficacy of NSAIDs versus paracetamol and the efficacy of multimodal treatments.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Behotas 1992

Study characteristics	
Methods	Multi-arm RCT - 3 groups
Participants	Women whose post-episiotomy pain warranted analgesia Hospital 'Sainte-Antonie', Paris Participants were followed up on day-1 postpartum Women with hepatic or renal malfunction, a previous duodenal ulcer and those whose condition contra-indicated treatment with NSAIDs, were excluded
Interventions	Intervention: ibuprofen 400 mg (N = 31) Comparison: paracetamol 1 g (N = 28) and placebo (N = 31)
Outcomes	• Pain intensity measured by VAS before, 30 minutes and thereafter hourly up to 6 hours (0 = no pain to 100 = worst possible pain); verbal scale at hour 0, hour 1 and hour 6 (0 = no pain to 5 = worst possible pain) • Degree of improvement in response to treatment (0 = no improvement to 4 = greatly improved). 4- and 6-hourly pain data were only available for ibuprofen and not for the comparator treatments

Behotas 1992 *(Continued)*

	Need for additional analgesia data (6 hours) were the only outcome data available for inclusion in the review
Notes	Dates of study: NR Funding sources: NR Declarations of interest: NR

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated.
Allocation concealment (selection bias)	Unclear risk	Identical white containers only – insufficient information as to whether these were sequentially-numbered and sealed
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No clear statement
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data provided for all 90 participants (0% attrition rate in all groups)
Selective reporting (reporting bias)	Low risk	Prespecified outcomes were all reported
Other bias	Low risk	Participants were similar in terms of geographical background, socio-professional status and their overall clinical picture

Bloomfield 1967

Study characteristics	
Methods	Multi-arm RCT - 5 groups
Participants	All women having a painful mediolateral episiotomy, an uncomplicated labour and delivery, and consenting to take an investigational drug in the obstetric service of Cincinnati General Hospital, USA The study was conducted between December 7th 1965 and April 22nd 1966 Women who were breastfeeding, were under age 18 and were known to have ASA sensitivity were excluded
Interventions	Intervention: chlorphenesin 400 mg (N = 16); chlorphenesin 800 mg (N = 16); chlorphenesin 400 mg + ASA 300 mg (N = 18) and ASA 600 mg (N = 16) Comparison: placebo (N = 18)

Bloomfield 1967 *(Continued)*

Outcomes	• Pain intensity (0 indicating no pain (none), 1 slight pain (a little), 2 moderate pain (medium), and 3 severe (a lot)) • Side effects. ASA 300 mg were the only data used in the review as the other drug treatment regimens were not NSAIDs Pain intensity was measured immediately before treatment and then hourly for 6 hours after administration
Notes	Dates of study: 7 Dec 1965 to 22 April 1966 Funding sources: USPHS grants HE 05622 and HE 07392 of the National Institutes of Health Declarations of interest: NR

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomly assigned under controlled conditions but does not state how sequence was generated
Allocation concealment (selection bias)	Low risk	Coded medication; identical black capsules but not clear if sequentially coded and sealed
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind; code could be broken without revealing the treatment received by other participants
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No clear statement
Incomplete outcome data (attrition bias) All outcomes	Low risk	5% attrition rate (1 of 16 women) in the ASA 600 mg group; 0% attrition in the placebo group (N = 18)
Selective reporting (reporting bias)	Low risk	Prespecified outcomes were all reported
Other bias	Unclear risk	Potential carry-over of effect of intrapartum analgesia

Bloomfield 1970

Study characteristics

Methods	Multi-arm RCT - 5 groups
Participants	Women on the postnatal wards with moderate to very severe episiotomy pain within 48 hours of an uncomplicated birth at Cincinnati General Hospital, USA Women who were breastfeeding were excluded.
Interventions	Interventions: flufenisal 300 mg (N = 20); flufenisal 600 mg (N = 21); aspirin 600 mg (N = 20); aspirin 1200 mg (N = 20)

Bloomfield 1970 *(Continued)*

	Comparison: placebo (N = 16)
Outcomes	• Pain relief (mean hourly PID scores and mean 8 hour SPID) • Side effects Subjective evaluation by a trained nurse observer; each participant asked to estimate the severity of pain intensity by 'How much do the stitches hurt you?'; each answer was transposed to an ordinal score of 0 = no pain (not at all); 1 = mild pain (a little); 2 = moderate pain (medium); 3 = severe pain (a lot); 4 = very severe pain (a whole lot). A pain intensity score was obtained immediately before the administration of medication and at hourly intervals for 8 hours after Pain relief was measured by 2 variables: % of participants with pain reduction > 50% and pain intensity difference (PID) scores
Notes	No data available for analyses as outcomes reported at 8 hours postpartum Dates of study: NR Funding sources: NR Declarations of interest: NR

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Stratified block (blocks of 5) randomisation based on pain intensity (moderate, severe and very severe) – no clear statement on method used
Allocation concealment (selection bias)	Unclear risk	Pre-packaged identical capsules, but not clear if sealed and sequentially numbered
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No clear statement
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data on all included participants reported
Selective reporting (reporting bias)	Low risk	Outcomes prespecified in the study methods reported
Other bias	Unclear risk	Baseline imbalance in body weight between groups; the group of participants receiving 300 mg of flufenisal had a distinctly lower mean body weight than the other 4 groups, especially the placebo group; 114.1 versus 136.7 pounds, respectively

Bloomfield 1974

Study characteristics

Bloomfield 1974 *(Continued)*

Methods	Multi-arm RCT – 4 groups.
Participants	An homogenous population of postpartum women with moderate to very severe episiotomy pain (mediolateral or midline incision) within 48 hours of an uncomplicated delivery at the University of Cincinnati Medical Centre; homogenous population of postpartum women Women who were unmarried, < 18 years old (but included if married and < 18 years), with history of aspirin allergy, given analgesics or sedatives, or other psychotropic drugs in the previous 6 hours, breastfeeding and with known drug dependence were excluded
Interventions	Intervention: ibuprofen 300 mg (N = 20); ibuprofen 900 mg (N = 20) and aspirin 900 mg (N = 20) Comparison: lactose placebo (N = 20).
Outcomes	• Changes in pain intensity (mean hourly PID scores, mean 6 hour summed PID scores) • Pain relief (pain reduction > 50%) • Side effects. Only 6-hour data available in extractable format
Notes	Dates of study: NR Funding sources: United States Public Health Service Grant HL-05622 and The Upjohn Company Declarations of interest: NR

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No clear statement on method used
Allocation concealment (selection bias)	Low risk	All treatments were in the form of film-coated tablets identical in appearance and taste and pre-packaged in coded number individual dose-vials
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No clear statement
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data provided for all 80 participants (0% attrition rate in all groups)
Selective reporting (reporting bias)	Low risk	Prespecified outcomes were all reported
Other bias	Unclear risk	Some baseline differences between group characteristics (e.g. weight higher in group receiving ibuprofen 900 mg and more unmarried in ibuprofen 300 mg group). Chance occurrences, but with an uncertain influence on the results

Daftary 1980

Study characteristics	
Methods	Multi-arm RCT – 3 groups
Participants	Postpartum women, reporting moderate and severe pain Noerosjee Wadia Hospital, Bombay, India Concurrent therapy with hypnotic-sedative drugs was not permitted from 23.00 the previous night until the end of the evaluation
Interventions	Intervention: dipyrone 500 mg (N = 101) Comparison: placebo (N = 98) and paracetamol 500 mg (N = 100)
Outcomes	• Pain relief (0 - 4 point scale; 0 = nil, 1 = slight, 2 = moderate, 3 = marked and 4 = complete) • Side effects of treatment if volunteered Pain relief was evaluated at 30 minutes and hourly intervals thereafter up to 6 hours following therapy; but we were unable to accurately extract data on pain relief, as graphical data only were available; thus we extracted and reported side effects data only in the review
Notes	Dates of study: NR Funding sources: NR Declarations of interest: NR

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No clear statement on method used
Allocation concealment (selection bias)	Low risk	Tablets were identical in appearance and from numbered sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No clear statement
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data provided for all 299 participants (0% attrition rate in all groups)
Selective reporting (reporting bias)	Low risk	Prespecified outcomes were all reported
Other bias	Low risk	Participant baseline characteristics were comparable

De Vroey 1978

Study characteristics	
Methods	Multi-arm RCT - 5 groups
Participants	Primiparous women aged between 16 - 40 years who had a medio-lateral episiotomy during the course of an otherwise uncomplicated delivery; delivery within previous 48 hours and complained of moderate to severe pain Department of Obstetrics and Gynaecology of the St. Christiana Clinic, Belgium
Interventions	Intervention: diflunisal 125 mg (N = 30); diflunisal 250 mg (N = 30); diflunisal 500 mg (N = 30) and aspirin 600 mg (N = 32) Comparison: placebo (N = 31)
Outcomes	• Pain/pain relief (presented as mean pain scores on a 4-point rating scale; 0 = none, 1 = mild, 2 = moderate and 3 = severe) • Maternal drug adverse effects Pain severity was assessed before drug administration and then at hourly intervals up to 6 - 8 hours; 4- and 6-hour data available and extracted separately
Notes	Dates of study: NR Funding sources: NR Declarations of interest: NR

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No clear statement on method used.
Allocation concealment (selection bias)	Unclear risk	No clear statement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No clear statement
Incomplete outcome data (attrition bias) All outcomes	Low risk	Clear information, including reasons, were provided on 5 exclusions after randomisation and on 3 withdrawals (9%) of the 32 women in the aspirin 600 mg group after treatment. (The attrition rate was 0% for all other groups)
Selective reporting (reporting bias)	Low risk	All prespecified outcomes were reported
Other bias	Low risk	None obvious; all women were primiparas with equal distribution across groups, based on initial severity of pain

Friedrich 1983

Study characteristics	
Methods	Multi-arm RCT – 4 groups
Participants	Women aged between 18 and 34 years with moderate or severe pain following episiotomy, at least 16 hours but no more than 48 hours following induction of anaesthesia Department of Obstetrics and Gynaecology, Barnes Hospital Plaza, Washington University, USA Women were excluded if they had current or recent history of gastrointestinal bleeding, peptic ulcer or other gastrointestinal disorders, alcohol or drug abuse, or disorders of the nervous system, kidney, heart or blood, known allergies to aspirin, or aspirin-like analgesia, conditions likely to interfere with absorption, distribution, metabolism or excretion of drugs, other pain requiring narcotic analgesics, acute dermatitis or other skin lesions, past or present malignancies, taking corticosteroids or other NSAIDs, anticoagulants or other drugs that might interfere with the study medication, experiencing pain due to other conditions or were breastfeeding
Interventions	Intervention: aspirin 650 mg (N = 39); etodolac 25 mg (N = 40) and etodolac 100 mg (N = 40) Comparison: placebo (N = 40)
Outcomes	• Pain intensity (1 = no pain, 2 = mild pain, 3 = moderate pain, 4 = severe, 5 = very severe) • Pain relief (1 = complete, 2 = a lot, 3 = some, 4 = little, 5 = no relief) • Onset of analgesia (N/A for review) • Duration of analgesia (N/A for review) • Side effects (N/A for review as not specific to 6-hour time-frame) • Global rating (N/A for review as assessed at end of 8 hours) Pain assessed at baseline, 30 minutes after and hourly thereafter up to 8 hours; data for 6 hours provided and used in the review as per protocol
Notes	Dates of study: NR Funding sources: NR Declarations of interest: NR

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No clear statement on method used
Allocation concealment (selection bias)	Unclear risk	No clear statement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Stated double-blind
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No clear statement
Incomplete outcome data (attrition bias)	Low risk	Data provided for all 159 participants (0% attrition rate in all groups)

Friedrich 1983 *(Continued)*

All outcomes		
Selective reporting (reporting bias)	Low risk	Prespecified outcomes were all reported
Other bias	Low risk	Groups were balanced on demographics and clinical features

Gleason 1987

Study characteristics	
Methods	Multi-arm RCT – 4 groups
Participants	Women aged 15 years and older with moderate to severe episiotomy pain within 24 hours of an uncomplicated vaginal birth and could read, comprehend and sign a consent form Hospital setting in Kansas, USA Nursing mothers, women with a history of reaction or hypersensitivity to NSAIDs or salicylates or women who had received topical perineal anaesthetic or analgesic, NSAID, sedative or psychotropic medication within 3½ hours of study entry, were excluded
Interventions	Intervention: meclofenamate 100 mg (N = 77); meclofenamate 200 mg (N = 80), and codeine 60 mg (N = 79) Comparison intervention: placebo (N = 79)
Outcomes	• Pain intensity (0 = none, 1 = slight, 2 = moderate and 3 = severe) • Pain relief (0 = none, 1 = a little, 2 = some, 3 = a lot and 4 = complete) • Adverse effects (N/A for analysis as unclear if these are after 1st dose or subsequent doses) • Supplemental analgesia (not provided for meclofenamate 200 mg) • Global rating of poor, fair and good (but unclear if rated after 1st dose or all doses – N/A for analysis) Pain measured before 1st dose, 30 minutes after and thereafter hourly up to 6 hours
Notes	Codeine 60 mg was not considered in the review as not a NSAID Dates of study: NR Funding sources: NR Declarations of interest: NR

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No clear statement on method used
Allocation concealment (selection bias)	Unclear risk	Only states each dose was packaged separately
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind

Gleason 1987 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No clear statement
Incomplete outcome data (attrition bias) All outcomes	Low risk	Of 327 women selected, 12 (4%) were excluded from the analysis due to protocol violations (taking other analgesic medication during the study). The attrition rates in the individual groups were: 1 of 81 (1%) in the meclofenamate 200 mg group, 3 of 80 (4%) in the meclofenamate 100 mg group, 3 of 83 (4%) in the placebo group (and 3 of 83 (4%) in the codeine group which was not included in this review)
Selective reporting (reporting bias)	Low risk	Prespecified outcomes were all reported
Other bias	Low risk	The 4 treatment groups did not differ significantly by demographic characteristics

Gruber 1979

Study characteristics	
Methods	Multi-arm RCT - 11 groups
Participants	Hospitalised postpartum women without complicating disease reporting uterine cramp or post-episiotomy wound pain (sub-grouped separately) following vaginal birth
Interventions	Intervention: propoxyphene napsylate 50 mg (N = 57), propoxyphene napsylate 100 mg (N = 54), propoxyphene napsylate 150 mg (N = 58), fenoprofen calcium 200 mg (N = 59), fenoprofen calcium 400 mg (N = 54), fenoprofen calcium 600 mg (N = 54), propoxyphene napsylate + fenoprofen calcium 50/200 mg (N = 55), propoxyphene napsylate+ fenoprofen calcium 100/400 mg (N = 50), propoxyphene napsylate + fenoprofen calcium 150/600 mg (N = 57), aspirin 650 mg (N = 59) Control: placebo (N = 56)
Outcomes	• Pain intensity measured on a scale from 0 - 4 as none, a little, some, a lot or complete • Pain relief measured on a scale from 0 - 4 as none, a little, some, a lot or complete • Side effects measured using a checklist
Notes	Propoxyphene napsylate groups and propoxyphene napsylate + fenoprofen calcium groups not considered in the review as not NSAID/pure NSAID. Unable also to extract data for NSAID medications only. Intervention and control group numbers reflect those treated for episiotomy pain only Dates of study: NR Funding sources: NR Declarations of interest: NR

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient information; states only that 11 treatments were randomised in each successive series of 11 envelopes

Gruber 1979 *(Continued)*

Allocation concealment (selection bias)	Low risk	Identical capsules, numbered sequentially and dispensed in coded envelopes
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No clear statement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	States that 1 observer at each institution gathered and recorded all of the data but not clear if blinded to group allocation
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unable to accurately assess due to how the data is presented in the Results section
Selective reporting (reporting bias)	Low risk	Outcomes prespecified in the study methods are all reported
Other bias	Unclear risk	Groups were further sub-grouped according to institution, type of pain (uterine or episiotomy) and intensity of pain at the start of study. If a sub-group was too small it would be discarded; unclear if this occurred or possible effect on results

Hebertson 1986

Study characteristics	
Methods	Multi-arm RCT– 4 groups
Participants	Women aged 15 years and older, moderate to severe episiotomy pain and uncomplicated vaginal birth Latter Day Saints Hospital, Utah, USA Women with a history of reaction or hyper-sensitivity to NSAIDs or salicylates, active gastric intestinal disease or other disease and received an analgesic, sedative or psychotropic medication or topical perineal anaesthetic within 3½ hours of entry into the study, were excluded
Interventions	Intervention: meclofenamate sodium 200 mg (N = 40); meclofenamate sodium 100 mg (N = 41) and codeine 60 mg (N = 39) Comparison: placebo (N = 41)
Outcomes	• Pain relief (4-point scale; 0 = none, 1 = slight, 2 = moderate, 3 = severe) • Pain intensity (4-point scale; 0 = none, 1 = a little, 2 = some, 3 = a lot, 4 = complete) • Additional medications • Side effects Pain intensity was rated just prior to the treatment and together with pain relief was measured at 30 minutes after administration and hourly thereafter up to 6 hours
Notes	Codeine 60 mg was not considered in the review, as not a NSAID Dates of study: NR Funding sources: Warner-Lambert/Parke-Davis Pharmaceutical Research

Hebertson 1986 *(Continued)*

Declarations of interest: NR

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random table
Allocation concealment (selection bias)	Unclear risk	No clear statement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No clear statement
Incomplete outcome data (attrition bias) All outcomes	Low risk	Of 168 women selected, 7 (4%) were excluded from the analysis due to protocol violations (i.e. had medication within 3½ hours before study entry). The attrition rates in the individual groups were: 2 of 42 (5%) in the meclofenamate 200 mg group, 1 of 42 (2%) in the meclofenamate 100 mg group, 3 of 42 (7%) in the placebo group (and 1 of 42 (2%) in the codeine group which was not included in this review)
Selective reporting (reporting bias)	Low risk	Prespecified outcomes were all reported
Other bias	Low risk	No differences in the distribution of participants across groups

Honorato 1990

Study characteristics

Methods	Multi-arm RCT – 4 groups
Participants	Women aged 18 - 35 years with intense post-episiotomy pain requiring analgesia 3 centres; Navarre Teaching Hospital, Pamplona, Spain; Legnano Civil Hospital, Legnano, Italy, and Montebelluna Civil Hospital, Montebelluna, Spain Women suffering little or no pain, who had peptic ulcer, serious liver or kidney failure, puerperal fever or any complication within the puerperium or any serious general disease that could interfere with the results and were already being treated with NSAID agents or systemic steroids, tranquillisers, sedatives, narcotics and/or local anaesthetics, were excluded Participants were not allowed to take any other drug that might interfere with the results
Interventions	Intervention: aceclofenac 50 mg (N = 18); aceclofenac 100 mg (N = 24) and aceclofenac 150 mg (N = 21) Comparison: placebo (N = 13)
Outcomes	• Pain intensity (4-point scale of 0 = no pain, 1 = mild pain, 2 = moderate pain and 3 = severe pain, and VAS 0 (no pain) to 100 (worst possible pain))

Honorato 1990 *(Continued)*

	• Overall evaluation (1 = good, 2 = fair, 3 = nil and 4 = worse) • Drug-related adverse effects (1 = good, 2 = fair, 3 = poor) Degree of pain was measured at baseline, 30 minutes after and hourly thereafter up to 6 hours
Notes	Dates of study: NR Funding sources: NR Declarations of interest: NR

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No clear statement on method used
Allocation concealment (selection bias)	Unclear risk	Suggests only that treatments were prepared so that neither the participant nor the investigator could distinguish between the doses
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No clear statement
Incomplete outcome data (attrition bias) All outcomes	Low risk	Loss of blood sample data in 18 of 45 participants of the 4 groups (not specified which groups); reasons provided. However, this outcome (serum concentration of aceclofenac) was not included in this review. 0% attrition rate for outcomes included in this review
Selective reporting (reporting bias)	Low risk	Results for the outcome 'Overall evaluation' are not provided, but important pain outcome data were all reported
Other bias	Unclear risk	No clear statement on balanced between-group characteristics; also fewer numbers in placebo group

Hopkinson 1980

Study characteristics

Methods	Multi-arm RCT – 4 groups
Participants	Women with moderate or severe post-episiotomy pain Abington Memorial Hospital, Pennsylvania, USA Women with eclampsia and those who had received analgesic drugs within 12 hours prior to study, were excluded
Interventions	Intervention: ibuprofen 400 mg (N = 80); ibuprofen 800 mg (N = 80) and propoxyphene 65 mg (N = 81) Comparison: placebo (N = 81)

Hopkinson 1980 *(Continued)*

Outcomes	• Pain intensity • Relief of pain • Additional analgesia • Side effects Evaluations of pain were recorded at 30 minutes, and hourly thereafter up to 4 hours after treatment administration
Notes	Propoxyphene 65 mg was not considered in the review as not a NSAID Dates of study: NR Funding sources: NR Declarations of interest: NR

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No clear statement on methods used
Allocation concealment (selection bias)	Unclear risk	No clear statement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No clear statement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Appear to be missing data (dropouts or withdrawals) at 2-, 3- and 4-hour assessments; no clear statement as to reasons in study publication
Selective reporting (reporting bias)	High risk	Side effects not mentioned/reported; no reason provided
Other bias	Low risk	There were no statistically significant differences between any of the groups on baseline parameters or characteristics

Jain 1978

Study characteristics

Methods	Multi-arm RCT - 4 groups
Participants	Consenting postpartum women within 48 hrs of birth, aged between 18 and 39 years with moderate to severe episiotomy pain Tulane University School of Medicine, New Orleans, USA

Jain 1978 *(Continued)*

	Nursing mothers, those with systemic diseases and those allergic to aspirin were excluded
Interventions	Intervention: piroxicam 20 mg (N = 31), piroxicam 40 mg (N = 29) and aspirin 648 mg (N = 30) Control: placebo (N = 30)
Outcomes	• Pain intensity • Pain relief • Side effects • Extra analgesia (after 2 hrs of test medication) Measurement was at baseline and hourly up to 4 hours thereafter. Observer rating of intensity on a 4-point scale of 0 = none, 1 = slight, 2 = moderate and 3 = severe. Observer rating of relief on a 5-point scale of 0 = none, 1 = slight, 2 = moderate, 3 = marked and 4 = complete
Notes	Dates of study: NR Funding sources: NR Declarations of interest: NR

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No clear statement
Allocation concealment (selection bias)	Unclear risk	No clear statement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No clear statement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unable to accurately assess from the data presented in paper
Selective reporting (reporting bias)	High risk	Prespecified outcomes (in study methods) of pain intensity and pain relief by observer rating are not reported (only states that it is comparable to self-rating); additional analgesia is also not reported
Other bias	Low risk	Groups were comparable in age, weight, height and initial degree of pain

Jain 1985

Study characteristics

Methods	Multi-arm RCT – 4 groups

Jain 1985 *(Continued)*

Participants	Postpartum women at least 18 years old who had undergone episiotomy and had at least moderate intensity pain Tulane University School of Medicine and Clinical Research Centre, New Orleans, USA Women who received analgesics or tranquillisers within at least 4 hours of study entry, intended to breastfeed, had a history of convulsive disorders, known peptic ulcer, renal, hepatic or haematological disease or known allergic reactions to NSAIDs, were excluded
Interventions	Intervention: aspirin 600 mg (N = 30); indoprofen 50 mg (N = 30); indoprofen 100 mg (N = 30) Comparison: placebo (N = 30)
Outcomes	• Pain intensity (0 = none, 1 = mild, 2 = moderate and 3 = severe) • Pain relief (0 = none, 1 = a little, 2 = some, 3 = a lot and 4 = complete) • Re-medication • Adverse effects (observed) • Overall evaluation of efficacy (0 = poor, 1 = fair and 2 = good) Pain assessed at baseline, 30 minutes after and thereafter through to 5 hours. 5-hour data were used in the review (considered within 6-hour time-frame data)
Notes	Only aspirin included in the review, since indoprofen was withdrawn from the market Dates of study: NR Funding sources: Adria Laboratories Declarations of interest: NR

