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Nonsteroidal anti-inflammatory drugs (NSAIDs) and non-opioids for acute renal colic (Review)

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Nonsteroidal anti-inflammatory drugs (NSAIDs) and non-opioids for acute renal colic.
Cochrane Database of Systematic Reviews 2015, Issue 6. Art. No.: CD006027.
DOI: 10.1002/14651858.CD006027.pub2.

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TABLE OF CONTENTS

[Intervention Review]

Nonsteroidal anti-inflammatory drugs (NSAIDs) and non-opioids for acute renal colic

Kourosh Afshar[1], Siavash Jafari[2], Andrew J Marks[3], Arash Eftekhari[4], Andrew E MacNeily[3]

[1]Department of Urology, University of British Columbia, British Columbia's Children's Hospital, Vancouver, Canada. [2]School of Population and Public Health, University of British Columbia, Vancouver, Canada. [3]Department of Urology, University of British Columbia, Vancouver, Canada. [4]University of British Columbia, Vancouver, Canada

Contact: Kourosh Afshar, Department of Urology, University of British Columbia, British Columbia's Children's Hospital, Children's Ambulatory Care Building, Urology Clinic, K0-134, 4480 Oak Street, Vancouver, BC, V6H 3V4, Canada. kafshar@cw.bc.ca.

Editorial group: Cochrane Kidney and Transplant Group.
Publication status and date: New, published in Issue 6, 2015.

Citation: Afshar K, Jafari S, Marks AJ, Eftekhari A, MacNeily AE. Nonsteroidal anti-inflammatory drugs (NSAIDs) and non-opioids for acute renal colic. *Cochrane Database of Systematic Reviews* 2015, Issue 6. Art. No.: CD006027. DOI: 10.1002/14651858.CD006027.pub2.

ABSTRACT

Background

Renal colic is acute pain caused by urinary stones. The prevalence of urinary stones is between 10% and 15% in the United States, making renal colic one of the common reasons for urgent urological care. The pain is usually severe and the first step in the management is adequate analgesia. Many different classes of medications have been used in this regard including non-steroidal anti-inflammatory drugs and narcotics.

Objectives

The aim of this review was to assess benefits and harms of different NSAIDs and non-opioids in the treatment of adult patients with acute renal colic and if possible to determine which medication (or class of medications) are more appropriate for this purpose. Clinically relevant outcomes such as efficacy of pain relief, time to pain relief, recurrence of pain, need for rescue medication and side effects were explored.

Search methods

We searched the Cochrane Renal Group's Specialised Register (to 27 November 2014) through contact with the Trials' Search Co-ordinator using search terms relevant to this review.

Selection criteria

Only randomised or quasi randomised studies were included. Other inclusion criteria included adult patients with a clinical diagnosis of renal colic due to urolithiasis, at least one treatment arm included a non-narcotic analgesic compared to placebo or another non-narcotic drug, and reporting of pain outcome or medication adverse effect. Patient-rated pain by a validated tool, time to relief, need for rescue medication and pain recurrence constituted the outcomes of interest. Any adverse effects (minor or major) reported in the studies were included.

Data collection and analysis

Abstracts were reviewed by at least two authors independently. Papers meeting the inclusion criteria were fully reviewed and relevant data were recorded in a standardized Cochrane Renal Group data collection form. For dichotomous outcomes relative risks and 95% confidence intervals were calculated. For continuous outcomes the weighted mean difference was estimated. Both fixed and random models were used for meta-analysis. We assessed the analgesic effects using four different outcome variables: patient-reported pain relief using a visual analogue scale (VAS); proportion of patients with at least 50% reduction in pain; need for rescue medication; and pain recurrence. Heterogeneity was assessed using the I^2 test.

Main results

A total of 50 studies (5734 participants) were included in this review and 37 studies (4483 participants) contributed to our meta-analyses. Selection bias was low in 34% of the studies or unclear in 66%; performance bias was low in 74%, high in 14% and unclear in 12%; attrition bias was low in 82% and high in 18%; selective reporting bias low in 92% of the studies; and other biases (industry funding) was high in 4%, unclear in 18% and low in 78%.