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No clear statement on method used
Allocation concealment (selection bias)	Unclear risk	No clear statement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No clear statement
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data provided for all 120 participants (0% attrition rate in all groups)
Selective reporting (reporting bias)	Low risk	Prespecified outcomes were all reported
Other bias	Low risk	Demographic data indicated groups were similar in age, race, height, weight and initial pain intensity

Jain 1988

Study characteristics	
Methods	Multi-arm RCT – 3 groups
Participants	Women with moderate to severe pain following episiotomy Clinical research centre, New Orleans, USA Women with known hypersensitivity to NSAID agents, history of allergy to aspirin, ibuprofen or caffeine, history of asthma, clinically significant renal, hepatic, endocrine, pulmonary, cardiac, neurologic, or cerebral dysfunction or with a history of peptic ulcer disease or gastrointestinal blood loss, uncontrolled diabetes, drug abuse or alcoholism, were excluded Use of caffeine, anti-inflammatory agent, tranquilliser or sedative was prohibited during the 4 hours prior to administration of test medication as well as during the study period
Interventions	Intervention: caffeine 100 mg + ibuprofen 200 mg (N = 50) and ibuprofen 400 mg (N = 49) Comparison: placebo (N = 48)
Outcomes	• Pain intensity (0 = none, 1 = slight, 2 = moderate and 3 = severe) • Pain relief (0 = none, 1 = slight or 25%, 2 = some or 50%, 3 = a lot or 75% and 4 = complete or 100% relief) • Rescue/additional medication (only included if requested after 2 hours of receiving study drug) • Side effects • Global impression and overall evaluation of study medication Pain assessed at baseline and 30 minutes after and thereafter hourly up to 6 hours. Only 6-hour data used in this review (4-hour data could not be extracted)
Notes	Caffeine 100 mg + ibuprofen 200 mg combination therapy not include in the review, as not pure NSAID Dates of study: NR Funding sources: NR Declarations of interest: NR

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation schedule
Allocation concealment (selection bias)	Unclear risk	Supplied in unit dose bottles containing identical tablets; no information if sequentially-numbered and sealed
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No clear statement
Incomplete outcome data (attrition bias)	Low risk	Of 161 women selected, 14 (9%) were excluded from the analysis; 11 due to rescue medication before the 2-hour follow-up (4 in the ibuprofen 400 mg

Jain 1988 *(Continued)*

All outcomes		group, 4 in the placebo group (and 3 in the ibuprofen 200 mg + caffeine group which was not included in this review)), 2 due to use of confounding agents and 1 because she was under 18 years old (not specified from which group). Attrition rates could not be calculated due to non-report of the exact number of participants in each group at the start of the study
Selective reporting (reporting bias)	Low risk	Prespecified outcomes were all reported
Other bias	Low risk	No statistical differences across groups by demographic variables and baseline pain intensity measures

Kamondetdecha 2008

Study characteristics	
Methods	Parallel RCT - 2 groups.
Participants	Women with mediolateral episiotomy without a 3rd- or 4th-degree tear after a normal uncomplicated delivery, at term, who had not used any analgesic drugs within 4 hours preceding the study King Chulalongkorn Memorial Hospital, Bangkok, Thailand Women with an allergy to either study drug, a history of drug dependence, regular use of analgesic drugs before or during pregnancy, and any medical condition known to be potentially exacerbated by acetaminophen or NSAIDS, including a history of gastrointestinal ulcer or bleeding, significant renal or liver impairment and asthma, postpartum haemorrhage or any other major postpartum complications, were excluded
Interventions	Intervention: ibuprofen 400 mg (N = 106) Comparison: acetaminophen 500 mg (N = 104)
Outcomes	• Pain severity (10-cm VAS from 0 = no pain to 10 = worst pain ever) • Side effects • Rescue medication; supplemental analgesic after 4-hour evaluation as a rescue drug • Maternal satisfaction with relief of perineal pain (after 24 hours of treatment = N/A for review) An initial pain rating was recorded before participants took the first dose of analgesia and at 1, 2, 3 and 4 hours after
Notes	Dates of study: June to November 2006 Funding sources: NR Declarations of interest: NR

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No clear statement on method used; states only "stratified random sampling technique".
Allocation concealment (selection bias)	Unclear risk	No clear statement

Kamondetdecha 2008 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessor blind to treatment group
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data provided for all 210 participants (0% attrition rate in all groups)
Selective reporting (reporting bias)	Low risk	Prespecified outcomes were all reported
Other bias	Low risk	Treatment groups were similar in demographic data and clinical features; the severity of perineal pain did not differ between the groups before the treatment

Laska 1981a

Study characteristics	
Methods	Multi-arm RCT (2 studies reported in 1 publication; study E1).
Participants	Women with severe pain only, who gave consent, no complicating illness, were not breastfeeding and were expected to tolerate medication well Maternity hospital, Caracus, Venezuela
Interventions	Intervention: E1 study: fenoprofen 50 mg (N = 27); fenoprofen 100 mg (N = 27); fenoprofen 200 mg (N = 26) and fenoprofen 300 mg (N = 27)
Outcomes	• Pain relief (0 = none, 1 = 25%, 2 = 50%, 3 = 75%, 4 = 100%) • Pain intensity (0 = no pain, 1 = slight pain, 2 = moderate pain, 3 = severe pain) • Additional (rescue) medication Data were obtained at baseline, and 1, 2, 3, 4 and 5 hours after taking the medication. 5-hour data used in this review (included at 6-hour time-frame)
Notes	Dates of study: NR Funding sources: NR Declarations of interest: NR

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No clear statement on method used
Allocation concealment (selection bias)	Unclear risk	No clear statement

Laska 1981a *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No clear statement
Incomplete outcome data (attrition bias) All outcomes	High risk	Data on withdrawals due to need for rescue medication at < 2 hours not provided (or referred to in Results section)
Selective reporting (reporting bias)	High risk	Need for rescue medication prespecified in the study methods but not reported
Other bias	Low risk	None apparent; "no significant differences between treatment groups".

Laska 1981b

Study characteristics	
Methods	Multi-arm RCT (2 studies reported in 1 publication; study E2)
Participants	Women with severe pain only, who gave consent, no complicating illness, were not breastfeeding and were expected to tolerate medication well Maternity hospital, Caracus, Venezuela
Interventions	E2 study: fenoprofen 12.5 mg (N = 24); fenoprofen 25 mg (N = 23); fenoprofen 50 mg (N = 23); fenoprofen 100 mg (N = 23) and fenoprofen 200 mg (N = 23) Comparison: placebo in both E1 study (N = 27) and E2 study (N = 23)
Outcomes	• Pain relief (0 = none, 1 = 25%, 2 = 50%, 3 = 75%, 4 = 100%) • Pain intensity (0 = no pain, 1 = slight pain, 2 = moderate pain, 3 = severe pain) • Additional (rescue) medication. Data were obtained at baseline, and 1, 2, 3, 4 and 5 hours after taking the medication. 5-hour data used in this review (included at 6-hour time-frame)
Notes	Dates of study: NR Funding sources: NR Declarations of interest: NR

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No clear statement on method used
Allocation concealment (selection bias)	Unclear risk	No clear statement

Laska 1981b *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No clear statement
Incomplete outcome data (attrition bias) All outcomes	High risk	Data on withdrawals due to need for rescue medication at < 2 hours not provided (or referred to in results section)
Selective reporting (reporting bias)	High risk	Need for rescue medication prespecified in the study methods but not reported.
Other bias	Low risk	None apparent; "no significant differences between treatment groups".

Lim 2008

Study characteristics	
Methods	Parallel RCT – 2 groups.
Participants	Women who spontaneously delivered a singleton fetus and sustained perineal damage requiring repair; women were randomised as soon as possible after completion of perineal suturing A state-funded public maternity hospital which also serves as an affiliated teaching hospital in Penang, Malaysia Women with known allergy to NSAIDs, epidural during labour, 3rd- or higher-degree tear, instrumental vaginal birth, a history of peptic ulcer, asthma, thrombocytopenia, renal impairment or severe postpartum haemorrhage > 1500 mL, were excluded
Interventions	Intervention: celecoxib 200 mg (N = 163) Comparison: diclofenac 100 mg (N = 165)
Outcomes	• Pain scores on VAS of 0 - 10 • Pain relief = overall relief satisfaction score on VAS of 0 - 10 (N/A for review as results presented at 24 hours post-treatment) • Adverse symptoms (on questionnaire – yes/no) - (N/A for review as results presented at 24 hours post-treatment) • Rescue medication (N/A for review as results presented at 24 hours post-treatment) Pain score (VAS) were completed by women at baseline and 1, 2, 4, 8, 12 and 24 hours. 4-hour data used in the review
Notes	Dates of study: January to June 2006 Funding sources: NR Declarations of interest: NR
Risk of bias	

Lim 2008 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No clear statement on method used
Allocation concealment (selection bias)	Low risk	Numbered sealed opaque envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No clear statement
Incomplete outcome data (attrition bias) All outcomes	Low risk	Incomplete outcome data balanced across groups (attrition rates: 15 of 164 (9%) in the celecoxib groups and 15 of 165 (9%) in the diclofenac group). Analysis by intention-to-treat
Selective reporting (reporting bias)	Low risk	Prespecified outcomes were all reported
Other bias	Low risk	No significant differences between the groups in any characteristics

London 1983

Study characteristics	
Methods	Multi-arm RCT – 4 groups
Participants	Women between the ages of 18 and 40, no systemic medical illness and experienced moderate to severe episiotomy pain within 48 hours following an otherwise uncomplicated vaginal delivery Department of Obstetrics and Gynaecology, Sinai Hospital of Baltimore, USA Exclusion criteria were those used by Hermann et al 1980 and included; women with pain not due directly to the episiotomy (e.g. uterine cramps), except for cleansing, all wound care was suspended for the whole study period; patients who appeared unlikely to communicate meaningful information about their pain; women with only mild pain; those under 16 years of age; history of drug allergy; any relevant psychiatric, neurologic, cardiovascular, pulmonary, hepatic, gastrointestinal, or renal disorders and women given analgesics, sedatives, or other psychotropic drugs within 3 hours were excluded
Interventions	Intervention: fluproquazone 200 mg (N = 39); fluproquazone 100 mg (N = 41), and aspirin 650 mg (N = 40) Comparison: placebo (N = 40)
Outcomes	• Pain intensity (SPID) • Pain relief (TOTPAR) • Adverse reactions • Overall impression (poor, fair, good, very good, excellent).

London 1983 *(Continued)*

	Rating scale information for pain intensity and pain relief measures are not provided; unable to use formula to calculate adequate pain relief, but adequate pain relief could be derived from good to excellent overall impression rating
Notes	Dates of study: NR Funding sources: NR Declarations of interest: NR

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No clear statement
Allocation concealment (selection bias)	Unclear risk	States sealed envelopes, but unclear if consecutively-numbered or opaque
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No clear statement
Incomplete outcome data (attrition bias) All outcomes	Low risk	The attrition rate was 0%, but of the 166 participants, 160 were included in the analysis (4% excluded). Provides reasons for exclusions after entering study; the data of 6 patients were not included since they did not follow the assigned protocol.
Selective reporting (reporting bias)	Low risk	Prespecified outcomes were all reported.
Other bias	Unclear risk	No clear statement on baseline characteristics or balance across groups

Melzack 1983

Study characteristics

Methods	Multi-arm RCT - 3 groups
Participants	Women in Quebec, Canada who had uncomplicated vaginal births, were judged to be in excellent health, did not receive any analgesics within 6 hrs of the study, and had moderate to severe post-episiotomy pain
Interventions	Intervention: Diflunisal 1000 mg (N = 30) and acetominophen 650 mg (N = 30) Control: Placebo (N = 30)
Outcomes	• Pain intensity measured using a self-rating record as none, slight, moderate or severe • Pain relief measured on a self-rating record as none, a little, some, a lot or complete relief • Unusual/side effects from taking the medication

Melzack 1983 *(Continued)*

	Outcomes measured at 30, 60, 90 minutes, and hourly from 2 to 12 hours thereafter
Notes	Acetominophen 650 mg not considered for the review as not an NSAID. Data only extractable for outcomes at 12 hours post-treatment only Dates of study: NR Funding sources: This was supported by a grant from Merck Frosst Canada Inc Declarations of interest: NR

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random-number allocator
Allocation concealment (selection bias)	Unclear risk	States only that all capsules were identical in appearance, odourless, peach-coloured and film-coated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No clear statement
Incomplete outcome data (attrition bias) All outcomes	High risk	20% (6/30) were excluded from the intervention group after randomisation as 5 requested additional analgesia and 1 had loss of data; 40% (12/30) were excluded from the intervention group as 11 requested additional analgesia and 1 had loss of data. Although the reasons for attrition are provided, attrition is high and imbalanced across groups. The analysis is not by intention-to-treat as those who requested additional medication during the study were excluded; twice the number in the placebo group compared to the NSAID group were excluded (5 versus 11) which has the potential to influence results
Selective reporting (reporting bias)	Low risk	Outcomes prespecified in the study Methods are all reported
Other bias	Low risk	Nothing to indicate any other source of bias

Movilia 1989

Study characteristics

Methods	Parallel RCT– 2 groups
Participants	Women aged 18 - 38 years with intense post-episiotomy pain requiring analgesia Legnano Civil Hospital, Italy

Movilia 1989 *(Continued)*

	Women with liver or kidney failure, peptic ulcer and hypersensitivity to paracetamol or NSAID, were excluded
Interventions	Intervention: aceclofenac single tablet 100 mg (N = 30; pain intensity could not be assessed in 1 due to vomiting; N = 29) Comparison: paracetamol 650 mg (N = 30)
Outcomes	• Pain intensity (VAS 0 - 100 with 0 = no pain and 100 = extremely severe pain); and rated by investigator on 5-point scale (0 = absent, 1 = mild, 2 = moderate, 3 = severe, 4 = extremely severe) • Overall global efficacy (0 = unsatisfactory, 1 = fair, 2 = excellent) • Overall global tolerability (0 = unsatisfactory, 1 = fair, 2 = good) Pain assessed before treatment administration, at 30 minutes after and hourly thereafter through to 6 hours
Notes	Dates of study: NR Funding sources: NR Declarations of interest: NR

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No clear statement on method used
Allocation concealment (selection bias)	Unclear risk	No clear statement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No clear statement
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 (3%) of 30 lost to analysis for pain intensity in aceclofenac 100 mg group due to vomiting. 0% attrition rate for the paracetamol 650 mg group
Selective reporting (reporting bias)	Low risk	Prespecified outcomes were all reported
Other bias	Low risk	Randomisation produced 2 homogenous groups

Mukherjee 1980

Study characteristics

Methods	Multi-arm RCT – 3 groups

Mukherjee 1980 *(Continued)*

Participants	Women were selected from an otherwise healthy population of parturient women whose chief complaint was moderate to severe pain following episiotomy New Delhi, India Women with known sensitivity to dipyrone and aspirin or who had received analgesics 8 hours before entry to the study, were excluded
Interventions	Intervention: dipyrone 500 mg (N = 89) and aspirin 500 mg (N = 90) Comparison: placebo (N = 88)
Outcomes	• Pain relief (measured in % and converted to a scale of 1 - 4; 25% = 1, slight, 50% = 2, moderate, 75% = 3, marked and 100% = 4, complete). • Side effects Pain relief was measured at baseline, at 30 minutes post-treatment and hourly thereafter to 6 hours. We were unable to accurately extract mean pain relief scores from the graphs; numbers converted from percentages of reported pain as provided in the paper for 6-hour time-frame
Notes	Dates of study: NR Funding sources: NR Declarations of interest: NR

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No clear statement on method used
Allocation concealment (selection bias)	Unclear risk	No clear statement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No clear statement
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data provided for all 267 participants (0% attrition rate in all groups)
Selective reporting (reporting bias)	Low risk	Prespecified outcomes were all reported
Other bias	Low risk	Baseline characteristics comparable

Okun 1982

Study characteristics

Okun 1982 *(Continued)*

Methods	Multi-arm RCT - 5 groups
Participants	Hospitalised women within 48hrs of birth and with moderate, severe or very severe uterine or episiotomy pain Department of Clinical Pharmacology, Cedars-Sinai Medical Center, Los Angeles, USA Women who were breast feeding, and/or had received any analgesic, sedative or psychotropic medication within 6 hrs of the study were excluded
Interventions	Interventions: fendosal 100 mg (N = 19), fendosal 200 mg (N = 19), fendosal 400 mg (N = 18) and aspirin 650 mg (N = 20) Control: placebo (N = 18)
Outcomes	• Adverse effects • Pain intensity difference (PID) • Pain relief • Requiring additional analgesia Pain intensity was measured on a 5-point scale of 1 = no pain, 2 = mild pain, 3 = moderate pain, 4 = severe pain and 5 = very severe pain, just before and then hourly from drug administration up to 8 hours, which was the study period. Participants were questioned at 1 and 2 hours whether their pain relief was 50% or greater
Notes	Results are extractable for 8 hours after the intervention only Dates of study: NR Funding sources: NR Declarations of interest: NR

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No clear statement
Allocation concealment (selection bias)	Unclear risk	States only that the capsules were identical looking; unclear if numbered sequentially or coded
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	1 nurse observer measured the outcomes, but it is not clear if the observer was blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing or incomplete data
Selective reporting (reporting bias)	Low risk	Outcomes prespecified in the study methods are all reported

Okun 1982 *(Continued)*

Other bias	Low risk	Mean ages, body weights, and pain intensity and type of pain at baseline were comparable across the 5 groups

Olson 1997

Study characteristics	
Methods	Multi-arm RCT – 5 groups
Participants	Women 18 years or older and able to communicate meaningfully with the nurse-observer, severe episiotomy pain after uncomplicated delivery, could tolerate oral medication and had no medications that might confound the results were permitted during the study or for the 4 hours before entry to the study Hospital Maternidad Concepcion Palacios, Caracas, Venezuela Women planning to breastfeed within 24 hours after administration of study medication, with serious complicating illness, abnormal postpartum bleeding, active peptic ulcer disease or other gastrointestinal disease associated with blood loss, who received any other investigational drug within 1 month before enrolment in study or with a history of drug or alcohol abuse or known allergic sensitivities to the study medications, were excluded
Interventions	Intervention: diclofenac 25 mg (N = 52); diclofenac 50 mg (N = 50); diclofenac 100 mg (N = 51) and aspirin 650 mg (N = 50) Comparison: placebo (N = 52)
Outcomes	• Pain intensity (4-point scale of 0 = none, 1 = slight, 2 = moderate and 3 = severe) • Pain relief (0 = none, 1 = a little (25%), 2 = some (50%), 3 = a lot (75%) and 4 = complete (100%)) • Adverse reactions (recorded if they were observed or volunteered) • Overall improvement (7-point scale from 1 = very much worse to 7 = very much better) • Study medication global rating (0 = poor, 1 = fair, 2 = good and 3 = excellent) Pain intensity was measured prior to, 30 minutes after, and hourly thereafter up to 8 hours following drug administration. 4-hour data used in the review (6-hour data could not be extracted)
Notes	Dates of study: NR Funding sources: Ciba-Geigy Corporation Declarations of interest: NR

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated random permutation
Allocation concealment (selection bias)	Unclear risk	Doses were identical in appearance and packaging but no indication if sequentially numbered and sealed
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind

Olson 1997 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No clear statement
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data provided for all 255 participants (0% attrition rate in all groups)
Selective reporting (reporting bias)	Low risk	All prespecified outcomes were reported
Other bias	Low risk	No significant differences between groups in terms of characteristics and clinical features; all had severe episiotomy pain on entry to the study

Olson 1999

Study characteristics	
Methods	Multi-arm RCT – 4 groups
Participants	Women 18 years or older and able to communicate meaningfully with nurse-observer, hospitalised and were in good health, could tolerate oral medication and had severe post-episiotomy pain after term delivery with no medical complications Hospital Maternidad Concepcion Palacios, Caracas, Venezuela Women who were breastfeeding or who planned to breastfeed within 48 hours after drug administration, with none or suspected hypersensitivity to dipyrone, ketoprofen or other NSAID agents or who received any other investigational drug within 1 month prior to enrolment in the study, were excluded
Interventions	Intervention: ketoprofen oral solution 5%, 25 mg prepared in 0.45 mL (N = 28); ketoprofen oral solution 5%, 50 mg prepared in 0.90 mL (N = 26) and dipyrone oral solution 500 mg prepared in 1 mL or 30 drops (N = 27) Comparison: placebo oral solution (N = 27)
Outcomes	• Pain intensity (0 = none, 1 = slight, 2 = moderate, 3 = severe) • Pain relief (0 = none, 1 = a little (25%), 2 = some (50%), 3 = a lot (75%), 4 = complete (100%)) • Additional analgesia (included in analysis if requested after 1 hour) • Adverse effects • Global rating of study medication (0 = poor, 1 = fair, 2 = good and 3 = excellent) Pain intensity and relief collected at baseline prior to treatment, at; 15, 30, 60, 90 and 120 minutes after treatment and hourly thereafter for a total of 6 hours
Notes	Dipyrone oral solution not considered for the review as not NSAID Dates of study: NR Funding sources: NR Declarations of interest: NR

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

Olson 1999 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	No clear statement on method used
Allocation concealment (selection bias)	Unclear risk	States individual randomisation envelope was prepared for each participant, and sealed (and opened later by nurse A), but does not state if opaque and consecutively labelled
Blinding of participants and personnel (performance bias) All outcomes	High risk	Nurse A prepared and gave the medication to the participants, so was aware of their allocation; although Nurse B was the observer and did not know the allocations, there is a risk of bias here as nurse A (although instructed not to disclose drug) could have
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No clear statement
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data provided for all 108 participants (0% attrition rate in all groups)
Selective reporting (reporting bias)	Low risk	Prespecified outcomes were all reported
Other bias	High risk	No significant differences among the treatment groups for characteristics and clinical features; The study was prematurely terminated due to administrative changes, so fewer than half of the sample size estimate was recruited

Schachtel 1989

Study characteristics	
Methods	Multi-arm RCT – 3 groups
Participants	Hospitalised women with moderate or severe episiotomy pain after normal uncomplicated birth New York Women with eclampsia or any other medical complication, allergic hypersensitivity to treatment drugs or had any analgesia or NSAID in 4 hours prior to study entry, were excluded
Interventions	Intervention: ibuprofen 400 mg (N = 36) Comparison: placebo (N = 38) and acetaminophen 1000 mg (N = 37)
Outcomes	• Pain intensity (4 point scale; 0 = none to 3 = severe) • Pain relief (5-point scale; 0 = none to 4 = complete) • Overall evaluation (5-point scale; 0 = poor to 5 = excellent) • Supplemental analgesia (after 1 hour) Pain measured before medication, 30 minutes and 1 - 4 hours after
Notes	Dates of study: NR Funding sources: Whitehall Laboratories Declarations of interest: NR

Schachtel 1989 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random code
Allocation concealment (selection bias)	Unclear risk	No clear statement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No clear statement
Incomplete outcome data (attrition bias) All outcomes	Low risk	4 of 115 (3%) participants removed after randomisation due to re-medicated but time not known and not specified from which group
Selective reporting (reporting bias)	Low risk	Prespecified outcomes were all reported
Other bias	Low risk	The groups were similar in demographics and clinical features

Suhrabi 2013

Study characteristics	
Methods	Parallel RCT – 2 groups
Participants	Women 18 - 35 years of age, vaginal birth with mediolateral episiotomy, absorbable and continuous sutures and singleton, live baby. Iran. Women were excluded if they had known allergy to NSAIDs or a history of alimentary canal disorders, underlying illness, instrumental delivery, perineal rupture (3rd or 4th degree), postpartum haemorrhage, pre-eclampsia and eclampsia
Interventions	Intervention: celecoxib 100 mg every 12 hours (N = 85) Comparison: ibuprofen 400 mg every 6 hours (N = 85)
Outcomes	• Pain levels using VAS • Additional analgesia (N/A for review as assume measurement at end of study period = 12 hours). • Adverse effects (N/A for review as assume measurement at end of study period = 12 hours). Pain levels were measured before the intervention and at 1, 2, 4, 8 and 12 hours after suturing using a VAS; but no information provided on scale intervals 4-hour continuous data only included in the review
Notes	Dates of study: March 2009 to November 2010 Funding sources: there was no funding or support

Suhrabi 2013 *(Continued)*

Declarations of interest: none declared.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No clear statement on method used
Allocation concealment (selection bias)	Low risk	Sealed opaque envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	Single-blind only (the person assessing pain was blinded, but no report of blinding of the participants)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No clear statement
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data provided for all 170 participants (0% attrition rate in all groups)
Selective reporting (reporting bias)	Low risk	All prespecified outcomes were reported.
Other bias	Low risk	No significant differences between the groups in terms of demographics or clinical characteristics

Sunshine 1983a

Study characteristics

Methods	Multi-arm RCT – 5 groups
Participants	Women 18 years or older who were able to communicate meaningfully with the nurse observer and gave written consent and had moderate or severe post-episiotomy pain after an uncomplicated birth and could tolerate oral medication Hospital Maternidad Concepcion Palacios, Caracas, Venezuela Women who were breastfeeding, had any complicating illness or abnormal postpartum bleeding, received any other investigational drug within 1 month prior to enrolment in the study or history of drug dependence or known allergic sensitivities to propionic acid derivatives and aspirin, were excluded
Interventions	Intervention: aspirin 600 mg (N = 29); flurbiprofen 25 mg (N = 32); flurbiprofen 50 mg (N = 29) and flurbiprofen 100 mg (N = 31) Comparison: placebo (N = 31)
Outcomes	• Pain intensity (0 = none, 1 = slight, 2 = moderate, 3 = severe) • Pain relief (0 = none, 1 = a little (25%), 2 = some (50%), 3 = a lot (75%), 4 = complete (100%)) • Adverse reactions (observed or volunteered). • Additional medication (included if administered after 1st hour of study medication).