Patient-reported pain (VAS) results varied widely with high heterogeneity observed. For those comparisons which could be pooled we observed the following: NSAIDs significantly reduced pain compared to antispasmodics (5 studies, 303 participants: MD -12.97, 95% CI -21.80 to - 4.14; I^2 = 74%) and combination therapy of NSAIDs plus antispasmodics was significantly more effective in pain control than NSAID alone (2 studies, 310 participants: MD -1.99, 95% CI -2.58 to -1.40; I^2 = 0%).

NSAIDs were significantly more effective than placebo in reducing pain by 50% within the first hour (3 studies, 197 participants: RR 2.28, 95% CI 1.47 to 3.51; I^2 = 15%). Indomethacin was found to be less effective than other NSAIDs (4 studies, 412 participants: RR 1.27, 95% CI 1.01 to 1.60; I^2 = 55%). NSAIDs were significantly more effective than hyoscine in pain reduction (5 comparisons, 196 participants: RR 2.44, 95% CI 1.61 to 3.70; I^2 = 28%). The combination of NSAIDs and antispasmodics was not superior to NSAIDs only (9 comparisons, 906 participants: RR 1.00, 95% CI 0.89 to 1.13; I^2 = 59%). The results were mixed when NSAIDs were compared to other non-opioid medications.

When the need for rescue medication was evaluated, Patients receiving NSAIDs were significantly less likely to require rescue medicine than those receiving placebo (4 comparisons, 180 participants: RR 0.35, 95% CI 0.20 to 0.60; I^2 = 24%) and NSAIDs were more effective than antispasmodics (4 studies, 299 participants: RR 0.34, 95% CI 0.14 to 0.84; I^2 = 65%). Combination of NSAIDs and antispasmodics was not superior to NSAIDs (7 comparisons, 589 participants: RR 0.99, 95% CI 0.62 to 1.57; I^2 = 10%). Indomethacin was less effective than other NSAIDs (4 studies, 517 participants: RR 1.36, 95% CI 0.96 to 1.94; I^2 = 14%) except for lysine acetyl salicylate (RR 0.15, 95% CI 0.04 to 0.65).

Pain recurrence was reported by only three studies which could not be pooled: a higher proportion of patients treated with 75 mg diclofenac (IM) showed pain recurrence in the first 24 hours of follow-up compared to those treated with 40 mg piroxicam (IM) (60 participants: RR 0.05, 95% CI 0.00 to 0.81); no significant difference in pain recurrence at 72 hours was observed between piroxicam plus phloroglucinol and piroxicam plus placebo groups (253 participants: RR 2.52, 95% CI 0.15 to12.75); and there was no significant difference in pain recurrence within 72 hours of discharge between IM piroxicam and IV paracetamol (82 participants: RR 1.00, 95% CI 0.65 to 1.54).

Side effects were presented inconsistently, but no major events were reported.

Authors' conclusions

Although due to variability in studies (inclusion criteria, outcome variables and interventions) and the evidence is not of highest quality, we still believe that NSAIDs are an effective treatment for renal colic when compared to placebo or antispasmodics. The addition of antispasmodics to NSAIDS does not result in better pain control. Data on other types of non-opioid, non-NSAID medication was scarce.

Major adverse effects are not reported in the literature for the use of NSAIDs for treatment of renal colic.

PLAIN LANGUAGE SUMMARY

Nonsteroidal anti-inflammatory drugs are effective treatment for acute renal colic

Acute renal colic is the pain caused by the blockage of urine flow secondary to urinary stones. The prevalence of kidney stone is thought to be between 2% to 3%, and the incidence has been increasing in recent years due to changes in diet and lifestyle. The renal colic pain is usually a sudden intense pain located in the flank or abdominal areas. This usually happens when a urinary stone blocks the ureter (the tube connecting the kidneys to the bladder). Different types of pain killers are used to ease the discomfort. Nonsteroidal anti-inflammatory drugs (NSAIDs) and antispasmodics (treatment that suppresses muscle spasms) are used commonly to relieve pain and discomfort. This review aimed to assess the effectiveness of commonly used non-opioid pain killers in adult patients with acute renal colic pain. Fifty studies enrolling 5734 participants were included in this review. Treatments varied greatly and combining of studies was difficult. We found that overall NSAIDs were more effective than other non-opioid pain killers including antispasmodics for pain reduction and need for additional medication. We also found that the combining NSAIDs with antispasmodics did not increase the efficacy. No serious adverse effects were reported by any of the included studies.