Sunshine 1983a *(Continued)*

	Pain assessed prior to and hourly up to 6 hours after drug administration
Notes	Dates of study: NR Funding sources: NR Declarations of interest: NR

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated
Allocation concealment (selection bias)	Unclear risk	States identical in appearance and packaging but insufficient information about sequentially numbered and sealed
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No clear statement
Incomplete outcome data (attrition bias) All outcomes	Low risk	16 of 168 (10%) were dropped from the analysis because they received oxytocic medication (4 of 33 (12%) in the aspirin 600 mg group, 3 of 35 (9%) in the flurbiprofen 25 mg group, 5 of 34 (15%) in the flurbiprofen 50 mg group, 3 of 34 (9%) in the flurbiprofen 100 mg group, and 1 of 32 (3%) in the placebo group)
Selective reporting (reporting bias)	Low risk	Prespecified outcomes were all reported
Other bias	Low risk	No significant differences between groups in characteristics and clinical features; all had moderate or severe episiotomy pain on entry to the study

Sunshine 1983b

Study characteristics

Methods	Multi-arm RCT – 4 groups
Participants	Women with severe post-episiotomy pain after uncomplicated delivery, > 18 years old and could tolerate oral medication Hospital Maternidad Concepcion Palacios, Caracus, Venezuela Women with known allergic sensitivities to study medications, abnormal postpartum bleeding, or complicated illnesses, breastfeeding or with a history of drug dependence or had received other investigational drugs prior to entry into study, were excluded
Interventions	Intervention: ibuprofen 400 mg (N = 30); zomepirac 100 mg (N = 30) and aspirin 600 mg (N = 30) Comparison: placebo (N = 30)

Sunshine 1983b *(Continued)*

Outcomes	• Pain intensity (0 = none, 1 = slight, 2 = moderate, 3 = severe) • Pain relief (% and overall improvement; none = 0%, 1 = 25%, 2 = 50%, 3 = 75%, 4 = 100%) • Additional medications • Adverse reactions • Overall pain rating (7-point scale; 1 = very much worse, 2 = much worse, 3 = a little worse, 4 = no change, 5 = a little better, 6 = much better, 7 = very much better) • Overall medication rating (4-point scale; 0 = poor, 1 = fair, 2 = good, 3 = excellent) Measurements were taken at the time of medication, 30 minutes later, and then hourly up to 4 hours. No medications were given within 4 hours of the study medication being given; if women required additional analgesia within 1 hour after administration of study medication, they were subsequently excluded from the study
Notes	Dates of study: NR Funding sources: NR Declarations of interest: NR

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No clear statement on method used
Allocation concealment (selection bias)	Unclear risk	No clear statement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No clear statement
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data provided for all 120 participants (0% attrition rate in all groups)
Selective reporting (reporting bias)	Low risk	Prespecified outcomes were all reported
Other bias	Low risk	Similar group baseline characteristics

Sunshine 1987b

Study characteristics	
Methods	Multi-arm RCT - 5 groups
Participants	Patients with post-episiotomy pain (no other information provided).

Sunshine 1987b *(Continued)*

Interventions	Intervention: flurbiprofen 25 mg, flurbiprofen 50 mg, BTS 24332 12.5 mg and BTS 24332 25 mg Control: placebo Numbers per group are not provided, only the total number included in the study of N = 149
Outcomes	Not described explicitly; assume measures of pain
Notes	Abstract publication; unable to obtain numbers per groups Dates of study: NR Funding sources: NR Declarations of interest: NR

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No clear statement
Allocation concealment (selection bias)	Unclear risk	No clear statement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No clear statement
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient information to accurately assess
Selective reporting (reporting bias)	Unclear risk	Insufficient information to accurately assess
Other bias	Unclear risk	Insufficient information accurately assess

Trop 1983

Study characteristics

Methods	Multi-arm RCT - 5 groups
Participants	Parturient women aged 16 - 38 who had an episiotomy in 1 obstetric and gynaecology unit in Quebec, Canada. Women who received tranquillizers, sedatives, hypnotics or other analgesics during the 4 hours preceding the study were excluded, as well as those who were breastfeeding their babies
Interventions	Interventions: tiaprofenic acid 200 mg + placebo, tiaprofenic acid 400 mg alone

Trop 1983 *(Continued)*

	Controls: ASA 600 mg + placebo and ASA 1200 mg alone The medications were administered 10.5 to 14.4 hours after episiotomy. The total number randomised to each group is not provided; states only that 150 women were included in the study
Outcomes	• Pain intensity • Side effects Pain intensity was measured using a 20-cms VAS divided into equal sections labelled *no pain, slight, moderate, severe, unbearable;* measured by putting a stroke on the appropriate place on the scale before drug administration and hourly thereafter for 4 hours. The research nurse also independently recorded her evaluation of the analgesic effect of the medication on a scale of 0 - 4 corresponding to *no pain to pain worse than before*
Notes	Unable to obtain numbers randomised to each group. Dates of study: NR Funding sources: NR Declarations of interest: NR

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No clear statement
Allocation concealment (selection bias)	Unclear risk	States only that tablets were identical; no other information provided.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The nurse evaluated the participants' 5 VAS scales only at the end of the testing period by superimposing them over a transparent ruler that recorded the level of pain on a scale of 0 - 20. By proceeding this way, the nurse was kept unaware of the participant's evaluation scores
Incomplete outcome data (attrition bias) All outcomes	Low risk	All 150 participants completed the study
Selective reporting (reporting bias)	Low risk	Outcomes prespecified in the study methods were all reported
Other bias	Low risk	Baseline characteristics equivalent across the groups

Wisanto 1981

Study characteristics

Methods	Parallel RCT – 2 groups

Wisanto 1981 *(Continued)*

Participants	Primiparas over 18 years old, had deliveries and episiotomies without complications and moderate to severe pain within 48 hours of procedure with an intensity of at least 60% on a VAS. All participants had undergone medio-lateral episiotomies with 3 - 4 non-absorbable surgical sutures using a local anaesthetic Belgium. Women with mild pain (< 60% on VAS), breastfeeding and excessive anxiety or emotional instability, were excluded
Interventions	Intervention: antrafenine 300 mg (N = 30) Comparison: placebo (N = 30)
Outcomes	• Total pain score reported by the participant and the investigator (0 = no pain, 1 = mild pain, 2 = moderate pain and 3 = severe pain) • Pain Intensity difference • Overall efficacy (nil, moderate, good or very good) • Onset and duration of action • Side effects • Rescue analgesia Pain measured at baseline, before drug administration, and hourly thereafter up to 6 hours. Only 6-hour data included in the review (4-hour data could not be extracted) 1 dose of rescue analgesia was permitted in cases of excessive pain 2 hours after study drugs administered - all other treatments were excluded
Notes	Dates of study: NR Funding sources: NR Declarations of interest: NR

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No clear statement on method used
Allocation concealment (selection bias)	Unclear risk	States identical-appearing tablets but no other details
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No clear statement
Incomplete outcome data (attrition bias) All outcomes	Low risk	2 of 60 (3%) of participants were excluded from the study after taking another analgesic (1 (3%) in each group)
Selective reporting (reporting bias)	Low risk	Pre-specified outcomes were all reported.

Wisanto 1981 *(Continued)*

Other bias	High risk	Delay between episiotomy and drug intake was significantly shorter in the placebo group; also 16 placebo-treated participants withdrew from the study due to lack of efficacy compared to 5 in the antrafenine group. (Participants who withdrew from the study due to lack of efficacy were still included in the analysis: their last self-rating on VAS was repeated)

Yonkeura 1987

Study characteristics	
Methods	Multi-arm RCT – 4 group
Participants	Women > 15 years with moderate to severe episiotomy pain after normal vaginal birth Women's Hospital, Los Angeles County, USA Women with a history of reaction or hypersensitivity to NSAID or salicylates, receiving perineal < 1 hour before entry to study, received analgesics, sedatives, psychotropic medications, or topical perineal anaesthetics within 4 hours of entering study or had an active disease that might interfere with the evaluation of study medications, were excluded
Interventions	Intervention: meclofenamate 200 mg (N = 55); meclofenamate 100 mg (N = 55) and codeine 60 mg (N = 53) Comparison: placebo (N = 52)
Outcomes	• Pain intensity (0 = none, 1 = slight, 2 = moderate, 3 = severe) • Pain relief (0 = none, 1 = a little, 2 = some, 3 = a lot, 4 = complete) • Additional medications (within 6 hours) • Side effects (this outcome was not considered in the analysis as adverse reactions were reported at 24 hours following the treatment regime (i.e. after more than single dose was administered) Pain measures were assessed at baseline prior to treatment, at 30 minutes after and hourly thereafter to 6 hours
Notes	Codeine 60 mg not considered for the review as not an NSAID Dates of study: NR Funding sources: NR Declarations of interest: NR

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No clear statement on method used
Allocation concealment (selection bias)	Unclear risk	No clear statement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind

Yonkeura 1987 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No clear statement
Incomplete outcome data (attrition bias) All outcomes	Low risk	The attrition rate was 0%, but 5 of 220 (2%) participants were excluded from efficacy analysis because of protocol violations
Selective reporting (reporting bias)	Low risk	Outcomes prespecified in the study methods were all reported
Other bias	Low risk	No differences in baseline characteristics

Yscla 1988

Study characteristics	
Methods	Parallel RCT – 2 groups
Participants	Only women with severe episiotomy pain, aged 18 - 39 years in the 48 hours following an uncomplicated delivery Mollet General Hospital, Barcelona, Spain Women with slight or moderate pain, gastroduodenal disorders, and liver or kidney failure, a known history of hypersensitivity to phynylacetic acid derivatives or to acetylsalicylic acid and similar substances, treated with NSAIDs or systemic steroids or exceeding the age limits and who did not give consent, were excluded
Interventions	Intervention: aceclofenac 100 mg (N = 20) Comparison: placebo (N = 20)
Outcomes	• Pain intensity (0 = no pain, 1 = mild, 2 = moderate and 3 = severe pain) • Pain relief (> 50% reduction) • Possible side effects • Overall evaluation Pain intensity was measured before treatment, 30 minutes and 1 hourly to 6 hours thereafter, but these data could not be extracted
Notes	Dates of study: NR Funding sources: NR Declarations of interest: NR

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No clear statement on method used
Allocation concealment (selection bias)	Unclear risk	Packaged in identical packs identifiable only by the letters A and B; but does not state if sequentially numbered and sealed

Yscla 1988 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No clear statement
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data provided for all 40 participants (0% attrition rate in all groups)
Selective reporting (reporting bias)	Low risk	Prespecified outcomes were all reported
Other bias	Low risk	Groups similar at baseline

ASA: acetylsalicylic acid; NR: not reported; NSAID: non-steroidal anti-inflammatory drug; PID: pain intensity difference; RCT: randomised controlled trial; SPID: Summed Pain Intensity Difference
TOTPAR: Total Pain Relief; VAS: visual analogue scale

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

Study	Reason for exclusion
Abedzadeh 2009	Treatment was not oral (gel versus suppository)
Akil 2014	Treatment was not oral (intravenous)
Altungul 2012	Treatment was not oral (suppository).
Bettigole 1981	Not a single dose
Bhounsule 1990	Not a RCT; quasi-RCT with concurrent allocation – 2-group comparison without randomisation
Bloomfield 1979	Treatment not a NSAID
Bloomfield 1980	Treatment not a NSAID
Bloomfield 1991	Not a RCT; personal communication related to non-completion of a registered trial
Bruni 1965	Not specific to perineal pain; rather postpartum pain in general
Bucheli 1994	Not a single dose
Buck 1978	Not a single dose
Cater 1985	Ibuprofen and codeine phosphate combination treatment was excluded from the review as not a pure NSAID. Zomepirac is an NSAID but was withdrawn voluntarily from the market by the manufacturer in 1983 because it was associated with fatal and near-fatal anaphylactoid reactions
Choi 2000	Treatment not oral (suppository)
Coburn 1966	Not a single dose

Study	Reason for exclusion
Cunha 2011	Not a single dose
De los Santos 1998	Comparator drug is a combination of paracetamol and codeine
Delaram 2012	Treatment not a NSAID
Delaram 2014	Comparator drug is Lidocaine topical cream
Facchinetti 2005	Examine the effectiveness of multiple doses (not a single dose)
Finch 1971	Not a RCT; cross-over trial and not exclusive to perineal pain
Fragen 1982	Comparator drug is a combination of NSAID and opioid
Gindhart 1971	Treatment not a NSAID
Gruber 1962	Examines postpartum pain (not specifically perineal pain)
Gruber 1976	Comparator drug is not an NSAID
Harrison 1987	Not exclusively oral treatment
Harrison 1992	Not a RCT; cross-over trial
Kantor 1984	Data not exclusive to perineal pain; treatment was administered for postpartum pain which may or may not have included post-episiotomy pain
Lataste 1981	Includes participants with pain other than perineal pain
Levin 1978	Not clear that the intervention is a single-dose of a NSAID. Author's contact details not found
Mazzarella 1989	Treatment not a NSAID
McCallum 1991	Registration form only – does not appear to focus on management of perineal pain
Norman 1985	Intervention drug is a combination of NSAID and opioid
Odigie 1988	Treatment was not oral (suppository)
Offen 1985	Examines postpartum pain and pain related to general surgery (not specifically perineal pain)
Ogunbode 1987	Not a single dose
Olson 1984	Not exclusive to perineal pain as includes other types of postpartum pain
Pedronetto 1975	Indoprofen was withdrawn from the market worldwide following reports of adverse reactions including reports of carcinogenicity in animal studies
Peter 2001	Comparator drug is not a NSAID
Pitton 1982	Treatment was not oral (intra-muscular injection)
Radman 1961	Not a single dose
Ray 1993	Treatment was not oral (suppository)

Study	Reason for exclusion
Rezaei 2014	Treatment was not oral (suppository)
Searles 1995	Treatment was not oral (suppository)
Searles 1998	Treatment was not oral (suppository)
Sunshine 1982	Treatment not a NSAID
Sunshine 1983c	Not exclusive to perineal pain as includes other types of postpartum pain
Sunshine 1983d	Treatment not a NSAID
Sunshine 1985	Abstract only; insufficient information to include; unclear also if pain is reported separately by pain type. Author's contact details could not be identified
Sunshine 1986	Examines postpartum pain (not specifically perineal pain)
Sunshine 1987a	Examines postpartum pain and incisional pain following surgery.(not specifically perineal pain)
Sunshine 1989	Measures the adjuvant effect of caffeine on NSAID not NSAID alone versus another NSAID or placebo
Szabados 1986	Not a single dose
Taina 1981	Not a single dose
Van Wering 1972	Examines postpartum pain (not specifically perineal pain)
Von Pein 1974	Not a single dose
Walters 1984	Comparator treatment does not meet inclusion criteria
Walters 1985	Comparator is an opioid; does not meet comparator inclusion criteria
Yoong 1997	Treatment was not oral (suppository)

NSAID: non-steroidal anti-inflammatory drug; RCT: randomised controlled trial

DATA AND ANALYSES

Comparison 1. NSAID (single administration, any dose) versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Adequate pain relief (4 hours after administration)	10	1573	Risk Ratio (M-H, Fixed, 95% CI)	1.91 [1.64, 2.23]
1.1.1 Aspirin 500 mg to 650 mg	4	183	Risk Ratio (M-H, Fixed, 95% CI)	2.69 [1.41, 5.10]
1.1.2 Ibuprofen 300 mg to 400 mg	3	240	Risk Ratio (M-H, Fixed, 95% CI)	2.64 [1.62, 4.30]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1.3 Ibuprofen 800 mg	1	121	Risk Ratio (M-H, Fixed, 95% CI)	1.83 [0.87, 3.87]
1.1.4 Diclofenac 25 mg	1	65	Risk Ratio (M-H, Fixed, 95% CI)	2.00 [0.86, 4.65]
1.1.5 Diclofenac 50 mg	1	63	Risk Ratio (M-H, Fixed, 95% CI)	2.21 [0.96, 5.11]
1.1.6 Diclofenac 100 mg	1	64	Risk Ratio (M-H, Fixed, 95% CI)	2.36 [1.03, 5.42]
1.1.7 Ketoprofen 25 mg	1	42	Risk Ratio (M-H, Fixed, 95% CI)	3.33 [1.19, 9.34]
1.1.8 Diflunisal 125 mg	1	41	Risk Ratio (M-H, Fixed, 95% CI)	2.91 [0.44, 19.22]
1.1.9 Meclofenamate sodium 100 mg	3	260	Risk Ratio (M-H, Fixed, 95% CI)	1.42 [1.10, 1.82]
1.1.10 Meclofenamate sodium 200 mg	3	262	Risk Ratio (M-H, Fixed, 95% CI)	1.42 [1.10, 1.83]
1.1.11 Ketoprofen 50 mg	1	40	Risk Ratio (M-H, Fixed, 95% CI)	3.23 [1.15, 9.10]
1.1.12 Diflunisal 250 mg	1	38	Risk Ratio (M-H, Fixed, 95% CI)	2.40 [0.35, 16.26]
1.1.13 Diflunisal 500 mg	1	38	Risk Ratio (M-H, Fixed, 95% CI)	3.73 [0.57, 24.29]
1.1.14 Flurbiprofen 25 mg	1	40	Risk Ratio (M-H, Fixed, 95% CI)	2.75 [0.41, 18.29]
1.1.15 Flurbiprofen 50 mg	1	37	Risk Ratio (M-H, Fixed, 95% CI)	4.14 [0.64, 26.76]
1.1.16 Flurbiprofen 100 mg	1	39	Risk Ratio (M-H, Fixed, 95% CI)	3.87 [0.60, 25.09]
1.2 Adequate pain relief (6 hours after administration)	17	2079	Risk Ratio (M-H, Fixed, 95% CI)	1.92 [1.69, 2.17]
1.2.1 Aspirin 500 mg to 650 mg	7	416	Risk Ratio (M-H, Fixed, 95% CI)	1.75 [1.37, 2.24]
1.2.2 Aspirin 900 mg	1	27	Risk Ratio (M-H, Fixed, 95% CI)	3.15 [0.97, 10.26]
1.2.3 Ibuprofen 300 mg to 400 mg	2	124	Risk Ratio (M-H, Fixed, 95% CI)	2.08 [1.30, 3.32]
1.2.4 Ibuprofen 900 mg	1	27	Risk Ratio (M-H, Fixed, 95% CI)	2.98 [0.91, 9.74]
1.2.5 Ketoprofen 25 mg	1	42	Risk Ratio (M-H, Fixed, 95% CI)	3.00 [1.06, 8.49]
1.2.6 Ketoprofen 50 mg	1	40	Risk Ratio (M-H, Fixed, 95% CI)	3.05 [1.08, 8.64]
1.2.7 Meclofenamate sodium 100 mg	3	260	Risk Ratio (M-H, Fixed, 95% CI)	1.36 [1.05, 1.76]
1.2.8 Meclofenamate sodium 200 mg	3	262	Risk Ratio (M-H, Fixed, 95% CI)	1.40 [1.07, 1.83]
1.2.9 Diflunisal 125 mg	1	41	Risk Ratio (M-H, Fixed, 95% CI)	3.15 [0.48, 20.69]