BACKGROUND

Description of the condition

Renal or ureteric colic is a symptom complex that is characteristic for the presence of obstructing urinary tract calculi. Urolithiasis is a relatively common disease and its incidence and prevalence is increasing worldwide due to lifestyle and dietary factors. The prevalence of urolithiasis is estimated at between 10% and 15% in the United States (Pearle 2012). Caucasian males are more likely to develop urinary calculi (Menon 2002).The symptoms include flank or abdominal pain radiating to the groin or genitalia. The central factors in the pathogenesis of renal colic are obstruction of the urinary flow and increased pressure proximal to the point of blockage. The increasing pressure stimulates the synthesis and release of prostaglandins. Prostaglandins promote vasodilation and increased urine output leading to higher pressure inside the collecting system. Renal colic pain is typically intense. Nausea and vomiting are common. Although most calculi pass spontaneously and do not need surgical intervention, during this period patients may suffer from severe pain. Therefore, satisfactory analgesia is of paramount importance in their management.

Description of the intervention

A wide range of drugs (opioids and non-opioids) are used to treat pain and discomfort in patients with acute renal colic. The non-opioid drugs include but not limited to: NSAIDs (nonsteroidal anti-inflammatory drugs), antispasmodics, acetaminophen, calcium channel blockers and desmopressin. NSAIDs are commonly used as standard analgesics and opioids are used as rescue medications for acute renal colic. These two groups of medications have been compared in a previous review (Holdgate 2005a). In this present study we compared the analgesic effects of non-opioids for acute renal colic. NSAIDs mainly work by inhibiting the cyclooxygenase enzyme which induces a subsequent inhibition in prostaglandin synthesis (Vane 1971). Antispasmodic medications are sometimes used alone or in combination with other analgesics for treatment of acute renal colic and work by inducing smooth muscle relaxation in urinary tract. Acetaminophen which is a non-salicylate with weak anti-inflammatory potency is thought to work by inhibition of a third isoform of cyclooxygenase (COX-3) (Chandrasekharan 2002).

How the intervention might work

During the initial phase of obstruction glomerular vasodilation leads to increase urine output and further increase in intra-ureteral pressure. This in turn results in prostaglandin synthesis in the ureteral wall, contraction of smooth muscle and further pain. Thus, pain control may be aimed at inhibiting prostaglandin synthesis (prostaglandin inhibitors or non-steroidal anti-inflammatory drugs (NSAIDs)), reducing spastic ureteral contraction (antispasmodics) or diminishing the pain by intervening at the level of central nervous system (opioids) (Gulmi 2002).

Why it is important to do this review

A plethora of NSAIDs has been used for renal colic, belonging to different classes. In a systematic review by Holdgate 2005a, NSAIDs and opioids were both effective in the management of renal colic but there was higher risk of nausea and vomiting with opioids. There is no systematic review of the efficacy and side effects of these different agents or classes. In addition NSAIDs have not been compared to other non-opioid medications in terms of their efficacy and side effect profiles.

OBJECTIVES

The aim of this review was to assess benefits and harms of different NSAIDs and non-opioids in the treatment of adult patients with acute renal colic and if possible to determine which medication (or class of medications) are more appropriate for this purpose. Clinically relevant outcomes such as efficacy of pain relief, time to pain relief, recurrence of pain, need for rescue medication and side effects were explored.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised controlled trials (RCTs) and quasi-RCTs (RCTs in which allocation to treatment was obtained by alternation, use of alternate medical records, date of birth or other predictable methods) looking at the effect of NSAIDs and non-opioids (including calcium channel blockers and desmopressin) in the management of acute renal colic were included. The first period of randomised cross-over studies were also be included.

Types of participants

Inclusion criteria

Adults (> 16 years) with acute onset (< 48 hours) of clinically diagnosed renal colic due to urinary stones requiring treatment for pain.

Types of interventions

- NSAIDs versus placebo
- NSAID versus NSAID
- NSAIDs versus non-opioids (e.g. antispasmodics)
- Non-opioids (other than NSAIDs) versus placebo
- Non-opioid versus non-opioid (other than NSAIDs)

Any dosage, frequency, duration and route of administration were included.

Types of outcome measures

Studies with at least one of the following outcomes were included.