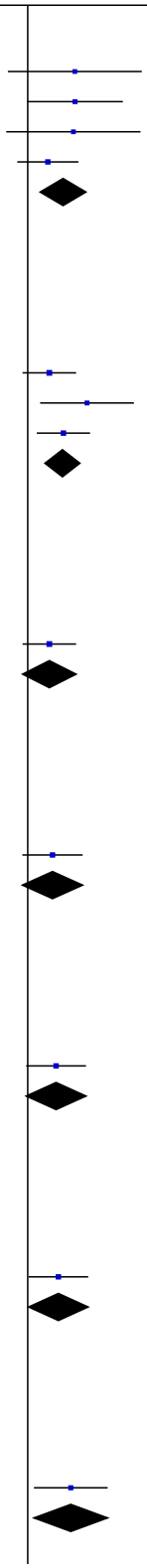
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.2.10 Diflunisal 250 mg	1	38	Risk Ratio (M-H, Fixed, 95% CI)	2.67 [0.40, 17.86]
1.2.11 Diflunisal 500 mg	1	38	Risk Ratio (M-H, Fixed, 95% CI)	4.27 [0.66, 27.51]
1.2.12 Dipyrone 500 mg	1	133	Risk Ratio (M-H, Fixed, 95% CI)	2.21 [1.44, 3.39]
1.2.13 Aceclofenac 50 mg	1	22	Risk Ratio (M-H, Fixed, 95% CI)	1.56 [0.57, 4.27]
1.2.14 Aceclofenac 100 mg	1	28	Risk Ratio (M-H, Fixed, 95% CI)	1.67 [0.62, 4.51]
1.2.15 Aceclofenac 150 mg	1	25	Risk Ratio (M-H, Fixed, 95% CI)	1.81 [0.67, 4.87]
1.2.16 Etodolac 25 mg	1	53	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.34, 2.33]
1.2.17 Etodolac 100 mg	1	53	Risk Ratio (M-H, Fixed, 95% CI)	1.22 [0.49, 3.02]
1.2.18 Antrafenine 300 mg	1	58	Risk Ratio (M-H, Fixed, 95% CI)	5.33 [1.74, 16.36]
1.2.19 Flurbiprofen 25 mg	1	40	Risk Ratio (M-H, Fixed, 95% CI)	3.25 [0.50, 21.31]
1.2.20 Flurbiprofen 50 mg	1	37	Risk Ratio (M-H, Fixed, 95% CI)	4.97 [0.78, 31.75]
1.2.21 Flurbiprofen 100 mg	1	39	Risk Ratio (M-H, Fixed, 95% CI)	4.90 [0.77, 31.33]
1.2.22 Fenoprofen 12.5 mg	1	29	Risk Ratio (M-H, Fixed, 95% CI)	2.08 [0.34, 12.80]
1.2.23 Fenoprofen 25 mg	1	28	Risk Ratio (M-H, Fixed, 95% CI)	2.39 [0.39, 14.53]
1.2.24 Fenoprofen 50 mg	2	62	Risk Ratio (M-H, Fixed, 95% CI)	3.38 [0.93, 12.26]
1.2.25 Fenoprofen 100 mg	2	62	Risk Ratio (M-H, Fixed, 95% CI)	3.95 [1.10, 14.19]
1.2.26 Fenoprofen 200 mg	2	61	Risk Ratio (M-H, Fixed, 95% CI)	3.95 [1.10, 14.19]
1.2.27 Fenoprofen 300 mg	1	34	Risk Ratio (M-H, Fixed, 95% CI)	4.93 [0.79, 30.74]
1.3 Need for additional analgesia (4 hours after administration)	4	486	Risk Ratio (M-H, Fixed, 95% CI)	0.39 [0.26, 0.58]
1.3.1 Aspirin 500 mg to 650 mg	2	125	Risk Ratio (M-H, Fixed, 95% CI)	0.47 [0.23, 0.93]
1.3.2 Ibuprofen 300 mg to 400 mg	3	240	Risk Ratio (M-H, Fixed, 95% CI)	0.32 [0.18, 0.56]
1.3.3 Ibuprofen 800 mg	1	121	Risk Ratio (M-H, Fixed, 95% CI)	0.51 [0.19, 1.36]
1.4 Need for additional analgesia (6 hours after administration)	10	1012	Risk Ratio (M-H, Fixed, 95% CI)	0.32 [0.26, 0.40]
1.4.1 Aspirin 500 mg to 650 mg	3	157	Risk Ratio (M-H, Fixed, 95% CI)	0.37 [0.22, 0.62]
1.4.2 Aspirin 900 mg	1	27	Risk Ratio (M-H, Fixed, 95% CI)	0.13 [0.01, 2.81]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.4.3 Ibuprofen 300 mg to 400 mg	3	186	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.20, 0.54]
1.4.4 Ibuprofen 900 mg	1	27	Risk Ratio (M-H, Fixed, 95% CI)	0.13 [0.01, 2.81]
1.4.5 Meclofenamate sodium 100 mg	3	299	Risk Ratio (M-H, Fixed, 95% CI)	0.34 [0.21, 0.53]
1.4.6 Meclofenamate sodium 200 mg	2	142	Risk Ratio (M-H, Fixed, 95% CI)	0.45 [0.29, 0.70]
1.4.7 Antrafenine 300 mg	1	58	Risk Ratio (M-H, Fixed, 95% CI)	0.31 [0.13, 0.74]
1.4.8 Flurbiprofen 25 mg	1	40	Risk Ratio (M-H, Fixed, 95% CI)	0.06 [0.01, 0.49]
1.4.9 Flurbiprofen 50 mg	1	37	Risk Ratio (M-H, Fixed, 95% CI)	0.03 [0.00, 0.56]
1.4.10 Flurbiprofen 100 mg	1	39	Risk Ratio (M-H, Fixed, 95% CI)	0.03 [0.00, 0.53]
1.5 Maternal drug adverse effects (6 hours after administration)	13	1388	Risk Ratio (M-H, Fixed, 95% CI)	1.38 [0.71, 2.70]
1.5.1 Aspirin 500 mg to 650 mg	6	365	Risk Ratio (M-H, Fixed, 95% CI)	1.31 [0.38, 4.60]
1.5.2 Aspirin 900 mg	1	27	Risk Ratio (M-H, Fixed, 95% CI)	1.75 [0.24, 12.51]
1.5.3 Ibuprofen 300 mg to 400 mg	3	186	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.27, 3.85]
1.5.4 Ibuprofen 900 mg	1	27	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.13, 8.52]
1.5.5 Ketoprofen 25 mg	1	42	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.5.6 Ketoprofen 50 mg	1	40	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.5.7 Aceclofenac 50 mg	1	22	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.04, 16.59]
1.5.8 Aceclofenac 100 mg	1	28	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.5.9 Aceclofenac 150 mg	1	25	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.5.10 Diflunisal 125 mg	1	41	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.5.11 Diflunisal 250 mg	1	38	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.5.12 Diflunisal 500 mg	1	38	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.5.13 Dipyrone 500 mg	2	335	Risk Ratio (M-H, Fixed, 95% CI)	2.48 [0.49, 12.46]
1.5.14 Antrafenine 300 mg	1	58	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.5.15 Flurbiprofen 25 mg	1	40	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.5.16 Flurbiprofen 50 mg	1	37	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.5.17 Flurbiprofen 100 mg	1	39	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

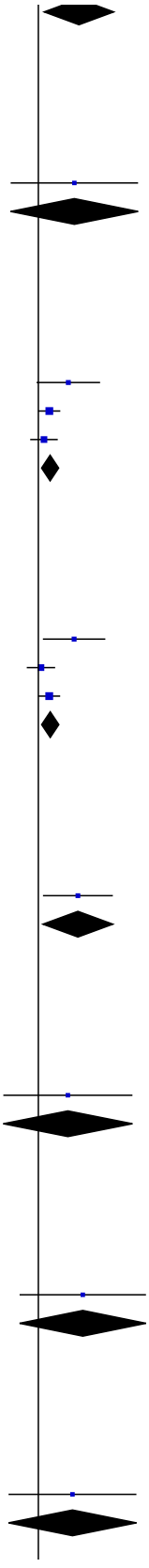
Analysis 1.1. Comparison 1: NSAID (single administration, any dose) versus placebo, Outcome 1: Adequate pain relief (4 hours after administration)

Study or Subgroup	NSAID Events	NSAID Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.1.1 Aspirin 500 mg to 650 mg						
De Vroey 1978	14	30	1	8	0.9%	3.73 [0.57 , 24.29]
Sunshine 1983b	15	30	2	15	1.5%	3.75 [0.98 , 14.31]
Sunshine 1983a	13	29	1	8	0.9%	3.59 [0.55 , 23.44]
Olson 1997	27	50	4	13	3.5%	1.75 [0.75 , 4.12]
Subtotal (95% CI)		**139**		**44**	**6.7%**	**2.69 [1.41 , 5.10]**
Total events:	69		8			
Heterogeneity: Chi² = 1.40, df = 3 (P = 0.71); I² = 0%						
Test for overall effect: Z = 3.02 (P = 0.003)						
1.1.2 Ibuprofen 300 mg to 400 mg						
Hopkinson 1980	25	80	7	41	5.1%	1.83 [0.87 , 3.87]
Sunshine 1983b	21	30	2	15	1.5%	5.25 [1.41 , 19.48]
Schachtel 1989	18	36	7	38	3.8%	2.71 [1.29 , 5.72]
Subtotal (95% CI)		**146**		**94**	**10.4%**	**2.64 [1.62 , 4.30]**
Total events:	64		16			
Heterogeneity: Chi² = 1.98, df = 2 (P = 0.37); I² = 0%						
Test for overall effect: Z = 3.88 (P = 0.0001)						
1.1.3 Ibuprofen 800 mg						
Hopkinson 1980	25	80	7	41	5.1%	1.83 [0.87 , 3.87]
Subtotal (95% CI)		**80**		**41**	**5.1%**	**1.83 [0.87 , 3.87]**
Total events:	25		7			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.58 (P = 0.11)						
1.1.4 Diclofenac 25 mg						
Olson 1997	32	52	4	13	3.5%	2.00 [0.86 , 4.65]
Subtotal (95% CI)		**52**		**13**	**3.5%**	**2.00 [0.86 , 4.65]**
Total events:	32		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.61 (P = 0.11)						
1.1.5 Diclofenac 50 mg						
Olson 1997	34	50	4	13	3.5%	2.21 [0.96 , 5.11]
Subtotal (95% CI)		**50**		**13**	**3.5%**	**2.21 [0.96 , 5.11]**
Total events:	34		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.86 (P = 0.06)						
1.1.6 Diclofenac 100 mg						
Olson 1997	37	51	4	13	3.5%	2.36 [1.03 , 5.42]
Subtotal (95% CI)		**51**		**13**	**3.5%**	**2.36 [1.03 , 5.42]**
Total events:	37		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.02 (P = 0.04)						
1.1.7 Ketoprofen 25 mg						
Olson 1999	20	28	3	14	2.2%	3.33 [1.19 , 9.34]
Subtotal (95% CI)		**28**		**14**	**2.2%**	**3.33 [1.19 , 9.34]**
Total events:	20		3			



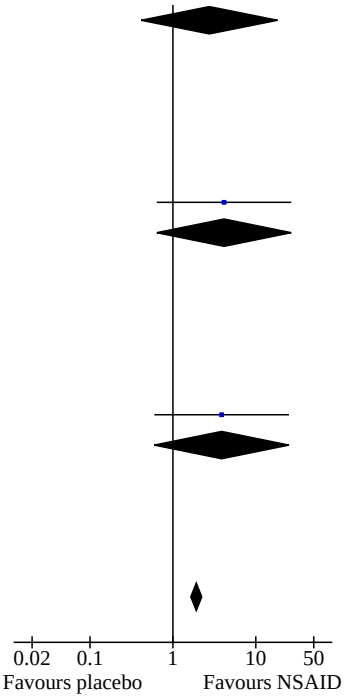
Analysis 1.1. (Continued)

Subtotal (95% CI)		**28**		**14**	**2.2%**	**3.33 [1.19 , 9.34]**	
Total events:	20		3				
Heterogeneity: Not applicable							
Test for overall effect: Z = 2.29 (P = 0.02)							
1.1.8 Diflunisal 125 mg							
De Vroey 1978	12	33	1	8	0.9%	2.91 [0.44 , 19.22]	
Subtotal (95% CI)		**33**		**8**	**0.9%**	**2.91 [0.44 , 19.22]**	
Total events:	12		1				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.11 (P = 0.27)							
1.1.9 Meclofenamate sodium 100 mg							
Hebertson 1986	19	41	4	21	2.9%	2.43 [0.95 , 6.24]	
Gleason 1987	56	77	21	40	15.3%	1.39 [1.00 , 1.92]	
Yonkeura 1987	35	55	14	26	10.5%	1.18 [0.79 , 1.78]	
Subtotal (95% CI)		**173**		**87**	**28.7%**	**1.42 [1.10 , 1.82]**	
Total events:	110		39				
Heterogeneity: $Chi^2 = 2.05$, df = 2 (P = 0.36); $I^2 = 2\%$							
Test for overall effect: Z = 2.71 (P = 0.007)							
1.1.10 Meclofenamate sodium 200 mg							
Hebertson 1986	22	40	4	21	2.9%	2.89 [1.14 , 7.28]	
Yonkeura 1987	32	55	14	26	10.5%	1.08 [0.71 , 1.65]	
Gleason 1987	58	80	21	40	15.5%	1.38 [1.00 , 1.91]	
Subtotal (95% CI)		**175**		**87**	**28.9%**	**1.42 [1.10 , 1.83]**	
Total events:	112		39				
Heterogeneity: $Chi^2 = 3.93$, df = 2 (P = 0.14); $I^2 = 49\%$							
Test for overall effect: Z = 2.72 (P = 0.007)							
1.1.11 Ketoprofen 50 mg							
Olson 1999	18	26	3	14	2.2%	3.23 [1.15 , 9.10]	
Subtotal (95% CI)		**26**		**14**	**2.2%**	**3.23 [1.15 , 9.10]**	
Total events:	18		3				
Heterogeneity: Not applicable							
Test for overall effect: Z = 2.22 (P = 0.03)							
1.1.12 Diflunisal 250 mg							
De Vroey 1978	9	30	1	8	0.9%	2.40 [0.35 , 16.26]	
Subtotal (95% CI)		**30**		**8**	**0.9%**	**2.40 [0.35 , 16.26]**	
Total events:	9		1				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.90 (P = 0.37)							
1.1.13 Diflunisal 500 mg							
De Vroey 1978	14	30	1	8	0.9%	3.73 [0.57 , 24.29]	
Subtotal (95% CI)		**30**		**8**	**0.9%**	**3.73 [0.57 , 24.29]**	
Total events:	14		1				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.38 (P = 0.17)							
1.1.14 Flurbiprofen 25 mg							
Sunshine 1983a	11	32	1	8	0.9%	2.75 [0.41 , 18.29]	
Subtotal (95% CI)		**32**		**8**	**0.9%**	**2.75 [0.41 , 18.29]**	
Total events:	11		1				



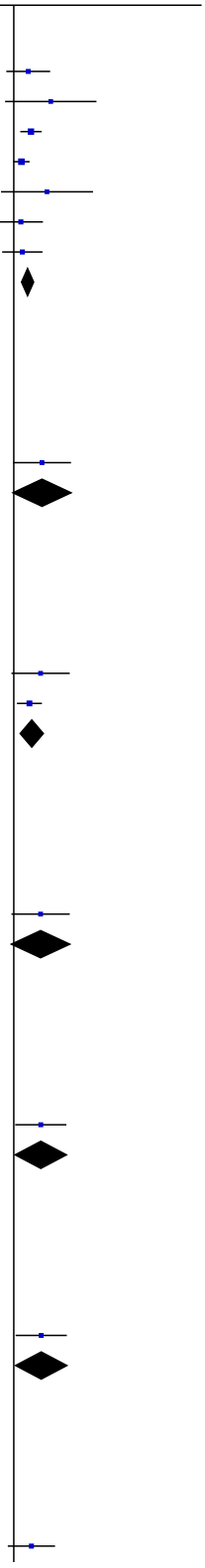
Analysis 1.1. (Continued)

Subtotal (95% CI)		**32**		**8**	**0.9%**	**2.75 [0.41 , 18.29]**
Total events:	11		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.05 (P = 0.30)						
1.1.15 Flurbiprofen 50 mg						
Sunshine 1983a	15	29	1	8	0.9%	4.14 [0.64 , 26.76]
Subtotal (95% CI)		**29**		**8**	**0.9%**	**4.14 [0.64 , 26.76]**
Total events:	15		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.49 (P = 0.14)						
1.1.16 Flurbiprofen 100 mg						
Sunshine 1983a	15	31	1	8	0.9%	3.87 [0.60 , 25.09]
Subtotal (95% CI)		**31**		**8**	**0.9%**	**3.87 [0.60 , 25.09]**
Total events:	15		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.42 (P = 0.16)						
Total (95% CI)		**1105**		**468**	**100.0%**	**1.91 [1.64 , 2.23]**
Total events:	597		133			
Heterogeneity: Chi^2 = 30.77, df = 24 (P = 0.16); I^2 = 22%						
Test for overall effect: Z = 8.39 (P < 0.00001)						
Test for subgroup differences: Chi^2 = 16.12, df = 15 (P = 0.37), I^2 = 6.9%						



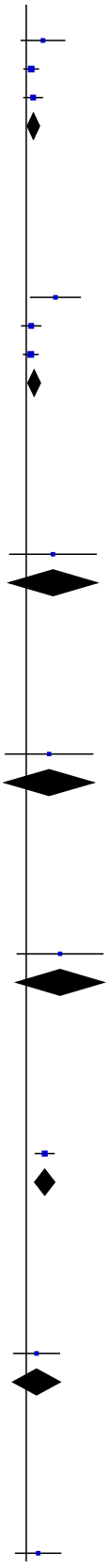
Analysis 1.2. Comparison 1: NSAID (single administration, any dose) versus placebo, Outcome 2: Adequate pain relief (6 hours after administration)

Study or Subgroup	NSAID Events	NSAID Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.2.1 Aspirin 500 mg to 650 mg						
Bloomfield 1967	8	16	5	18	1.8%	1.80 [0.74 , 4.39]
De Vroey 1978	18	32	1	8	0.6%	4.50 [0.70 , 28.87]
Mukherjee 1980	61	89	15	44	7.7%	2.01 [1.30 , 3.10]
London 1983	30	40	22	40	8.4%	1.36 [0.98 , 1.90]
Sunshine 1983a	14	29	1	8	0.6%	3.86 [0.59 , 25.10]
Friedrich 1983	16	39	4	13	2.3%	1.33 [0.54 , 3.27]
Jain 1985	17	30	4	10	2.3%	1.42 [0.62 , 3.22]
Subtotal (95% CI)		**275**		**141**	**23.6%**	**1.75 [1.37 , 2.24]**
Total events:	164		52			
Heterogeneity: Chi² = 4.86, df = 6 (P = 0.56); I² = 0%						
Test for overall effect: Z = 4.49 (P < 0.00001)						
1.2.2 Aspirin 900 mg						
Bloomfield 1974	18	20	2	7	1.1%	3.15 [0.97 , 10.26]
Subtotal (95% CI)		**20**		**7**	**1.1%**	**3.15 [0.97 , 10.26]**
Total events:	18		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.91 (P = 0.06)						
1.2.3 Ibuprofen 300 mg to 400 mg						
Bloomfield 1974	17	20	2	7	1.1%	2.98 [0.91 , 9.74]
Jain 1988	27	49	14	48	5.4%	1.89 [1.14 , 3.14]
Subtotal (95% CI)		**69**		**55**	**6.5%**	**2.08 [1.30 , 3.32]**
Total events:	44		16			
Heterogeneity: Chi² = 0.49, df = 1 (P = 0.49); I² = 0%						
Test for overall effect: Z = 3.05 (P = 0.002)						
1.2.4 Ibuprofen 900 mg						
Bloomfield 1974	17	20	2	7	1.1%	2.98 [0.91 , 9.74]
Subtotal (95% CI)		**20**		**7**	**1.1%**	**2.98 [0.91 , 9.74]**
Total events:	17		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.80 (P = 0.07)						
1.2.5 Ketoprofen 25 mg						
Olson 1999	18	28	3	14	1.5%	3.00 [1.06 , 8.49]
Subtotal (95% CI)		**28**		**14**	**1.5%**	**3.00 [1.06 , 8.49]**
Total events:	18		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.07 (P = 0.04)						
1.2.6 Ketoprofen 50 mg						
Olson 1999	17	26	3	14	1.5%	3.05 [1.08 , 8.64]
Subtotal (95% CI)		**26**		**14**	**1.5%**	**3.05 [1.08 , 8.64]**
Total events:	17		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.10 (P = 0.04)						
1.2.7 Meclofenamate sodium 100 mg						
Hebertson 1986	16	41	4	21	2.0%	2.05 [0.78 , 5.36]



Analysis 1.2. (Continued)

1.2.7 Meclofenamate sodium 100 mg						
Hebertson 1986	16	41	4	21	2.0%	2.05 [0.78 , 5.36]
Gleason 1987	50	77	21	40	10.5%	1.24 [0.88 , 1.73]
Yonkeura 1987	37	55	13	26	6.7%	1.35 [0.88 , 2.06]
Subtotal (95% CI)		**173**		**87**	**19.3%**	**1.36 [1.05 , 1.76]**
Total events:	103		38			
Heterogeneity: Chi² = 1.00, df = 2 (P = 0.61); I² = 0%						
Test for overall effect: Z = 2.31 (P = 0.02)						
1.2.8 Meclofenamate sodium 200 mg						
Hebertson 1986	20	40	3	21	1.5%	3.50 [1.17 , 10.44]
Yonkeura 1987	34	55	13	26	6.7%	1.24 [0.80 , 1.91]
Gleason 1987	51	80	21	40	10.7%	1.21 [0.87 , 1.70]
Subtotal (95% CI)		**175**		**87**	**18.9%**	**1.40 [1.07 , 1.83]**
Total events:	105		37			
Heterogeneity: Chi² = 3.72, df = 2 (P = 0.16); I² = 46%						
Test for overall effect: Z = 2.48 (P = 0.01)						
1.2.9 Diflunisal 125 mg						
De Vroey 1978	13	33	1	8	0.6%	3.15 [0.48 , 20.69]
Subtotal (95% CI)		**33**		**8**	**0.6%**	**3.15 [0.48 , 20.69]**
Total events:	13		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.20 (P = 0.23)						
1.2.10 Diflunisal 250 mg						
De Vroey 1978	10	30	1	8	0.6%	2.67 [0.40 , 17.86]
Subtotal (95% CI)		**30**		**8**	**0.6%**	**2.67 [0.40 , 17.86]**
Total events:	10		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.01 (P = 0.31)						
1.2.11 Diflunisal 500 mg						
De Vroey 1978	16	30	1	8	0.6%	4.27 [0.66 , 27.51]
Subtotal (95% CI)		**30**		**8**	**0.6%**	**4.27 [0.66 , 27.51]**
Total events:	16		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.53 (P = 0.13)						
1.2.12 Dipyrone 500 mg						
Mukherjee 1980	67	89	15	44	7.7%	2.21 [1.44 , 3.39]
Subtotal (95% CI)		**89**		**44**	**7.7%**	**2.21 [1.44 , 3.39]**
Total events:	67		15			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.63 (P = 0.0003)						
1.2.13 Aceclofenac 50 mg						
Honorato 1990	14	18	2	4	1.2%	1.56 [0.57 , 4.27]
Subtotal (95% CI)		**18**		**4**	**1.2%**	**1.56 [0.57 , 4.27]**
Total events:	14		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.86 (P = 0.39)						
1.2.14 Aceclofenac 100 mg						
Honorato 1990	20	24	2	4	1.3%	1.67 [0.62 , 4.51]

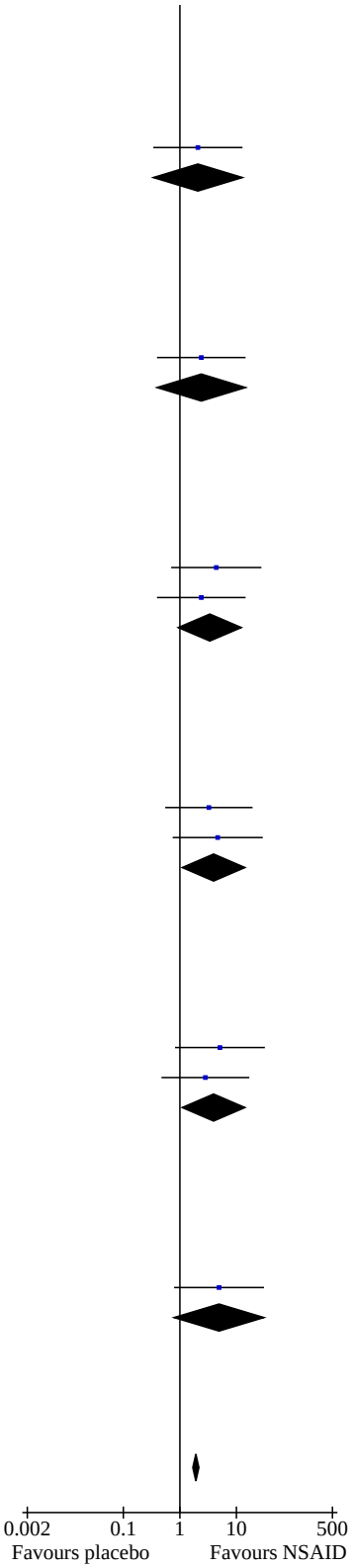


Analysis 1.2. (Continued)

1.2.14 Aceclofenac 100 mg						
Honorato 1990	20	24	2	4	1.3%	1.67 [0.62 , 4.51]
Subtotal (95% CI)		**24**		**4**	**1.3%**	**1.67 [0.62 , 4.51]**
Total events:	20		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.01 (P = 0.31)						
1.2.15 Aceclofenac 150 mg						
Honorato 1990	19	21	2	4	1.3%	1.81 [0.67 , 4.87]
Subtotal (95% CI)		**21**		**4**	**1.3%**	**1.81 [0.67 , 4.87]**
Total events:	19		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.17 (P = 0.24)						
1.2.16 Etodolac 25 mg						
Friedrich 1983	11	40	4	13	2.3%	0.89 [0.34 , 2.33]
Subtotal (95% CI)		**40**		**13**	**2.3%**	**0.89 [0.34 , 2.33]**
Total events:	11		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.23 (P = 0.82)						
1.2.17 Etodolac 100 mg						
Friedrich 1983	15	40	4	13	2.3%	1.22 [0.49 , 3.02]
Subtotal (95% CI)		**40**		**13**	**2.3%**	**1.22 [0.49 , 3.02]**
Total events:	15		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.43 (P = 0.67)						
1.2.18 Antrafenine 300 mg						
Wisanto 1981	16	29	3	29	1.1%	5.33 [1.74 , 16.36]
Subtotal (95% CI)		**29**		**29**	**1.1%**	**5.33 [1.74 , 16.36]**
Total events:	16		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.93 (P = 0.003)						
1.2.19 Flurbiprofen 25 mg						
Sunshine 1983a	13	32	1	8	0.6%	3.25 [0.50 , 21.31]
Subtotal (95% CI)		**32**		**8**	**0.6%**	**3.25 [0.50 , 21.31]**
Total events:	13		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.23 (P = 0.22)						
1.2.20 Flurbiprofen 50 mg						
Sunshine 1983a	18	29	1	8	0.6%	4.97 [0.78 , 31.75]
Subtotal (95% CI)		**29**		**8**	**0.6%**	**4.97 [0.78 , 31.75]**
Total events:	18		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.69 (P = 0.09)						
1.2.21 Flurbiprofen 100 mg						
Sunshine 1983a	19	31	1	8	0.6%	4.90 [0.77 , 31.33]
Subtotal (95% CI)		**31**		**8**	**0.6%**	**4.90 [0.77 , 31.33]**
Total events:	19		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.68 (P = 0.09)						

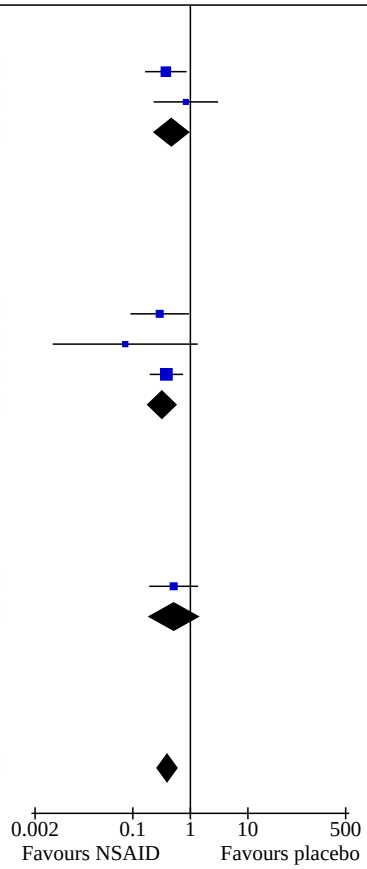
Analysis 1.2. (Continued)

Heterogeneity: Not applicable						
Test for overall effect: Z = 1.68 (P = 0.09)						
1.2.22 Fenoprofen 12.5 mg						
Laska 1981b	10	24	1	5	0.6%	2.08 [0.34 , 12.80]
Subtotal (95% CI)		**24**		**5**	**0.6%**	**2.08 [0.34 , 12.80]**
Total events:	10		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.79 (P = 0.43)						
1.2.23 Fenoprofen 25 mg						
Laska 1981b	11	23	1	5	0.6%	2.39 [0.39 , 14.53]
Subtotal (95% CI)		**23**		**5**	**0.6%**	**2.39 [0.39 , 14.53]**
Total events:	11		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.95 (P = 0.34)						
1.2.24 Fenoprofen 50 mg						
Laska 1981a	17	27	1	7	0.6%	4.41 [0.70 , 27.68]
Laska 1981b	11	23	1	5	0.6%	2.39 [0.39 , 14.53]
Subtotal (95% CI)		**50**		**12**	**1.2%**	**3.38 [0.93 , 12.26]**
Total events:	28		2			
Heterogeneity: Chi² = 0.22, df = 1 (P = 0.64); I² = 0%						
Test for overall effect: Z = 1.85 (P = 0.06)						
1.2.25 Fenoprofen 100 mg						
Laska 1981b	15	23	1	5	0.6%	3.26 [0.55 , 19.30]
Laska 1981a	18	27	1	7	0.6%	4.67 [0.75 , 29.21]
Subtotal (95% CI)		**50**		**12**	**1.2%**	**3.95 [1.10 , 14.19]**
Total events:	33		2			
Heterogeneity: Chi² = 0.08, df = 1 (P = 0.78); I² = 0%						
Test for overall effect: Z = 2.11 (P = 0.04)						
1.2.26 Fenoprofen 200 mg						
Laska 1981a	19	26	1	7	0.6%	5.12 [0.82 , 31.87]
Laska 1981b	13	23	1	5	0.6%	2.83 [0.47 , 16.92]
Subtotal (95% CI)		**49**		**12**	**1.2%**	**3.95 [1.10 , 14.19]**
Total events:	32		2			
Heterogeneity: Chi² = 0.21, df = 1 (P = 0.65); I² = 0%						
Test for overall effect: Z = 2.10 (P = 0.04)						
1.2.27 Fenoprofen 300 mg						
Laska 1981a	19	27	1	7	0.6%	4.93 [0.79 , 30.74]
Subtotal (95% CI)		**27**		**7**	**0.6%**	**4.93 [0.79 , 30.74]**
Total events:	19		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.71 (P = 0.09)						
Total (95% CI)		**1455**		**624**	**100.0%**	**1.92 [1.69 , 2.17]**
Total events:	870		200			
Heterogeneity: Chi² = 46.13, df = 40 (P = 0.23); I² = 13%						
Test for overall effect: Z = 10.30 (P < 0.00001)						
Test for subgroup differences: Chi² = 27.82, df = 26 (P = 0.37), I² = 6.5%						

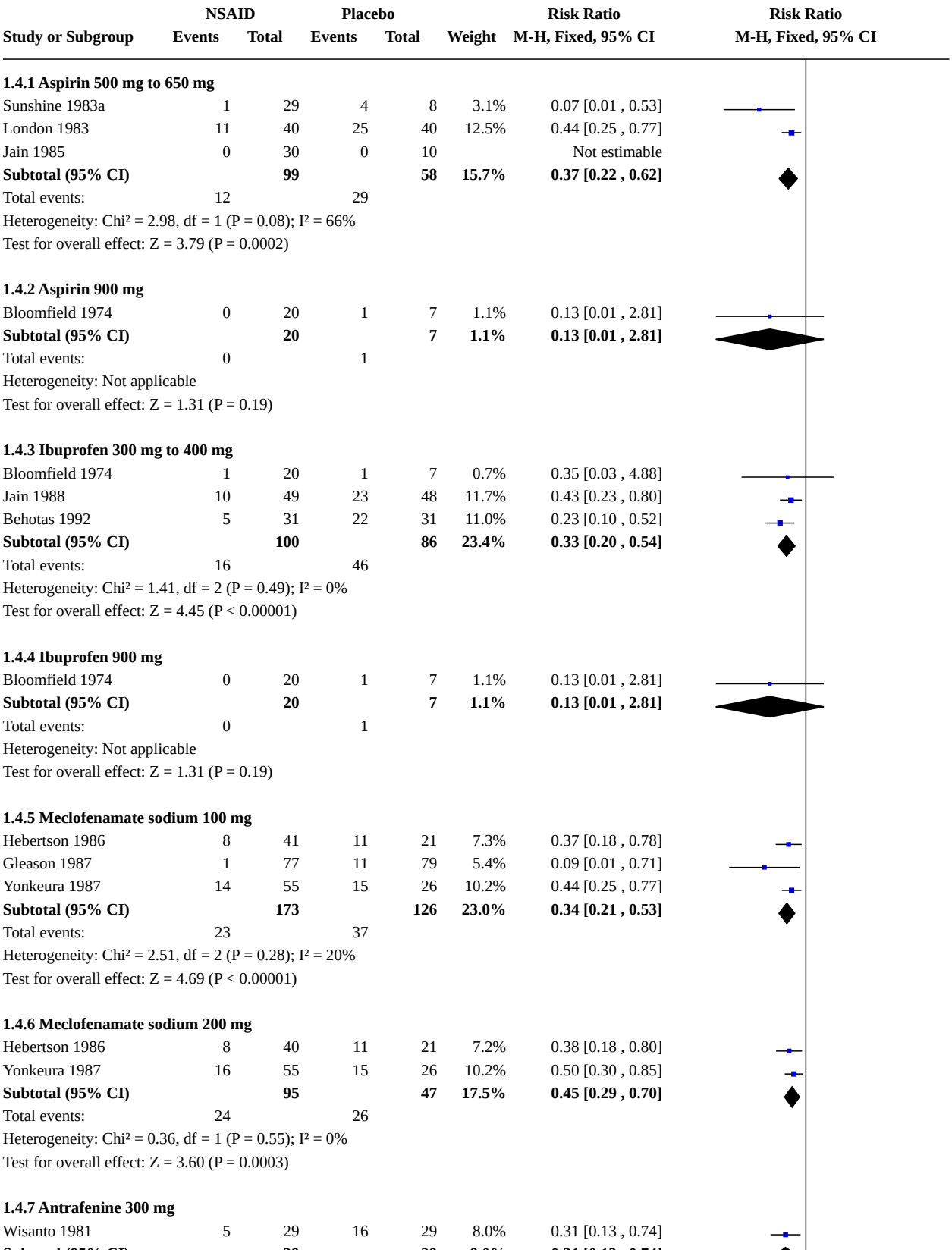


Analysis 1.3. Comparison 1: NSAID (single administration, any dose) versus placebo, Outcome 3: Need for additional analgesia (4 hours after administration)

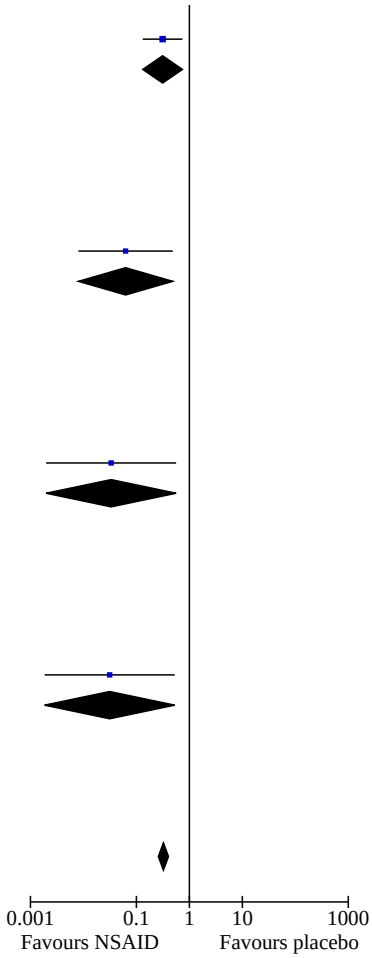
Study or Subgroup	NSAID Events	NSAID Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.3.1 Aspirin 500 mg to 650 mg						
London 1983	6	40	16	40	24.8%	0.38 [0.16 , 0.86]
Sunshine 1983b	5	30	3	15	6.2%	0.83 [0.23 , 3.03]
Subtotal (95% CI)		**70**		**55**	**31.0%**	**0.47 [0.23 , 0.93]**
Total events:	11		19			
Heterogeneity: Chi² = 1.04, df = 1 (P = 0.31); I² = 4%						
Test for overall effect: Z = 2.17 (P = 0.03)						
1.3.2 Ibuprofen 300 mg to 400 mg						
Hopkinson 1980	4	80	7	41	14.3%	0.29 [0.09 , 0.94]
Sunshine 1983b	0	30	3	15	7.2%	0.07 [0.00 , 1.34]
Schachtel 1989	8	36	22	38	33.2%	0.38 [0.20 , 0.75]
Subtotal (95% CI)		**146**		**94**	**54.7%**	**0.32 [0.18 , 0.56]**
Total events:	12		32			
Heterogeneity: Chi² = 1.29, df = 2 (P = 0.52); I² = 0%						
Test for overall effect: Z = 3.97 (P < 0.0001)						
1.3.3 Ibuprofen 800 mg						
Hopkinson 1980	7	80	7	41	14.3%	0.51 [0.19 , 1.36]
Subtotal (95% CI)		**80**		**41**	**14.3%**	**0.51 [0.19 , 1.36]**
Total events:	7		7			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.34 (P = 0.18)						
Total (95% CI)		**296**		**190**	**100.0%**	**0.39 [0.26 , 0.58]**
Total events:	30		58			
Heterogeneity: Chi² = 3.13, df = 5 (P = 0.68); I² = 0%						
Test for overall effect: Z = 4.63 (P < 0.00001)						
Test for subgroup differences: Chi² = 1.04, df = 2 (P = 0.59), I² = 0%						



Analysis 1.4. Comparison 1: NSAID (single administration, any dose) versus placebo, Outcome 4: Need for additional analgesia (6 hours after administration)



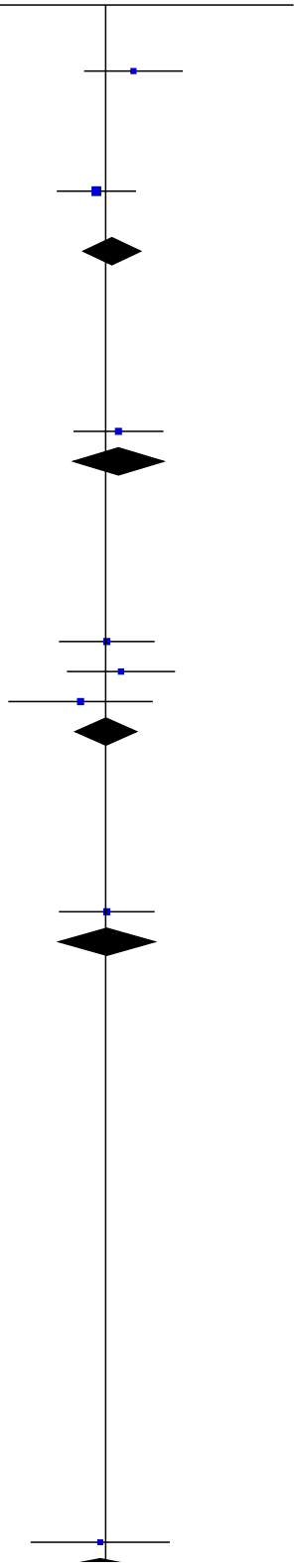
Analysis 1.4. (Continued)



1.4.7 Antrafenine 300 mg						
Wisanto 1981	5	29	16	29	8.0%	0.31 [0.13 , 0.74]
Subtotal (95% CI)		**29**		**29**	**8.0%**	**0.31 [0.13 , 0.74]**
Total events:	5		16			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.64 (P = 0.008)						
1.4.8 Flurbiprofen 25 mg						
Sunshine 1983a	1	32	4	8	3.2%	0.06 [0.01 , 0.49]
Subtotal (95% CI)		**32**		**8**	**3.2%**	**0.06 [0.01 , 0.49]**
Total events:	1		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.65 (P = 0.008)						
1.4.9 Flurbiprofen 50 mg						
Sunshine 1983a	0	29	4	8	3.5%	0.03 [0.00 , 0.56]
Subtotal (95% CI)		**29**		**8**	**3.5%**	**0.03 [0.00 , 0.56]**
Total events:	0		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.36 (P = 0.02)						
1.4.10 Flurbiprofen 100 mg						
Sunshine 1983a	0	31	4	8	3.5%	0.03 [0.00 , 0.53]
Subtotal (95% CI)		**31**		**8**	**3.5%**	**0.03 [0.00 , 0.53]**
Total events:	0		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.40 (P = 0.02)						
Total (95% CI)		**628**		**384**	**100.0%**	**0.32 [0.26 , 0.40]**
Total events:	81		168			
Heterogeneity: Chi² = 18.77, df = 15 (P = 0.22); I² = 20%						
Test for overall effect: Z = 10.04 (P < 0.00001)						
Test for subgroup differences: Chi² = 10.56, df = 9 (P = 0.31), I² = 14.7%						

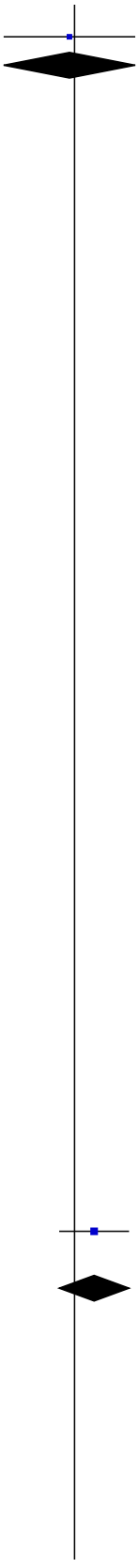
Analysis 1.5. Comparison 1: NSAID (single administration, any dose) versus placebo, Outcome 5: Maternal drug adverse effects (6 hours after administration)

Study or Subgroup	NSAID Events	NSAID Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.5.1 Aspirin 500 mg to 650 mg						
Bloomfield 1967	3	16	1	18	6.9%	3.38 [0.39 , 29.28]
De Vroey 1978	0	32	0	8		Not estimable
Mukherjee 1980	0	89	0	45		Not estimable
Sunshine 1983a	0	29	0	8		Not estimable
London 1983	2	40	3	40	21.9%	0.67 [0.12 , 3.78]
Jain 1985	0	30	0	10		Not estimable
Subtotal (95% CI)		**236**		**129**	**28.8%**	**1.31 [0.38 , 4.60]**
Total events:	5		4			
Heterogeneity: Chi² = 1.32, df = 1 (P = 0.25); I² = 24%						
Test for overall effect: Z = 0.43 (P = 0.67)						
1.5.2 Aspirin 900 mg						
Bloomfield 1974	5	20	1	7	10.8%	1.75 [0.24 , 12.51]
Subtotal (95% CI)		**20**		**7**	**10.8%**	**1.75 [0.24 , 12.51]**
Total events:	5		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.56 (P = 0.58)						
1.5.3 Ibuprofen 300 mg to 400 mg						
Bloomfield 1974	3	20	1	7	10.8%	1.05 [0.13 , 8.52]
Jain 1988	2	49	1	48	7.4%	1.96 [0.18 , 20.90]
Behotas 1992	0	31	1	31	11.0%	0.33 [0.01 , 7.88]
Subtotal (95% CI)		**100**		**86**	**29.1%**	**1.01 [0.27 , 3.85]**
Total events:	5		3			
Heterogeneity: Chi² = 0.77, df = 2 (P = 0.68); I² = 0%						
Test for overall effect: Z = 0.02 (P = 0.99)						
1.5.4 Ibuprofen 900 mg						
Bloomfield 1974	3	20	1	7	10.8%	1.05 [0.13 , 8.52]
Subtotal (95% CI)		**20**		**7**	**10.8%**	**1.05 [0.13 , 8.52]**
Total events:	3		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.05 (P = 0.96)						
1.5.5 Ketoprofen 25 mg						
Olson 1999	0	28	0	14		Not estimable
Subtotal (95% CI)		**28**		**14**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
1.5.6 Ketoprofen 50 mg						
Olson 1999	0	26	0	14		Not estimable
Subtotal (95% CI)		**26**		**14**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
1.5.7 Aceclofenac 50 mg						
Honorato 1990	1	18	0	4	5.8%	0.79 [0.04 , 16.59]



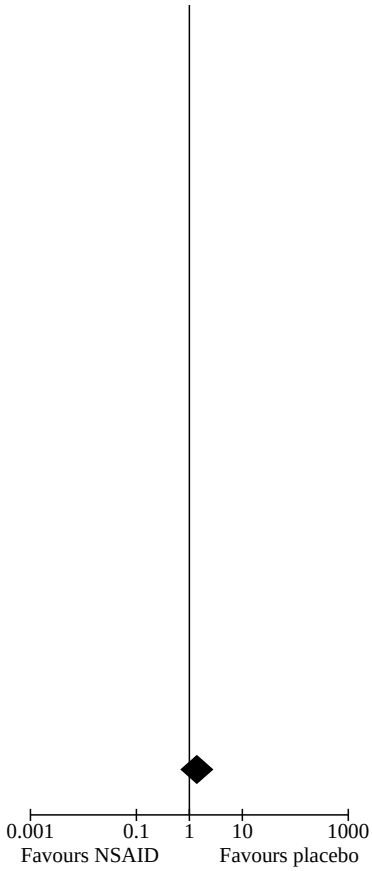
Analysis 1.5. (Continued)

Honorato 1990	1	18	0	4	5.8%	0.79 [0.04 , 16.59]
Subtotal (95% CI)		**18**		**4**	**5.8%**	**0.79 [0.04 , 16.59]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.15 (P = 0.88)						
1.5.8 Aceclofenac 100 mg						
Honorato 1990	0	24	0	4		Not estimable
Subtotal (95% CI)		**24**		**4**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
1.5.9 Aceclofenac 150 mg						
Honorato 1990	0	21	0	4		Not estimable
Subtotal (95% CI)		**21**		**4**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
1.5.10 Diflunisal 125 mg						
De Vroey 1978	0	33	0	8		Not estimable
Subtotal (95% CI)		**33**		**8**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
1.5.11 Diflunisal 250 mg						
De Vroey 1978	0	30	0	8		Not estimable
Subtotal (95% CI)		**30**		**8**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
1.5.12 Diflunisal 500 mg						
De Vroey 1978	0	30	0	8		Not estimable
Subtotal (95% CI)		**30**		**8**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
1.5.13 Dipyrone 500 mg						
Daftary 1980	5	101	2	100	14.7%	2.48 [0.49 , 12.46]
Mukherjee 1980	0	89	0	45		Not estimable
Subtotal (95% CI)		**190**		**145**	**14.7%**	**2.48 [0.49 , 12.46]**
Total events:	5		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.10 (P = 0.27)						
1.5.14 Antrafenine 300 mg						
Wisanto 1981	0	29	0	29		Not estimable
Subtotal (95% CI)		**29**		**29**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						



Analysis 1.5. (Continued)

Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
1.5.15 Flurbiprofen 25 mg						
Sunshine 1983a	0	32	0	8		Not estimable
Subtotal (95% CI)		**32**		**8**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
1.5.16 Flurbiprofen 50 mg						
Sunshine 1983a	0	29	0	8		Not estimable
Subtotal (95% CI)		**29**		**8**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
1.5.17 Flurbiprofen 100 mg						
Sunshine 1983a	0	31	0	8		Not estimable
Subtotal (95% CI)		**31**		**8**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**897**		**491**	**100.0%**	**1.38 [0.71 , 2.70]**
Total events:	24		11			
Heterogeneity: Chi² = 3.01, df = 8 (P = 0.93); I² = 0%						
Test for overall effect: Z = 0.95 (P = 0.34)						
Test for subgroup differences: Chi² = 0.96, df = 5 (P = 0.97), I² = 0%						



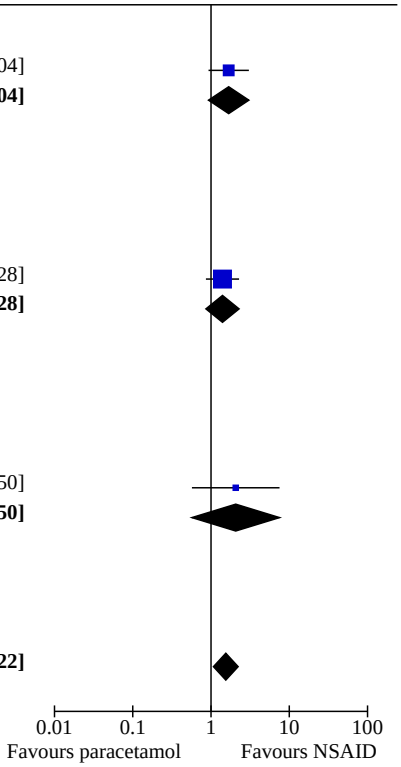
Comparison 2. NSAID (single administration, any dose) versus paracetamol

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Adequate pain relief (4 hours after administration)	3	342	Risk Ratio (M-H, Fixed, 95% CI)	1.54 [1.07, 2.22]
2.1.1 Ibuprofen 300 mg to 400 mg versus paracetamol 1000 mg	1	73	Risk Ratio (M-H, Fixed, 95% CI)	1.68 [0.93, 3.04]
2.1.2 Ibuprofen 300 mg to 400 mg versus paracetamol 500 mg	1	210	Risk Ratio (M-H, Fixed, 95% CI)	1.40 [0.86, 2.28]
2.1.3 Aceclofenac 100 mg versus paracetamol 650 mg	1	59	Risk Ratio (M-H, Fixed, 95% CI)	2.07 [0.57, 7.50]
2.2 Adequate pain relief (6 hours after administration)	2	99	Risk Ratio (M-H, Random, 95% CI)	1.82 [0.61, 5.47]
2.2.1 Aceclofenac 100 mg versus paracetamol 650 mg	2	99	Risk Ratio (M-H, Random, 95% CI)	1.82 [0.61, 5.47]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.3 Need for additional analgesia (4 hours after administration)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.3.1 Ibuprofen 300 mg to 400 mg versus paracetamol 1000 mg	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.4 Need for additional analgesia (6 hours after administration)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.4.1 Ibuprofen 300 mg to 400 mg versus paracetamol 1000 mg	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.5 Maternal drug adverse effects (6 hours after administration)	3	300	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.27, 2.08]
2.5.1 Dipyrone 500 mg versus paracetamol 500 mg	1	201	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.23, 2.15]
2.5.2 Aceclofenac 100 mg versus paracetamol 650 mg	2	99	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.07, 14.90]