- Patient rated pain by a validated tool
- Time to relief
- Need for rescue medication
- Pain recurrence
- Major adverse event (e.g. gastrointestinal bleed, kidney dysfunction)
- Minor adverse event (e.g. gastrointestinal disturbances, dizziness)

Exclusion criteria

- Patients who had any contraindications to NSAIDs or other non-opioid drugs were excluded
- Any interventions including opioids

- Incomplete data precluding calculation or estimation of effect size.

Primary outcomes

- The primary objective of this review was to explore the analgesic efficacy of non-opioids medications commonly used to treat acute renal colic. The degree of pain relief achieved by study medications was explored and when possible different analgesics were compared. Therefore the primary outcome were:
  - Change in pain scores within the first hour
  - Proportion of patients with significant pain relief (see below)
- Proportion of patients who needed rescue medication (opioids, another type of analgesic medications or a second dose of the same study treatment) within 6 hours observation period
- Rate of pain recurrence

Secondary outcomes

- Medication side effects were explored as a secondary outcome.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Renal Group's Specialised Register (to 27 November 2014) through contact with the Trials' Search Co-ordinator using search terms relevant to this review. The Cochrane Renal Group's Specialised Register contains studies identified from the following sources.

1. Monthly searches of the Cochrane Central Register of Controlled Trials CENTRAL
2. Weekly searches of MEDLINE OVID SP
3. Handsearching of renal-related journals & the proceedings of major renal conferences
4. Searching of the current year of EMBASE OVID SP
5. Weekly current awareness alerts for selected renal-journals
6. Searches of the International Clinical Trials Register (ICTRP) Search Portal & ClinicalTrials.gov

Studies contained in the Specialised Register are identified through search strategies for CENTRAL, MEDLINE, and EMBASE based on the scope of the Cochrane Renal Group. Details of these strategies as well as a list of handsearched journals, conference proceedings and current awareness alerts are available in the 'Specialised Register' section of information about the Cochrane Renal Group.

See Appendix 1 for search terms used in strategies for this review.

Searching other resources

1. Reference lists of nephrology, urology and emergency medicine textbooks, review articles and relevant trials.
2. Letters seeking information about unpublished or incomplete trials to investigators known to be involved in previous trials.

Data collection and analysis

Selection of studies

The search strategy described was used to obtain titles and abstracts of studies that may be relevant to the review. The titles and abstracts was screened independently by two authors, who discarded studies that were not applicable, however studies and reviews that included relevant data or information on trials were retained initially. Two authors independently assessed retrieved abstracts and, if necessary the full text, of these studies to determine which studies satisfied the inclusion criteria.

Data extraction and management

Data extraction was carried out by the same reviewers independently using standard data extraction forms. Studies reported in non-English language journals were translated before assessment. Where more than one publication of one trial existed, only the publication with the most complete data was included. Disagreements were resolved in consultation with a third author.

Two authors independently carried out data abstraction and quality assessments. Again, a consensus meeting was held with all authors to agree on the assessments for each included study.

Assessment of risk of bias in included studies

The following items were independently assessed by two authors using the risk of bias assessment tool (Higgins 2011) (*see* Appendix 2).

- Was there adequate sequence generation (selection bias)?
- Was allocation adequately concealed (selection bias)?
- Was knowledge of the allocated interventions adequately prevented during the study?
  - Participants and personnel (performance bias)
  - Outcome assessors (detection bias)
- Were incomplete outcome data adequately addressed (attrition bias)?
- Are reports of the study free of suggestion of selective outcome reporting (reporting bias)?
- Was the study apparently free of other problems that could put it at a risk of bias?

We also used funnel plots to assess publication bias, whenever the number of included studies allowed.

Measures of treatment effect

For dichotomous outcomes results were expressed as relative risk (RR) with 95% confidence intervals (95% CI). Data was pooled using the random effects model. Where continuous scales of measurement were used to assess the effects of treatment (patient-rated pain scores, time to pain relief), the mean difference (MD) was used. When different scales were used and adequate data was not available to calculate standardized mean difference, we classified the findings into two categories: reduction in pain score more than 50% and less than 50%. Need for rescue medication and pain recurrence were treated as dichotomous outcomes.