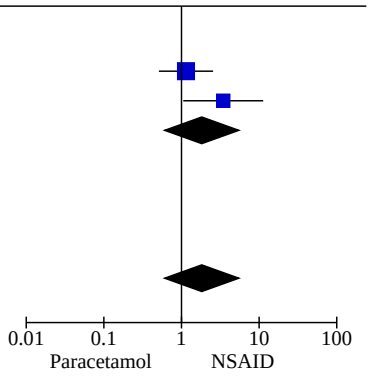
Analysis 2.1. Comparison 2: NSAID (single administration, any dose) versus paracetamol, Outcome 1: Adequate pain relief (4 hours after administration)

Study or Subgroup	NSAID Events	NSAID Total	Paracetamol Events	Paracetamol Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.1.1 Ibuprofen 300 mg to 400 mg versus paracetamol 1000 mg						
Schachtel 1989	18	36	11	37	31.0%	1.68 [0.93 , 3.04]
Subtotal (95% CI)		**36**		**37**	**31.0%**	**1.68 [0.93 , 3.04]**
Total events:	18		11			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.72 (P = 0.09)						
2.1.2 Ibuprofen 300 mg to 400 mg versus paracetamol 500 mg						
Kamondetdecha 2008	30	106	21	104	60.6%	1.40 [0.86 , 2.28]
Subtotal (95% CI)		**106**		**104**	**60.6%**	**1.40 [0.86 , 2.28]**
Total events:	30		21			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.36 (P = 0.17)						
2.1.3 Aceclofenac 100 mg versus paracetamol 650 mg						
Movilia 1989	6	29	3	30	8.4%	2.07 [0.57 , 7.50]
Subtotal (95% CI)		**29**		**30**	**8.4%**	**2.07 [0.57 , 7.50]**
Total events:	6		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.11 (P = 0.27)						
Total (95% CI)		**171**		**171**	**100.0%**	**1.54 [1.07 , 2.22]**
Total events:	54		35			
Heterogeneity: Chi² = 0.43, df = 2 (P = 0.81); I² = 0%						
Test for overall effect: Z = 2.35 (P = 0.02)						
Test for subgroup differences: Chi² = 0.43, df = 2 (P = 0.81), I² = 0%						



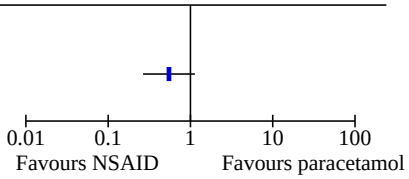
Analysis 2.2. Comparison 2: NSAID (single administration, any dose) versus paracetamol, Outcome 2: Adequate pain relief (6 hours after administration)

Study or Subgroup	NSAID Events	NSAID Total	Paracetamol Events	Paracetamol Total	Weight	Risk Ratio M-H, Random, 95% CI
2.2.1 Aceclofenac 100 mg versus paracetamol 650 mg						
Yscla 1988	8	20	7	20	57.7%	1.14 [0.51 , 2.55]
Movilia 1989	10	29	3	30	42.3%	3.45 [1.05 , 11.28]
Subtotal (95% CI)		**49**		**50**	**100.0%**	**1.82 [0.61 , 5.47]**
Total events:	18		10			
Heterogeneity: Tau² = 0.38; Chi² = 2.41, df = 1 (P = 0.12); I² = 59%						
Test for overall effect: Z = 1.07 (P = 0.28)						
Total (95% CI)		**49**		**50**	**100.0%**	**1.82 [0.61 , 5.47]**
Total events:	18		10			
Heterogeneity: Tau² = 0.38; Chi² = 2.41, df = 1 (P = 0.12); I² = 59%						
Test for overall effect: Z = 1.07 (P = 0.28)						
Test for subgroup differences: Not applicable						



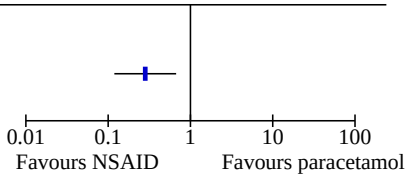
Analysis 2.3. Comparison 2: NSAID (single administration, any dose) versus paracetamol, Outcome 3: Need for additional analgesia (4 hours after administration)

Study or Subgroup	NSAID Events	NSAID Total	Paracetamol Events	Paracetamol Total	Risk Ratio M-H, Fixed, 95% CI
2.3.1 Ibuprofen 300 mg to 400 mg versus paracetamol 1000 mg					
Schachtel 1989	8	36	15	37	0.55 [0.27 , 1.13]



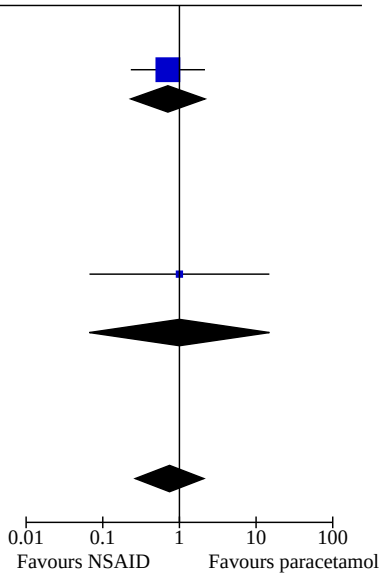
Analysis 2.4. Comparison 2: NSAID (single administration, any dose) versus paracetamol, Outcome 4: Need for additional analgesia (6 hours after administration)

Study or Subgroup	NSAID Events	NSAID Total	Paracetamol Events	Paracetamol Total	Risk Ratio M-H, Fixed, 95% CI
2.4.1 Ibuprofen 300 mg to 400 mg versus paracetamol 1000 mg					
Behotas 1992	5	31	16	28	0.28 [0.12 , 0.67]



Analysis 2.5. Comparison 2: NSAID (single administration, any dose) versus paracetamol, Outcome 5: Maternal drug adverse effects (6 hours after administration)

Study or Subgroup	NSAID Events	NSAID Total	Paracetamol Events	Paracetamol Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.5.1 Dipyrone 500 mg versus paracetamol 500 mg						
Daftary 1980	5	101	7	100	87.6%	0.71 [0.23 , 2.15]
Subtotal (95% CI)		**101**		**100**	**87.6%**	**0.71 [0.23 , 2.15]**
Total events:	5		7			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.61 (P = 0.54)						
2.5.2 Aceclofenac 100 mg versus paracetamol 650 mg						
Yscla 1988	1	20	1	20	12.4%	1.00 [0.07 , 14.90]
Movilia 1989	0	29	0	30		Not estimable
Subtotal (95% CI)		**49**		**50**	**12.4%**	**1.00 [0.07 , 14.90]**
Total events:	1		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.00 (P = 1.00)						
Total (95% CI)		**150**		**150**	**100.0%**	**0.74 [0.27 , 2.08]**
Total events:	6		8			
Heterogeneity: Chi^2 = 0.05, df = 1 (P = 0.82); I^2 = 0%						
Test for overall effect: Z = 0.56 (P = 0.57)						
Test for subgroup differences: Chi^2 = 0.05, df = 1 (P = 0.82), I^2 = 0%						



Comparison 3. NSAID versus a different NSAID

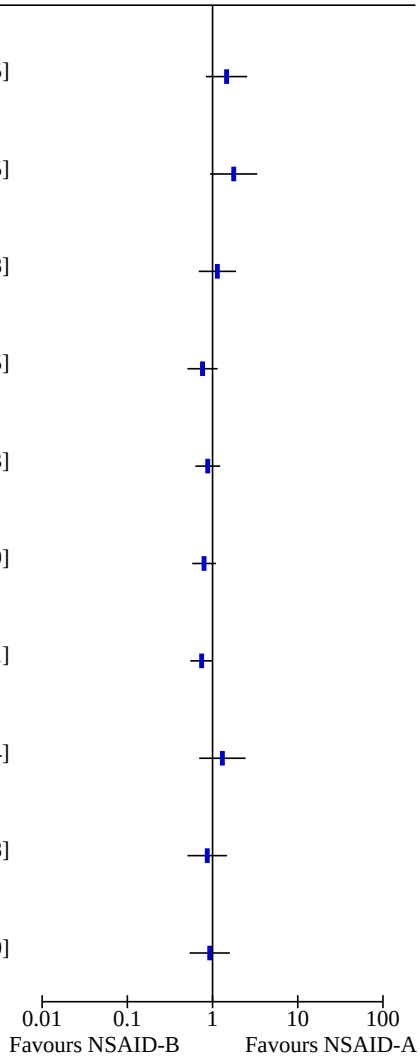
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Adequate pain relief (4 hours after administration)	4		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.1.1 Aspirin 500 mg to 650 mg (A) versus Diflunisal 125 mg (B)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.1.2 Aspirin 500 mg to 650 mg (A) versus Diflunisal 250 mg (B)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.1.3 Aspirin 500 mg to 650 mg (A) versus Diflunisal 500 mg (B)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.1.4 Aspirin 500 mg to 650 mg (A) versus Ibuprofen 300 mg to 400 mg (B)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.1.5 Aspirin 500 mg to 650 mg (A) versus Diclofenac 25 mg (B)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.1.6 Aspirin 500 mg to 650 mg (A) versus Diclofenac 50 mg (B)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.1.7 Aspirin 500 mg to 650 mg (A) versus Diclofenac 100 mg (B)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.1.8 Aspirin 500 mg to 650 mg (A) versus Flurbiprofen 25 mg (B)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.1.9 Aspirin 500 mg to 650 mg (A) versus Flurbiprofen 50 mg (B)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.1.10 Aspirin 500 mg to 650 mg (A) versus Flurbiprofen 100 mg (B)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.2 Adequate pain relief (6 hours after administration)	5		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.2.1 Aspirin 900 mg (A) versus Ibuprofen 300 mg to 400 mg (B)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.2.2 Aspirin 900 mg (A) versus Ibuprofen 900 mg (B)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.2.3 Aspirin 500 mg to 650 mg (A) versus Diflunisal 125 mg (B)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.2.4 Aspirin 500 mg to 650 mg (A) versus Diflunisal 250 mg (B)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.2.5 Aspirin 500 mg to 650 mg (A) versus Diflunisal 500 mg (B)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.2.6 Aspirin 500 mg to 650 mg (A) versus Etodolac 25 mg (B)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.2.7 Aspirin 500 mg to 650 mg (A) versus Etodolac 100 mg (B)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.2.8 Aspirin 500 mg to 650 mg (A) versus Flurbiprofen 25 mg (B)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.2.9 Aspirin 500 mg to 650 mg (A) versus Flurbiprofen 50 mg (B)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.2.10 Aspirin 500 mg to 650 mg (A) versus Flurbiprofen 100 mg (B)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.2.11 Aspirin 500 mg to 650 mg (A) versus Dipyrone 500 mg (B)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.3 Need for additional analgesia (4 hours after administration)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.3.1 Aspirin 500 mg to 650 mg (A) versus Ibuprofen 300 mg to 400 mg (B)	1	60	Risk Ratio (M-H, Fixed, 95% CI)	11.00 [0.64, 190.53]
3.4 Need for additional analgesia (6 hours after administration)	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.4.1 Aspirin 900 mg (A) versus Ibuprofen 300 mg to 400 mg (B)	1	40	Risk Ratio (M-H, Fixed, 95% CI)	3.00 [0.13, 69.52]
3.4.2 Aspirin 900 mg (A) versus Ibuprofen 900 mg (B)	1	40	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
3.4.3 Aspirin 500 mg to 650 mg (A) versus Flurbiprofen 25 mg (B)	1	61	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.07, 16.85]
3.4.4 Aspirin 500 mg to 650 mg (A) versus Flurbiprofen 50 mg (B)	1	58	Risk Ratio (M-H, Fixed, 95% CI)	3.00 [0.13, 70.74]
3.4.5 Aspirin 500 mg to 650 mg (A) versus Flurbiprofen 100 mg (B)	1	60	Risk Ratio (M-H, Fixed, 95% CI)	3.20 [0.14, 75.55]
3.5 Maternal drug adverse effects (6 hours after administration)	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.5.1 Aspirin 900 mg (A) versus Ibuprofen 300 mg to 400 mg (B)	1	40	Risk Ratio (M-H, Fixed, 95% CI)	1.67 [0.46, 6.06]
3.5.2 Aspirin 900 mg (A) versus Ibuprofen 900 mg (B)	1	40	Risk Ratio (M-H, Fixed, 95% CI)	1.67 [0.46, 6.06]
3.5.3 Aspirin 500 mg to 650 mg (A) versus Dipyrone 500 mg (B)	1	178	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
3.5.4 Aspirin 500 mg to 650 mg (A) versus Flurbiprofen 25 mg (B)	1	61	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.5.5 Aspirin 500 mg to 650 mg (A) versus Flurbiprofen 50 mg (B)	1	58	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
3.5.6 Aspirin 500 mg to 650 mg (A) versus Flurbiprofen 100 mg (B)	1	60	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
3.5.7 Aspirin 500 mg to 650 mg (A) versus Diflunisal 125 mg (B)	1	65	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
3.5.8 Aspirin 500 mg to 650 mg (A) versus Diflunisal 250 mg (B)	1	62	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
3.5.9 Aspirin 500 mg to 650 mg (A) versus Diflunisal 500 mg (B)	1	62	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

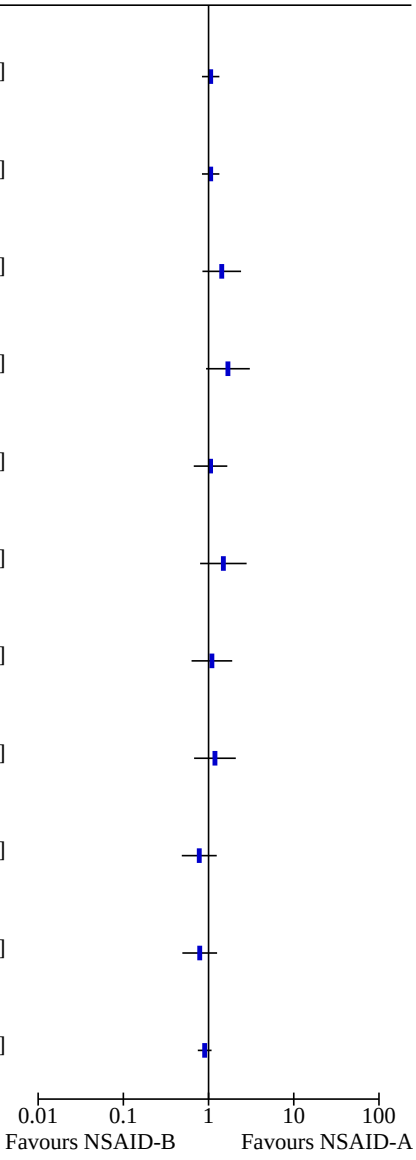
Analysis 3.1. Comparison 3: NSAID versus a different NSAID, Outcome 1: Adequate pain relief (4 hours after administration)

Study or Subgroup	NSAID-A Events	NSAID-A Total	NSAID-B Events	NSAID-B Total	Risk Ratio M-H, Fixed, 95% CI
3.1.1 Aspirin 500 mg to 650 mg (A) versus Diflunisal 125 mg (B)					
De Vroey 1978	17	32	12	33	1.46 [0.84 , 2.55]
3.1.2 Aspirin 500 mg to 650 mg (A) versus Diflunisal 250 mg (B)					
De Vroey 1978	17	32	9	30	1.77 [0.94 , 3.35]
3.1.3 Aspirin 500 mg to 650 mg (A) versus Diflunisal 500 mg (B)					
De Vroey 1978	17	32	14	30	1.14 [0.69 , 1.88]
3.1.4 Aspirin 500 mg to 650 mg (A) versus Ibuprofen 300 mg to 400 mg (B)					
Sunshine 1983b	16	30	21	30	0.76 [0.51 , 1.15]
3.1.5 Aspirin 500 mg to 650 mg (A) versus Diclofenac 25 mg (B)					
Olson 1997	27	50	32	52	0.88 [0.63 , 1.23]
3.1.6 Aspirin 500 mg to 650 mg (A) versus Diclofenac 50 mg (B)					
Olson 1997	27	50	34	50	0.79 [0.58 , 1.09]
3.1.7 Aspirin 500 mg to 650 mg (A) versus Diclofenac 100 mg (B)					
Olson 1997	27	50	37	51	0.74 [0.55 , 1.01]
3.1.8 Aspirin 500 mg to 650 mg (A) versus Flurbiprofen 25 mg (B)					
Sunshine 1983a	13	29	11	32	1.30 [0.70 , 2.44]
3.1.9 Aspirin 500 mg to 650 mg (A) versus Flurbiprofen 50 mg (B)					
Sunshine 1983a	13	29	15	29	0.87 [0.51 , 1.48]
3.1.10 Aspirin 500 mg to 650 mg (A) versus Flurbiprofen 100 mg (B)					
Sunshine 1983a	13	29	15	31	0.93 [0.54 , 1.60]



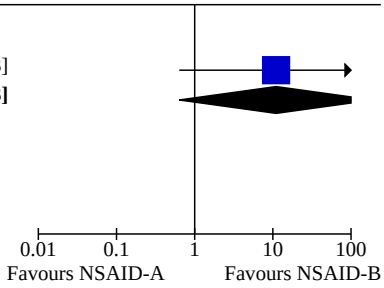
Analysis 3.2. Comparison 3: NSAID versus a different NSAID, Outcome 2: Adequate pain relief (6 hours after administration)

Study or Subgroup	NSAID-A Events	NSAID-A Total	NSAID-B Events	NSAID-B Total	Risk Ratio M-H, Fixed, 95% CI
3.2.1 Aspirin 900 mg (A) versus Ibuprofen 300 mg to 400 mg (B)					
Bloomfield 1974	18	20	17	20	1.06 [0.84 , 1.34]
3.2.2 Aspirin 900 mg (A) versus Ibuprofen 900 mg (B)					
Bloomfield 1974	18	20	17	20	1.06 [0.84 , 1.34]
3.2.3 Aspirin 500 mg to 650 mg (A) versus Diflunisal 125 mg (B)					
De Vroey 1978	18	32	13	33	1.43 [0.85 , 2.41]
3.2.4 Aspirin 500 mg to 650 mg (A) versus Diflunisal 250 mg (B)					
De Vroey 1978	18	32	10	30	1.69 [0.93 , 3.05]
3.2.5 Aspirin 500 mg to 650 mg (A) versus Diflunisal 500 mg (B)					
De Vroey 1978	18	32	16	30	1.05 [0.67 , 1.66]
3.2.6 Aspirin 500 mg to 650 mg (A) versus Etodolac 25 mg (B)					
Friedrich 1983	16	39	11	40	1.49 [0.80 , 2.80]
3.2.7 Aspirin 500 mg to 650 mg (A) versus Etodolac 100 mg (B)					
Friedrich 1983	16	39	15	40	1.09 [0.63 , 1.89]
3.2.8 Aspirin 500 mg to 650 mg (A) versus Flurbiprofen 25 mg (B)					
Sunshine 1983a	14	29	13	32	1.19 [0.68 , 2.09]
3.2.9 Aspirin 500 mg to 650 mg (A) versus Flurbiprofen 50 mg (B)					
Sunshine 1983a	14	29	18	29	0.78 [0.49 , 1.25]
3.2.10 Aspirin 500 mg to 650 mg (A) versus Flurbiprofen 100 mg (B)					
Sunshine 1983a	14	29	19	31	0.79 [0.49 , 1.26]
3.2.11 Aspirin 500 mg to 650 mg (A) versus Dipyrone 500 mg (B)					
Mukherjee 1980	61	90	67	89	0.90 [0.75 , 1.08]



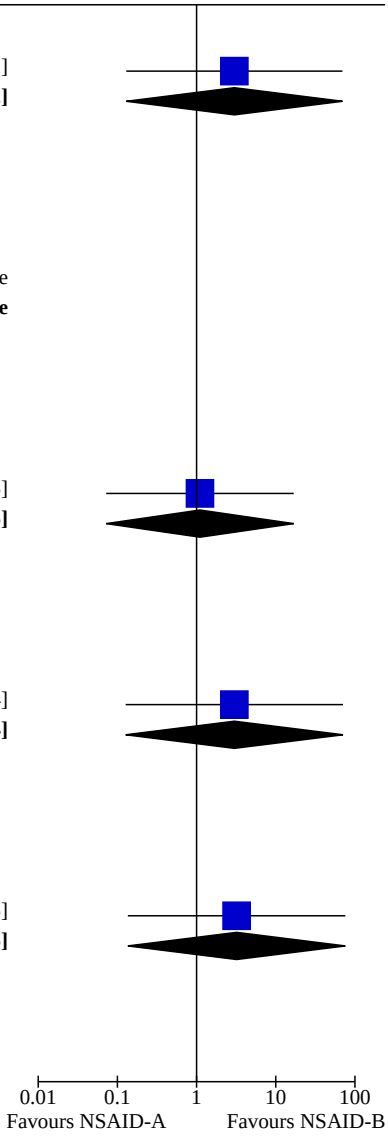
Analysis 3.3. Comparison 3: NSAID versus a different NSAID, Outcome 3: Need for additional analgesia (4 hours after administration)

Study or Subgroup	NSAID-A Events	NSAID-A Total	NSAID-B Events	NSAID-B Total	Weight	Risk Ratio M-H, Fixed, 95% CI
3.3.1 Aspirin 500 mg to 650 mg (A) versus Ibuprofen 300 mg to 400 mg (B)						
Sunshine 1983b	5	30	0	30	100.0%	11.00 [0.64 , 190.53]
Subtotal (95% CI)		**30**		**30**	**100.0%**	**11.00 [0.64 , 190.53]**
Total events:	5		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.65 (P = 0.10)						
Test for subgroup differences: Not applicable						



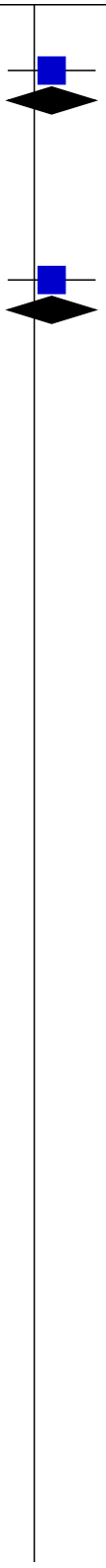
Analysis 3.4. Comparison 3: NSAID versus a different NSAID, Outcome 4: Need for additional analgesia (6 hours after administration)

Study or Subgroup	NSAID-A Events	NSAID-A Total	NSAID-B Events	NSAID-B Total	Weight	Risk Ratio M-H, Fixed, 95% CI
3.4.1 Aspirin 900 mg (A) versus Ibuprofen 300 mg to 400 mg (B)						
Bloomfield 1974	1	20	0	20	100.0%	3.00 [0.13 , 69.52]
Subtotal (95% CI)		**20**		**20**	**100.0%**	**3.00 [0.13 , 69.52]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.69 (P = 0.49)						
3.4.2 Aspirin 900 mg (A) versus Ibuprofen 900 mg (B)						
Bloomfield 1974	0	20	0	20		Not estimable
Subtotal (95% CI)		**20**		**20**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
3.4.3 Aspirin 500 mg to 650 mg (A) versus Flurbiprofen 25 mg (B)						
Sunshine 1983a	1	29	1	32	100.0%	1.10 [0.07 , 16.85]
Subtotal (95% CI)		**29**		**32**	**100.0%**	**1.10 [0.07 , 16.85]**
Total events:	1		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.07 (P = 0.94)						
3.4.4 Aspirin 500 mg to 650 mg (A) versus Flurbiprofen 50 mg (B)						
Sunshine 1983a	1	29	0	29	100.0%	3.00 [0.13 , 70.74]
Subtotal (95% CI)		**29**		**29**	**100.0%**	**3.00 [0.13 , 70.74]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.68 (P = 0.50)						
3.4.5 Aspirin 500 mg to 650 mg (A) versus Flurbiprofen 100 mg (B)						
Sunshine 1983a	1	29	0	31	100.0%	3.20 [0.14 , 75.55]
Subtotal (95% CI)		**29**		**31**	**100.0%**	**3.20 [0.14 , 75.55]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.72 (P = 0.47)						
Test for subgroup differences: $Chi^2 = 0.37$, df = 3 (P = 0.95), $I^2 = 0\%$						