Assessment of heterogeneity

Heterogeneity was analysed using a Chi^2 test on N-1 degrees of freedom, with an alpha of 0.05 used for statistical significance and with the I^2 test (Higgins 2003). I^2 values of 25%, 50% and 75% correspond to low, medium and high levels of heterogeneity. Heterogeneity among participants could be related to age and the pathology (e.g. size and location of stone). Heterogeneity in treatments could be related to prior agent(s) used and the agent, mode of administration dose and duration of therapy. Variability

in timing of post intervention assessment is another source of heterogeneity.

Data synthesis

VAS-100 mm (Visual Analogue Scale), VAS-10 cm, or total pain relief at the beginning of the study and at different time points during the study periods were collected. When the number or proportion of patients with at least 50% pain relief (dichotomous data) were available this was extracted. TOTPAR (total pain relief) or SPID (summed pain intensity difference) at the enrolment at and over 15 to 30 minutes, one to two hours, and six hours or sufficient data to allow their calculation were extracted.

A global rating of the effect of a single dose of study medication was extracted when no other information was available. Patient's global evaluation using a standard 3-point scale (no relief, partial relief, complete relief) or 2-point scale (complete to moderate relief, mild or no pain relief) was collected, and dichotomous information was extracted for each category. Information from the top two categories of the patient global rating has been shown to produce very similar estimates of analgesic efficacy to information from standard pain relief and pain intensity measurement scales (Collins 2001). Data on complete pain relief in 3-point scale and complete or to moderate relief in the 2-point scale was used for the purpose of this analysis. Weighted means (by inverse of variance) were calculated.

Subgroup analysis and investigation of heterogeneity

Subgroup analysis was conducted to compare NSAIDs to non-NSAIDs, placebo, antispasmodics, and a combination of antispasmodics and NSAIDs. We also conducted subgroup analysis to compare different NSAIDs when adequate data was available.

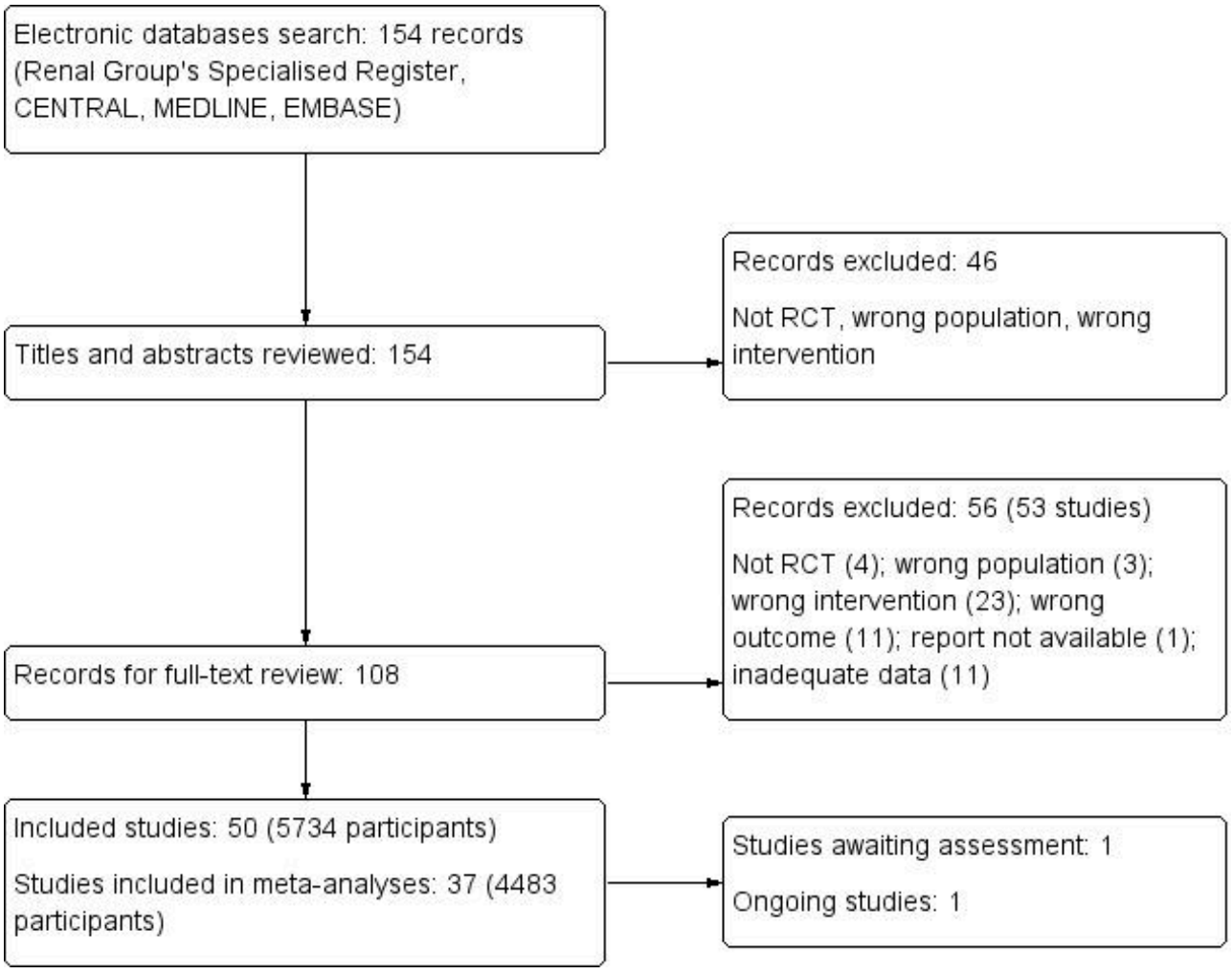
RESULTS

Description of studies

Results of the search

The initial review of the literature revealed 108 relevant records of which 56 (53 studies) were excluded upon further review. One study is awaiting classification (Tanko 1996) and there is one ongoing study (NCT01543165) (Figure 1). A total of 50 studies (5734 participants) were included in this review and 37 studies (4483 participants) contributed to our meta-analyses.

Figure 1. Flow chart showing study selection procedure



Included studies

Twenty three studies assessed intramuscular (IM) NSAIDs, given alone or in combination with other treatments and provided uncontaminated single dose data (Al Waili 1999; Arnau 1991; Boubaker 2010; Cohen 1998; Dash 2012; Ergene 2001; Fraga 2003; Grissa 2011; Kumar 2011; Laerum 1996; Lopes 2001; Lundstam 1980; Lupi 1986; Marthak 1991; Miralles 1987; Mora Durban 1995; Quilez 1983; Sanahuja 1990; Snir 2008; Stein 1996; Sanchez-Carpena 2007; Vignoni 1983; Walden 1993).

Eighteen studies assessed intravenous (IV) NSAIDs, given alone or in combination with other treatments and provided uncontaminated single dose data (al-Sahlawi 1996; Benyajati 1986; el-Sherif 1990; Galassi 1983; Glina 2011; Holmlund 1978; Jones 1998, Kekec 2000; Lehtonen 1983; Lloret 1987; Magrini 1984; Martin Carrasco 1993; Muriel 1993; Muriel-Villoria 1995; Pavlik 2004; Pellegrino 1999; Sanchez-Carpena 2003; Stankov 1994).

One study (Supervia 1998) assessed mucosal (sublingual) NSAIDs, given alone or in combination with other treatments and provided uncontaminated single dose data.

One study compared the oral effect of diclofenac (150 mg) to baralgan (Indudhara 1990), and one study compared oral diclofenac plus antispasmodics with oral baralgan (Chaudhary 1999).

In one study a bolus followed by continuous infusion of glucagon was compared with a placebo (Bahn Zobbe 1986).

Three studies assessed antispasmodics. Miano 1986 compare IV tyropramide with butylscopolamine; Romics 2003 compared IV drotaverine to placebo; and Iguchi 2002 compared butylscopolamine with local lidocaine.

One study (Kheirollahi 2010) compared intramuscular hyoscine-N-butylbromide given alone or in combination with intranasal desmopressin.

A number of studies allowed patients to receive a second dose of the medication within the observation period (e.g. after 30 minutes if adequate pain relief was not achieved). For these studies we extracted single dose information collected before the second dose was given.