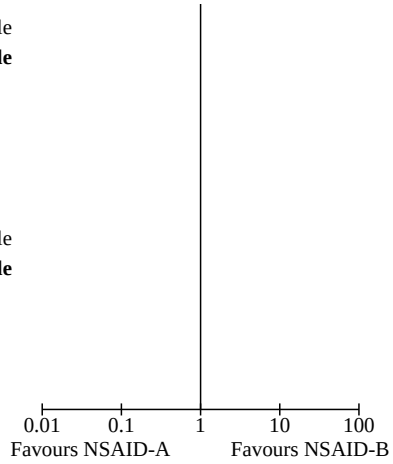
Analysis 3.5. Comparison 3: NSAID versus a different NSAID, Outcome 5: Maternal drug adverse effects (6 hours after administration)

Study or Subgroup	NSAID-A Events	NSAID-A Total	NSAID-B Events	NSAID-B Total	Weight	Risk Ratio M-H, Fixed, 95% CI
3.5.1 Aspirin 900 mg (A) versus Ibuprofen 300 mg to 400 mg (B)						
Bloomfield 1974	5	20	3	20	100.0%	1.67 [0.46 , 6.06]
Subtotal (95% CI)		**20**		**20**	**100.0%**	**1.67 [0.46 , 6.06]**
Total events:	5		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.78 (P = 0.44)						
3.5.2 Aspirin 900 mg (A) versus Ibuprofen 900 mg (B)						
Bloomfield 1974	5	20	3	20	100.0%	1.67 [0.46 , 6.06]
Subtotal (95% CI)		**20**		**20**	**100.0%**	**1.67 [0.46 , 6.06]**
Total events:	5		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.78 (P = 0.44)						
3.5.3 Aspirin 500 mg to 650 mg (A) versus Dipyrone 500 mg (B)						
Mukherjee 1980	0	89	0	89		Not estimable
Subtotal (95% CI)		**89**		**89**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
3.5.4 Aspirin 500 mg to 650 mg (A) versus Flurbiprofen 25 mg (B)						
Sunshine 1983a	0	29	0	32		Not estimable
Subtotal (95% CI)		**29**		**32**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
3.5.5 Aspirin 500 mg to 650 mg (A) versus Flurbiprofen 50 mg (B)						
Sunshine 1983a	0	29	0	29		Not estimable
Subtotal (95% CI)		**29**		**29**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
3.5.6 Aspirin 500 mg to 650 mg (A) versus Flurbiprofen 100 mg (B)						
Sunshine 1983a	0	29	0	31		Not estimable
Subtotal (95% CI)		**29**		**31**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
3.5.7 Aspirin 500 mg to 650 mg (A) versus Diflunisal 125 mg (B)						
De Vroey 1978	0	32	0	33		Not estimable
Subtotal (95% CI)		**32**		**33**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
3.5.8 Aspirin 500 mg to 650 mg (A) versus Diflunisal 250 mg (B)						
De Vroey 1978	0	32	0	30		Not estimable
Subtotal (95% CI)		**32**		**30**		**Not estimable**



Analysis 3.5. (Continued)

De Vroey 1978	0	32	0	30	Not estimable
Subtotal (95% CI)		**32**		**30**	**Not estimable**
Total events:	0		0		
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
3.5.9 Aspirin 500 mg to 650 mg (A) versus Diflunisal 500 mg (B)					
De Vroey 1978	0	32	0	30	Not estimable
Subtotal (95% CI)		**32**		**30**	**Not estimable**
Total events:	0		0		
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 1.00), I² = 0%					



Comparison 4. NSAID versus a different dose of the same NSAID

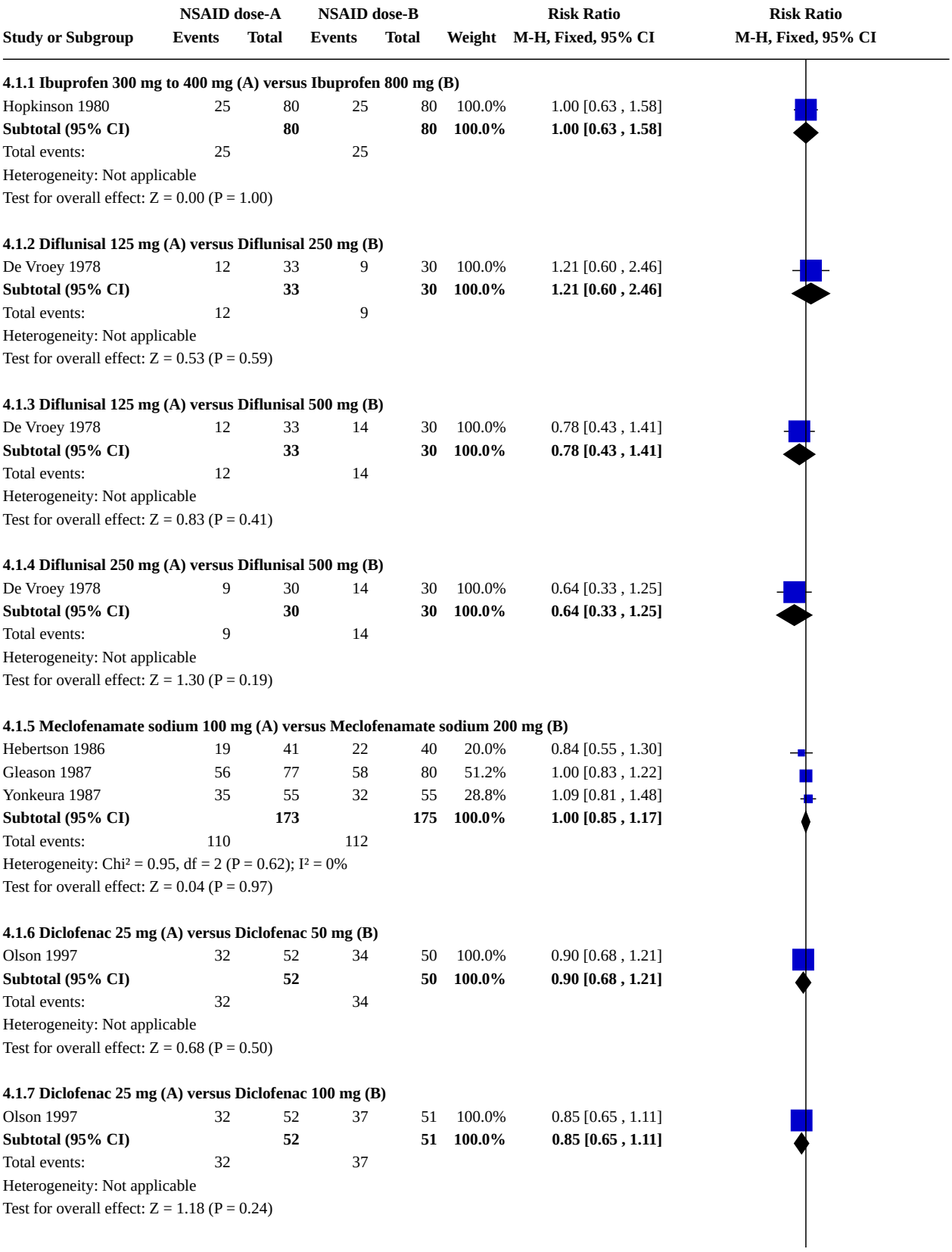
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Adequate pain relief (4 hours after administration)	9		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1.1 Ibuprofen 300 mg to 400 mg (A) versus Ibuprofen 800 mg (B)	1	160	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.63, 1.58]
4.1.2 Diflunisal 125 mg (A) versus Diflunisal 250 mg (B)	1	63	Risk Ratio (M-H, Fixed, 95% CI)	1.21 [0.60, 2.46]
4.1.3 Diflunisal 125 mg (A) versus Diflunisal 500 mg (B)	1	63	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.43, 1.41]
4.1.4 Diflunisal 250 mg (A) versus Diflunisal 500 mg (B)	1	60	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.33, 1.25]
4.1.5 Meclofenamate sodium 100 mg (A) versus Meclofenamate sodium 200 mg (B)	3	348	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.85, 1.17]
4.1.6 Diclofenac 25 mg (A) versus Diclofenac 50 mg (B)	1	102	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.68, 1.21]
4.1.7 Diclofenac 25 mg (A) versus Diclofenac 100 mg (B)	1	103	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.65, 1.11]
4.1.8 Ketoprofen 25 mg (A) versus Ketoprofen 50 mg (B)	1	54	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.73, 1.46]
4.1.9 Aceclofenac 50 mg (A) versus Aceclofenac 100 mg (B)	1	42	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.65, 1.54]
4.1.10 Aceclofenac 50 mg (A) versus Aceclofenac 150 mg (B)	1	39	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.56, 1.21]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1.11 Aceclofenac 100 mg (A) versus Aceclofenac 150 mg (B)	1	45	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.58, 1.17]
4.1.12 Flurbiprofen 25 mg (A) versus Flurbiprofen 50 mg (B)	1	61	Risk Ratio (M-H, Fixed, 95% CI)	0.66 [0.37, 1.20]
4.1.13 Flurbiprofen 25 mg (A) versus Flurbiprofen 50 mg (B)	1	63	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.39, 1.30]
4.1.14 Flurbiprofen 50 mg (A) versus Flurbiprofen 100 mg (B)	1	60	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.64, 1.77]
4.2 Adequate pain relief (6 hours after administration)	11		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.2.1 Ibuprofen 300 mg to 400 mg (A) versus Ibuprofen 900 mg (B)	1	40	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.77, 1.30]
4.2.2 Diflunisal 125 mg (A) versus Diflunisal 250 mg (B)	1	63	Risk Ratio (M-H, Fixed, 95% CI)	1.18 [0.61, 2.29]
4.2.3 Diflunisal 125 mg (A) versus Diflunisal 500 mg (B)	1	63	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.43, 1.27]
4.2.4 Diflunisal 250 mg (A) versus Diflunisal 500 mg (B)	1	60	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.34, 1.15]
4.2.5 Meclofenamate sodium 100 mg (A) versus Meclofenamate sodium 200 mg (B)	3	348	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.84, 1.18]
4.2.6 Ketoprofen 25 mg (A) versus Ketoprofen 50 mg (B)	1	54	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.66, 1.46]
4.2.7 Aceclofenac 50 mg (A) versus Aceclofenac 100 mg (B)	1	42	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.69, 1.27]
4.2.8 Aceclofenac 50 mg (A) versus Aceclofenac 150 mg (B)	1	39	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.65, 1.14]
4.2.9 Aceclofenac 100 mg (A) versus Aceclofenac 150 mg (B)	1	45	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.73, 1.16]
4.2.10 Etodolac 25 mg (A) versus Etodolac 100 mg (B)	1	80	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.39, 1.39]
4.2.11 Flurbiprofen 25 mg (A) versus Flurbiprofen 50 mg (B)	1	61	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.39, 1.09]
4.2.12 Flurbiprofen 25 mg (A) versus Flurbiprofen 100 mg (B)	1	63	Risk Ratio (M-H, Fixed, 95% CI)	0.66 [0.40, 1.10]
4.2.13 Flurbiprofen 50 mg (A) versus Flurbiprofen 100 mg (B)	1	60	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.68, 1.51]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.2.14 Fenoprofen 50 mg (A) versus Fenoprofen 100 mg (B)	2	100	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.62, 1.16]
4.2.15 Fenoprofen 50 mg (A) versus Fenoprofen 200 mg (B)	2	99	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.62, 1.17]
4.2.16 Fenoprofen 50 mg (A) versus Fenoprofen 300 mg (B)	1	54	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.61, 1.31]
4.2.17 Fenoprofen 100 mg (A) versus Fenoprofen 200 mg (B)	2	99	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.76, 1.34]
4.2.18 Fenoprofen 100 mg (A) versus Fenoprofen 300 mg (B)	1	53	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.74, 1.46]
4.2.19 Fenoprofen 200 mg (A) versus Fenoprofen 300 mg (B)	1	53	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.74, 1.46]
4.2.20 Fenoprofen 12.5 mg (A) versus Fenoprofen 25 mg (B)	1	47	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.46, 1.65]
4.2.21 Fenoprofen 12.5 mg (A) versus Fenoprofen 50 mg (B)	1	47	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.46, 1.65]
4.2.22 Fenoprofen 12.5 mg (A) versus Fenoprofen 100 mg (B)	1	47	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.37, 1.12]
4.2.23 Fenoprofen 12.5 mg (A) versus Fenoprofen 200 mg (B)	1	47	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.41, 1.33]
4.2.24 Fenoprofen 25 mg (A) versus Fenoprofen 50 mg (B)	1	46	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.55, 1.83]
4.2.25 Fenoprofen 25 mg (A) versus Fenoprofen 100 mg (B)	1	46	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.44, 1.23]
4.2.26 Fenoprofen 25 mg (A) versus Fenoprofen 200 mg (B)	1	46	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.48, 1.48]
4.3 Need for additional analgesia (4 hours after administration)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.3.1 Ibuprofen 300 mg to 400 mg (A) versus Ibuprofen 800 mg (B)	1	160	Risk Ratio (M-H, Fixed, 95% CI)	0.57 [0.17, 1.88]
4.4 Need for additional analgesia (6 hours after administration)	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.4.1 Ibuprofen 300 mg to 400 mg (A) versus Ibuprofen 900 mg (B)	1	40	Risk Ratio (M-H, Fixed, 95% CI)	3.00 [0.13, 69.52]
4.4.2 Meclofenamate sodium 100 mg (A) versus Meclofenamate sodium 200 mg (B)	2	191	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.55, 1.50]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.4.3 Flurbiprofen 25 mg (A) versus Flurbiprofen 50 mg (B)	1	61	Risk Ratio (M-H, Fixed, 95% CI)	2.73 [0.12, 64.42]
4.4.4 Flurbiprofen 25 mg (A) versus Flurbiprofen 100 mg (B)	1	63	Risk Ratio (M-H, Fixed, 95% CI)	2.91 [0.12, 68.81]
4.4.5 Flurbiprofen 50 mg (A) versus Flurbiprofen 100 mg (B)	1	60	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
4.5 Maternal drug adverse effects (6 hours after administration)	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.5.1 Ibuprofen 300 mg (A) versus Ibuprofen 900 mg (B)	1	40	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.23, 4.37]
4.5.2 Diflunisal 125 mg (A) versus Diflunisal 250 mg (B)	1	63	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
4.5.3 Diflunisal 125 mg (A) versus Diflunisal 500 mg (B)	1	63	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
4.5.4 Diflunisal 250 mg (A) versus Diflunisal 500 mg (B)	1	60	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
4.5.5 Ketoprofen 25 mg (A) versus Ketoprofen 50 mg (B)	1	54	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
4.5.6 Aceclofenac 50 mg (A) versus Aceclofenac 100 mg (B)	1	42	Risk Ratio (M-H, Fixed, 95% CI)	3.95 [0.17, 91.61]
4.5.7 Aceclofenac 50 mg (A) versus Aceclofenac 150 mg (B)	1	39	Risk Ratio (M-H, Fixed, 95% CI)	3.47 [0.15, 80.35]
4.5.8 Aceclofenac 100 mg (A) versus Aceclofenac 150 mg (B)	1	45	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
4.5.9 Flurbiprofen 25 mg (A) versus Flurbiprofen 100 mg (B)	1	61	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
4.5.10 Flurbiprofen 25 mg (A) versus Flurbiprofen 100 mg (B)	1	63	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
4.5.11 Flurbiprofen 50 mg (A) versus Flurbiprofen 100 mg (B)	1	60	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

Analysis 4.1. Comparison 4: NSAID versus a different dose of the same NSAID, Outcome 1: Adequate pain relief (4 hours after administration)



Analysis 4.1. (Continued)

Test for overall effect: Z = 1.18 (P = 0.24)

4.1.8 Ketoprofen 25 mg (A) versus Ketoprofen 50 mg (B)

Olson 1999	20	28	18	26	100.0%	1.03 [0.73 , 1.46]
Subtotal (95% CI)		**28**		**26**	**100.0%**	**1.03 [0.73 , 1.46]**
Total events:	20		18			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.18 (P = 0.86)

4.1.9 Aceclofenac 50 mg (A) versus Aceclofenac 100 mg (B)

Honorato 1990	12	18	16	24	100.0%	1.00 [0.65 , 1.54]
Subtotal (95% CI)		**18**		**24**	**100.0%**	**1.00 [0.65 , 1.54]**
Total events:	12		16			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)

4.1.10 Aceclofenac 50 mg (A) versus Aceclofenac 150 mg (B)

Honorato 1990	12	18	17	21	100.0%	0.82 [0.56 , 1.21]
Subtotal (95% CI)		**18**		**21**	**100.0%**	**0.82 [0.56 , 1.21]**
Total events:	12		17			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.98 (P = 0.33)

4.1.11 Aceclofenac 100 mg (A) versus Aceclofenac 150 mg (B)

Honorato 1990	16	24	17	21	100.0%	0.82 [0.58 , 1.17]
Subtotal (95% CI)		**24**		**21**	**100.0%**	**0.82 [0.58 , 1.17]**
Total events:	16		17			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.08 (P = 0.28)

4.1.12 Flurbiprofen 25 mg (A) versus Flurbiprofen 50 mg (B)

Sunshine 1983a	11	32	15	29	100.0%	0.66 [0.37 , 1.20]
Subtotal (95% CI)		**32**		**29**	**100.0%**	**0.66 [0.37 , 1.20]**
Total events:	11		15			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.35 (P = 0.18)

4.1.13 Flurbiprofen 25 mg (A) versus Flurbiprofen 50 mg (B)

Sunshine 1983a	11	32	15	31	100.0%	0.71 [0.39 , 1.30]
Subtotal (95% CI)		**32**		**31**	**100.0%**	**0.71 [0.39 , 1.30]**
Total events:	11		15			

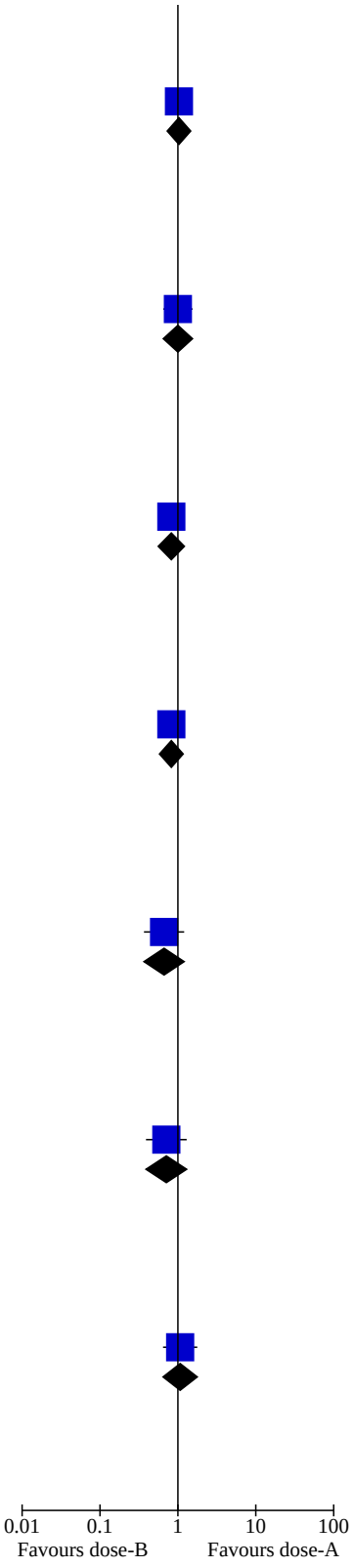
Heterogeneity: Not applicable
Test for overall effect: Z = 1.11 (P = 0.26)

4.1.14 Flurbiprofen 50 mg (A) versus Flurbiprofen 100 mg (B)

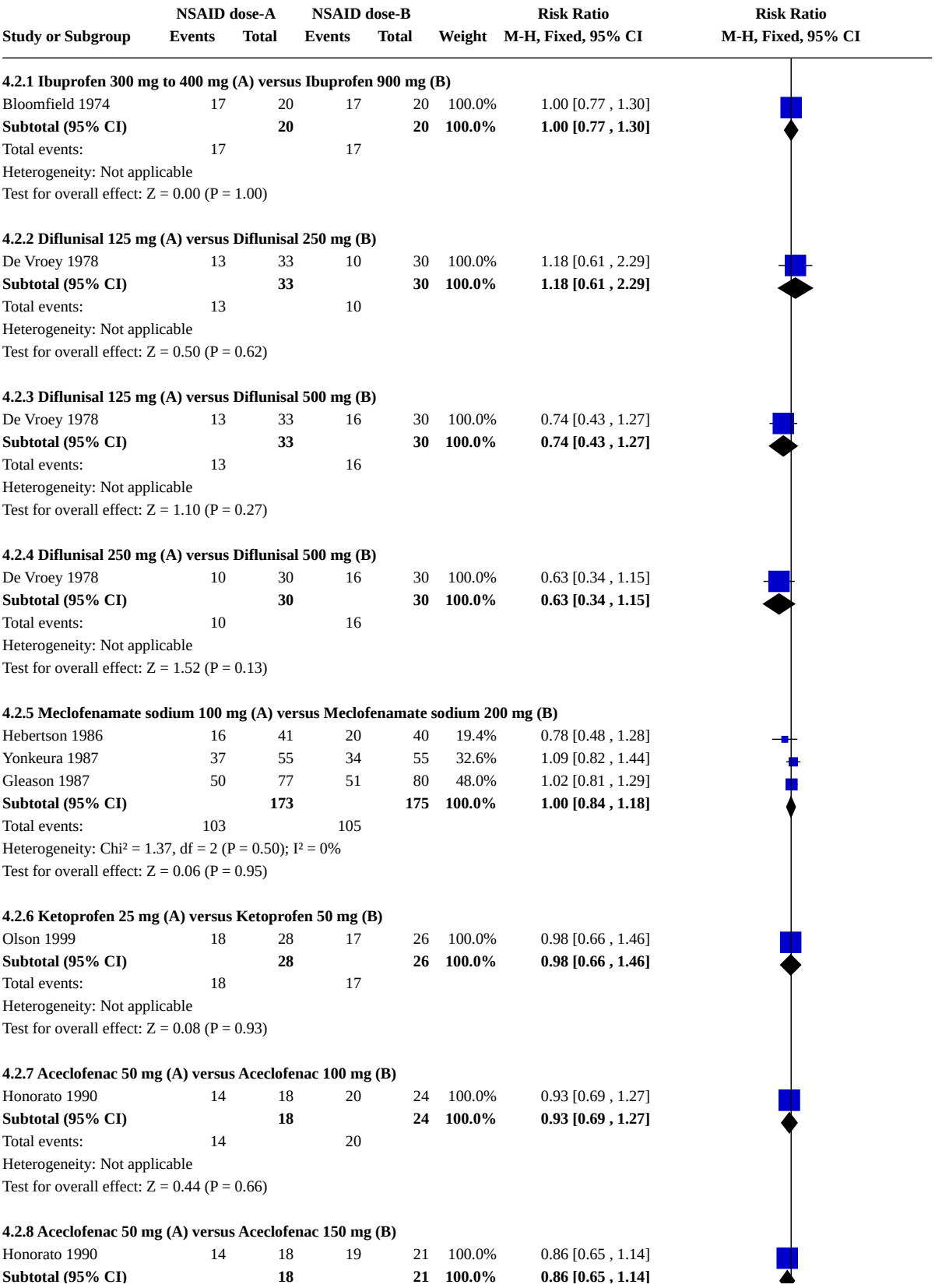
Sunshine 1983a	15	29	15	31	100.0%	1.07 [0.64 , 1.77]
Subtotal (95% CI)		**29**		**31**	**100.0%**	**1.07 [0.64 , 1.77]**
Total events:	15		15			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.26 (P = 0.80)

Test for subgroup differences: Chi² = 6.95, df = 13 (P = 0.90), I² = 0%

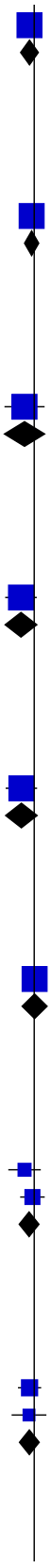


Analysis 4.2. Comparison 4: NSAID versus a different dose of the same NSAID, Outcome 2: Adequate pain relief (6 hours after administration)



Analysis 4.2. (Continued)

Honorato 1990	14	18	19	21	100.0%	0.86 [0.65 , 1.14]
Subtotal (95% CI)		**18**		**21**	**100.0%**	**0.86 [0.65 , 1.14]**
Total events:	14		19			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.05 (P = 0.30)						
4.2.9 Aceclofenac 100 mg (A) versus Aceclofenac 150 mg (B)						
Honorato 1990	20	24	19	21	100.0%	0.92 [0.73 , 1.16]
Subtotal (95% CI)		**24**		**21**	**100.0%**	**0.92 [0.73 , 1.16]**
Total events:	20		19			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.71 (P = 0.48)						
4.2.10 Etodolac 25 mg (A) versus Etodolac 100 mg (B)						
Friedrich 1983	11	40	15	40	100.0%	0.73 [0.39 , 1.39]
Subtotal (95% CI)		**40**		**40**	**100.0%**	**0.73 [0.39 , 1.39]**
Total events:	11		15			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.95 (P = 0.34)						
4.2.11 Flurbiprofen 25 mg (A) versus Flurbiprofen 50 mg (B)						
Sunshine 1983a	13	32	18	29	100.0%	0.65 [0.39 , 1.09]
Subtotal (95% CI)		**32**		**29**	**100.0%**	**0.65 [0.39 , 1.09]**
Total events:	13		18			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.64 (P = 0.10)						
4.2.12 Flurbiprofen 25 mg (A) versus Flurbiprofen 100 mg (B)						
Sunshine 1983a	13	32	19	31	100.0%	0.66 [0.40 , 1.10]
Subtotal (95% CI)		**32**		**31**	**100.0%**	**0.66 [0.40 , 1.10]**
Total events:	13		19			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.60 (P = 0.11)						
4.2.13 Flurbiprofen 50 mg (A) versus Flurbiprofen 100 mg (B)						
Sunshine 1983a	18	29	19	31	100.0%	1.01 [0.68 , 1.51]
Subtotal (95% CI)		**29**		**31**	**100.0%**	**1.01 [0.68 , 1.51]**
Total events:	18		19			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.06 (P = 0.95)						
4.2.14 Fenoprofen 50 mg (A) versus Fenoprofen 100 mg (B)						
Laska 1981b	11	23	15	23	45.5%	0.73 [0.44 , 1.23]
Laska 1981a	17	27	18	27	54.5%	0.94 [0.64 , 1.40]
Subtotal (95% CI)		**50**		**50**	**100.0%**	**0.85 [0.62 , 1.16]**
Total events:	28		33			
Heterogeneity: $Chi^2 = 0.59$, df = 1 (P = 0.44); $I^2 = 0\%$						
Test for overall effect: Z = 1.02 (P = 0.31)						
4.2.15 Fenoprofen 50 mg (A) versus Fenoprofen 200 mg (B)						
Laska 1981a	17	27	19	26	59.8%	0.86 [0.59 , 1.25]
Laska 1981b	11	23	13	23	40.2%	0.85 [0.48 , 1.48]
Subtotal (95% CI)		**50**		**49**	**100.0%**	**0.86 [0.62 , 1.17]**
Total events:	28		32			
Heterogeneity: $Chi^2 = 0.00$, df = 1 (P = 0.96); $I^2 = 0\%$						
Test for overall effect: Z = 0.97 (P = 0.33)						



Analysis 4.2. (Continued)

Test for overall effect: Z = 0.97 (P = 0.33)

4.2.16 Fenoprofen 50 mg (A) versus Fenoprofen 300 mg (B)

Laska 1981a	17	27	19	27	100.0%	0.89 [0.61 , 1.31]
Subtotal (95% CI)		**27**		**27**	**100.0%**	**0.89 [0.61 , 1.31]**
Total events:	17		19			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.58 (P = 0.57)

4.2.17 Fenoprofen 100 mg (A) versus Fenoprofen 200 mg (B)

Laska 1981b	15	23	13	23	40.2%	1.15 [0.72 , 1.84]
Laska 1981a	18	27	19	26	59.8%	0.91 [0.64 , 1.30]
Subtotal (95% CI)		**50**		**49**	**100.0%**	**1.01 [0.76 , 1.34]**
Total events:	33		32			

Heterogeneity: $Chi^2 = 0.63$, df = 1 (P = 0.43); $I^2 = 0\%$
Test for overall effect: Z = 0.06 (P = 0.95)

4.2.18 Fenoprofen 100 mg (A) versus Fenoprofen 300 mg (B)

Laska 1981a	19	26	19	27	100.0%	1.04 [0.74 , 1.46]
Subtotal (95% CI)		**26**		**27**	**100.0%**	**1.04 [0.74 , 1.46]**
Total events:	19		19			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.22 (P = 0.83)

4.2.19 Fenoprofen 200 mg (A) versus Fenoprofen 300 mg (B)

Laska 1981a	19	26	19	27	100.0%	1.04 [0.74 , 1.46]
Subtotal (95% CI)		**26**		**27**	**100.0%**	**1.04 [0.74 , 1.46]**
Total events:	19		19			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.22 (P = 0.83)

4.2.20 Fenoprofen 12.5 mg (A) versus Fenoprofen 25 mg (B)

Laska 1981b	10	24	11	23	100.0%	0.87 [0.46 , 1.65]
Subtotal (95% CI)		**24**		**23**	**100.0%**	**0.87 [0.46 , 1.65]**
Total events:	10		11			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.42 (P = 0.67)

4.2.21 Fenoprofen 12.5 mg (A) versus Fenoprofen 50 mg (B)

Laska 1981b	10	24	11	23	100.0%	0.87 [0.46 , 1.65]
Subtotal (95% CI)		**24**		**23**	**100.0%**	**0.87 [0.46 , 1.65]**
Total events:	10		11			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.42 (P = 0.67)

4.2.22 Fenoprofen 12.5 mg (A) versus Fenoprofen 100 mg (B)

Laska 1981b	10	24	15	23	100.0%	0.64 [0.37 , 1.12]
Subtotal (95% CI)		**24**		**23**	**100.0%**	**0.64 [0.37 , 1.12]**
Total events:	10		15			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.57 (P = 0.12)

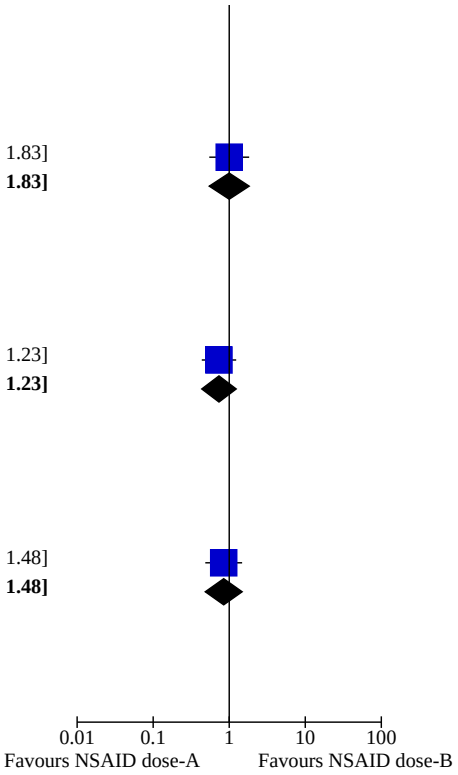
4.2.23 Fenoprofen 12.5 mg (A) versus Fenoprofen 200 mg (B)

Laska 1981b	10	24	13	23	100.0%	0.74 [0.41 , 1.33]
Subtotal (95% CI)		**24**		**23**	**100.0%**	**0.74 [0.41 , 1.33]**
Total events:	10		13			

Heterogeneity: Not applicable

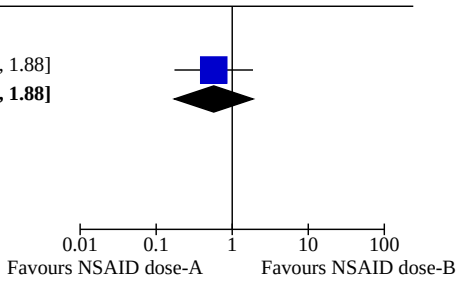
Analysis 4.2. (Continued)

Total events:	10		13			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.01 (P = 0.31)						
4.2.24 Fenoprofen 25 mg (A) versus Fenoprofen 50 mg (B)						
Laska 1981b	11	23	11	23	100.0%	1.00 [0.55 , 1.83]
Subtotal (95% CI)		**23**		**23**	**100.0%**	**1.00 [0.55 , 1.83]**
Total events:	11		11			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.00 (P = 1.00)						
4.2.25 Fenoprofen 25 mg (A) versus Fenoprofen 100 mg (B)						
Laska 1981b	11	23	15	23	100.0%	0.73 [0.44 , 1.23]
Subtotal (95% CI)		**23**		**23**	**100.0%**	**0.73 [0.44 , 1.23]**
Total events:	11		15			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.17 (P = 0.24)						
4.2.26 Fenoprofen 25 mg (A) versus Fenoprofen 200 mg (B)						
Laska 1981b	11	23	13	23	100.0%	0.85 [0.48 , 1.48]
Subtotal (95% CI)		**23**		**23**	**100.0%**	**0.85 [0.48 , 1.48]**
Total events:	11		13			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.59 (P = 0.56)						
Test for subgroup differences: Chi² = 13.30, df = 25 (P = 0.97), I² = 0%						



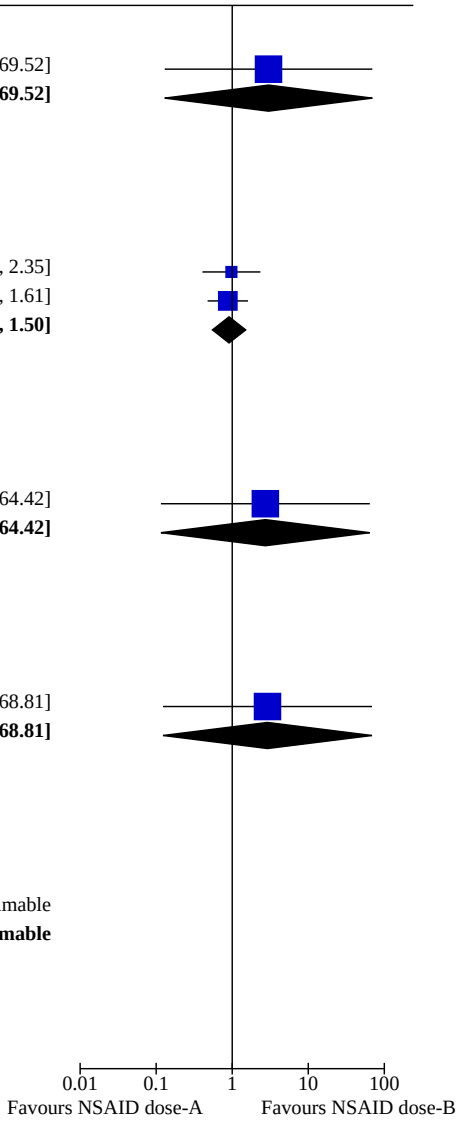
Analysis 4.3. Comparison 4: NSAID versus a different dose of the same NSAID, Outcome 3: Need for additional analgesia (4 hours after administration)

Study or Subgroup	NSAID dose-A Events	Total	NSAID dose-B Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
4.3.1 Ibuprofen 300 mg to 400 mg (A) versus Ibuprofen 800 mg (B)						
Hopkinson 1980	4	80	7	80	100.0%	0.57 [0.17 , 1.88]
Subtotal (95% CI)		**80**		**80**	**100.0%**	**0.57 [0.17 , 1.88]**
Total events:	4		7			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.92 (P = 0.36)						
Test for subgroup differences: Not applicable						



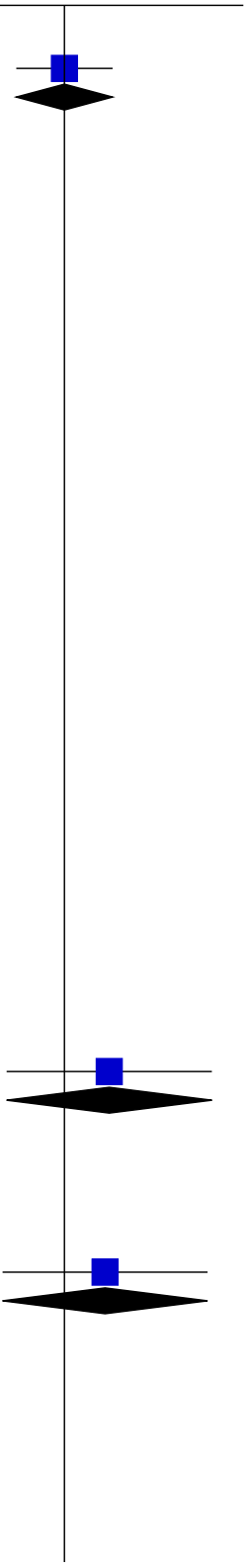
Analysis 4.4. Comparison 4: NSAID versus a different dose of the same NSAID, Outcome 4: Need for additional analgesia (6 hours after administration)

Study or Subgroup	NSAID dose-A Events	NSAID dose-A Total	NSAID dose-B Events	NSAID dose-B Total	Weight	Risk Ratio M-H, Fixed, 95% CI
4.4.1 Ibuprofen 300 mg to 400 mg (A) versus Ibuprofen 900 mg (B)						
Bloomfield 1974	1	20	0	20	100.0%	3.00 [0.13 , 69.52]
Subtotal (95% CI)		**20**		**20**	**100.0%**	**3.00 [0.13 , 69.52]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.69 (P = 0.49)						
4.4.2 Meclofenamate sodium 100 mg (A) versus Meclofenamate sodium 200 mg (B)						
Hebertson 1986	8	41	8	40	33.6%	0.98 [0.41 , 2.35]
Yonkeura 1987	14	55	16	55	66.4%	0.88 [0.47 , 1.61]
Subtotal (95% CI)		**96**		**95**	**100.0%**	**0.91 [0.55 , 1.50]**
Total events:	22		24			
Heterogeneity: $Chi^2 = 0.04$, df = 1 (P = 0.84); $I^2 = 0\%$						
Test for overall effect: Z = 0.37 (P = 0.71)						
4.4.3 Flurbiprofen 25 mg (A) versus Flurbiprofen 50 mg (B)						
Sunshine 1983a	1	32	0	29	100.0%	2.73 [0.12 , 64.42]
Subtotal (95% CI)		**32**		**29**	**100.0%**	**2.73 [0.12 , 64.42]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.62 (P = 0.53)						
4.4.4 Flurbiprofen 25 mg (A) versus Flurbiprofen 100 mg (B)						
Sunshine 1983a	1	32	0	31	100.0%	2.91 [0.12 , 68.81]
Subtotal (95% CI)		**32**		**31**	**100.0%**	**2.91 [0.12 , 68.81]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.66 (P = 0.51)						
4.4.5 Flurbiprofen 50 mg (A) versus Flurbiprofen 100 mg (B)						
Sunshine 1983a	0	29	0	31		Not estimable
Subtotal (95% CI)		**29**		**31**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Test for subgroup differences: $Chi^2 = 1.43$, df = 3 (P = 0.70), $I^2 = 0\%$						



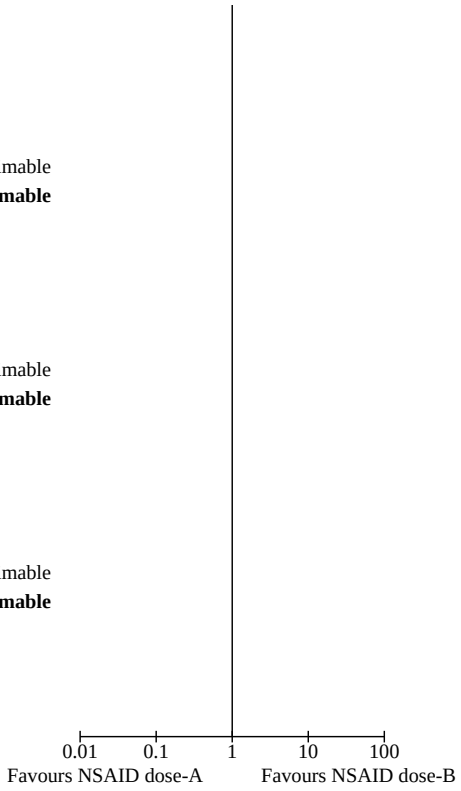
Analysis 4.5. Comparison 4: NSAID versus a different dose of the same NSAID, Outcome 5: Maternal drug adverse effects (6 hours after administration)

Study or Subgroup	NSAID dose-A Events	NSAID dose-A Total	NSAID dose-B Events	NSAID dose-B Total	Weight	Risk Ratio M-H, Fixed, 95% CI
4.5.1 Ibuprofen 300 mg (A) versus Ibuprofen 900 mg (B)						
Bloomfield 1974	3	20	3	20	100.0%	1.00 [0.23 , 4.37]
Subtotal (95% CI)		**20**		**20**	**100.0%**	**1.00 [0.23 , 4.37]**
Total events:	3		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.00 (P = 1.00)						
4.5.2 Diflunisal 125 mg (A) versus Diflunisal 250 mg (B)						
De Vroey 1978	0	33	0	30		Not estimable
Subtotal (95% CI)		**33**		**30**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
4.5.3 Diflunisal 125 mg (A) versus Diflunisal 500 mg (B)						
De Vroey 1978	0	33	0	30		Not estimable
Subtotal (95% CI)		**33**		**30**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
4.5.4 Diflunisal 250 mg (A) versus Diflunisal 500 mg (B)						
De Vroey 1978	0	30	0	30		Not estimable
Subtotal (95% CI)		**30**		**30**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
4.5.5 Ketoprofen 25 mg (A) versus Ketoprofen 50 mg (B)						
Olson 1999	0	28	0	26		Not estimable
Subtotal (95% CI)		**28**		**26**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
4.5.6 Aceclofenac 50 mg (A) versus Aceclofenac 100 mg (B)						
Honorato 1990	1	18	0	24	100.0%	3.95 [0.17 , 91.61]
Subtotal (95% CI)		**18**		**24**	**100.0%**	**3.95 [0.17 , 91.61]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.86 (P = 0.39)						
4.5.7 Aceclofenac 50 mg (A) versus Aceclofenac 150 mg (B)						
Honorato 1990	1	18	0	21	100.0%	3.47 [0.15 , 80.35]
Subtotal (95% CI)		**18**		**21**	**100.0%**	**3.47 [0.15 , 80.35]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.78 (P = 0.44)						
4.5.8 Aceclofenac 100 mg (A) versus Aceclofenac 150 mg (B)						
Honorato 1990	0	24	0	21		Not estimable
Subtotal (95% CI)		**24**		**21**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						



Analysis 4.5. (Continued)

Total events:	0		0		
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
4.5.9 Flurbiprofen 25 mg (A) versus Flurbiprofen 100 mg (B)					
Sunshine 1983a	0	32	0	29	Not estimable
Subtotal (95% CI)		**32**		**29**	**Not estimable**
Total events:	0		0		
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
4.5.10 Flurbiprofen 25 mg (A) versus Flurbiprofen 100 mg (B)					
Sunshine 1983a	0	32	0	31	Not estimable
Subtotal (95% CI)		**32**		**31**	**Not estimable**
Total events:	0		0		
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
4.5.11 Flurbiprofen 50 mg (A) versus Flurbiprofen 100 mg (B)					
Sunshine 1983a	0	29	0	31	Not estimable
Subtotal (95% CI)		**29**		**31**	**Not estimable**
Total events:	0		0		
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Test for subgroup differences: $Chi^2 = 0.93$, df = 2 (P = 0.63), $I^2 = 0\%$					



APPENDICES

Appendix 1. Search terms for ICTRP, ClinicalTrials.gov, OpenSIGLE and ProQuest Dissertations and Theses.

ICTRP

(searched with synonyms and each line was searched separately)

perine* AND pain AND postpartum

perine* AND pain AND postnatal

pain AND episiotomy

ClinicalTrials.gov

Advanced search

Interventional Studies | episiotomy pain

Interventional Studies | perineal pain

pain | Interventional Studies | perineum

OpenSIGLE and ProQuest Dissertations and Theses

episiotomy OR (perineal OR perineum) AND (tear OR tears OR pain)

WHAT'S NEW

Date	Event	Description
9 December 2019	New search has been performed	Search updated and 3 new studies assessed for inclusion.
9 December 2019	New citation required but conclusions have not changed	No new studies incorporated. Seven studies previously excluded have been included in this update. Conclusions remain unchanged.

HISTORY

Protocol first published: Issue 10, 2014
Review first published: Issue 7, 2016

Date	Event	Description
22 October 2016	Amended	Correction of a typographical error in the plain language summary.

CONTRIBUTIONS OF AUTHORS

F Wuytack drafted the protocol and is guarantor for the review.
F Wuytack and V Smith conducted the study selection, data extraction and 'Risk of bias' assessment.
F Wuytack, V Smith and B Cleary conceptualised the data analysis.
F Wuytack entered data into RevMan, performed the analysis and drafted the manuscript.
F Wuytack, V Smith and B Cleary reviewed the review for intellectual content and interpretation of the data.
All authors read and commented on the final draft of the manuscript prior to submission.

DECLARATIONS OF INTEREST

Francesca Wuytack: has received a Cochrane Fellowship (2013 - 2015), awarded by the Health Research Board Ireland, to support the conduct of this review.

Valerie Smith has acted in the capacity of Ms Wuytack's supervisor and principal investigator (PI) on the Cochrane HRB Fellowship grant application. The awarded grant is not salary or such support, but rather support for Dr Wuytack to attend Cochrane training workshops and other necessary consumables.

Brian J Cleary's institution has received EUR 500 from the State Claims Agency for a lecture that he gave about the historical context of the development and marketing of thalidomide in Ireland to a mediation process between the Irish state and survivors of the Thalidomide disaster. A sum of EUR 1500 was also paid to his institution (by Ferring Pharmaceuticals) for training provided to private-sector pharmacies and an infertility clinic on the use of a specialised drug delivery system used to delivery an infertility treatment from Ferring (Lutrelef). Brian's brother works for a drug company that sells analgesic products (Grunenthal). However Brian's institution does not currently use their products for the management of peripartum pain and their products are irrelevant to the content of this review. Brian has been publicly critical of Grunenthal and their historical actions in the context of the thalidomide disaster.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- Health Research Board, Ireland

  A Health Research Board, Ireland, Cochrane Fellowship was awarded to F Wuytack to support the conduct of this review (2016 update).

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We have used GRADE to assess the certainty of the body of the evidence and produced Summary of findings 1 and Summary of findings 2. This was not prespecified in our protocol (Wuytack 2014).

INDEX TERMS

Medical Subject Headings (MeSH)

Acetaminophen [administration & dosage]; Administration, Oral; Analgesia; Analgesics, Non-Narcotic [administration & dosage]; Anti-Inflammatory Agents, Non-Steroidal [*administration & dosage] [adverse effects]; Neuralgia [*drug therapy]; Perineum [*injuries]; *Postpartum Period; Randomized Controlled Trials as Topic; Time Factors

MeSH check words

Female; Humans; Pregnancy