Four studies reported 4-point VAS scores (Cohen 1998; Martin Carrasco 1993; Sanchez-Carpena 2003; Stein 1996); 18 studies reported mean (SD) VAS-10 (cm) scores (Al Waili 1999; Arnau 1991; Benyajati 1986; el-Sherif 1990; Ergene 2001; Galassi 1983; Kheirollahi 2010; Laerum 1996; Lopes 2001; Magrini 1984; Marthak 1991; Muriel-Villoria 1995; Pavlik 2004; Pellegrino 1999; Sanahuja 1990; Stankov 1994; Snir 2008; Supervia 1998).

Eighteen studies reported mean (SD) VAS-100 (mm) before or after treatment or both (Boubaker 2010; Chaudhary 1999; Dash 2012; Fraga 2003; Glina 2011; Grissa 2011; Iguchi 2002; Jones 1998; Kekec 2000; Kheirollahi 2010; Kumar 2011; Lloret 1987; Lundstam 1980; Martin Carrasco 1993; Miralles 1987; Romics 2003; Sanchez-Carpena 2007; Vignoni 1983). Walden 1993 reported median (95% CI) VAS-100. Lupi 1986 used Analogue Chromatic Continuous Scale (ACCS) for evaluating pain intensity and also reported the proportion of patients with a 50% pain reduction.

Indudhara 1990 used the 5-point verbal rating scale (VRS-5) and Miano 1986 used the Keele-Dundee scale.

It was not possible to calculate a pooled estimate of improvement in VAS score of participants in treatment groups because of inconsistency in reporting the data among studies. The time to assess patients varied from five minutes to several hours. To overcome this problem we only assessed and combined data for pain control within the first 60 minutes. This timing was uniformly reported and is clinically more relevant in the treatment of an acute pain. Eleven studies used an ordinal outcome measure (al-Sahlawi 1996; Bahn Zobbe 1986; el-Sherif 1990; Indudhara 1990; Kheirollahi 2010; Lehtonen 1983; Lloret 1987; Marthak 1991; Mora Durban 1995; Quilez 1983; Sanahuja 1990) and two studies had a binary outcome (Benyajati 1986; Holmlund 1978).

Excluded studies

We were not able to locate one study (Al-Faddagh 1996); Wandschneider 1973 assessed the effect of NSAIDs in urologic procedures; three studies (Altay 2007; Ho 2004; Nissen1990) assessed the same type of NSAIDs that were used by different routes in study arms; and eight studies did not provide adequate data (Bilora 2000; Breijo 2007; Catano 2004; Julian 1992; Pardo 1984; Phillips 2009; Roshani 2010; Timbal 1981). Four studies were not randomised (Al-Obadi 1997; Basar 1991; El-Sherif 1995; Ruiz 1988); sample size was very small (4) in one study (Godoy 2000); and medications were used as prophylaxis not treatment in one study (Cole 1989). The outcome of interest was stone expulsion in eight studies (Bach 1983; Dellabella 2003; Dellabella 2005; Engelstein 1992; Porpiglia 2000; Porpiglia 2004; Muller 1990; Yilmaz 2005). In 18 studies narcotics were used (Bergus 1996; Cordell 1996; Curry 1995; Elliott 1979; Hazhir 2010; Henry 1987; Kapoor 1989; Khalifa 1986; Lishner 1985; Lundstam 1982; Muller 1990; NCT00646061; NCT01339624; Oosterlinck 1982; Persson 1985; Primus 1989; Soleimanpour 2012; Viksmoen 1986). Reported data for three studies could not be used in the analysis (Galassi 1985; Grenabo 1984; Mortelmans 2006). Mortelmans 2006 evaluated the effect of antispasmodics to placebo and Yencilek 2008 compared IV papaverine to IV hyoscine-N-butylbromide; however all the patients received NSAIDs and antispasmodics at the beginning of the study. In Holdgate 2005 all participants received narcotics. One study was excluded for inappropriate use of VAS (Sala-Mateus 1989). One study only included patients with recurrent renal colic (Laerum 1995) and one study (Ohkawa 1997) evaluated the outcome before and at one, three and seven days after treatment. One study (Ayan 2013) was excluded as it compared adding an alternative medicine product (aromatherapy with essential rose oil) to the conventional therapy.

Ongoing studies

One study has been completed but as yet there are no published data (NCT01543165).

Studies awaiting classification

One study (Tanko 1996) is awaiting classification as it has yet to be translated.

Risk of bias in included studies

Our risk of bias assessment can be seen in Figure 2 and Figure 3.

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

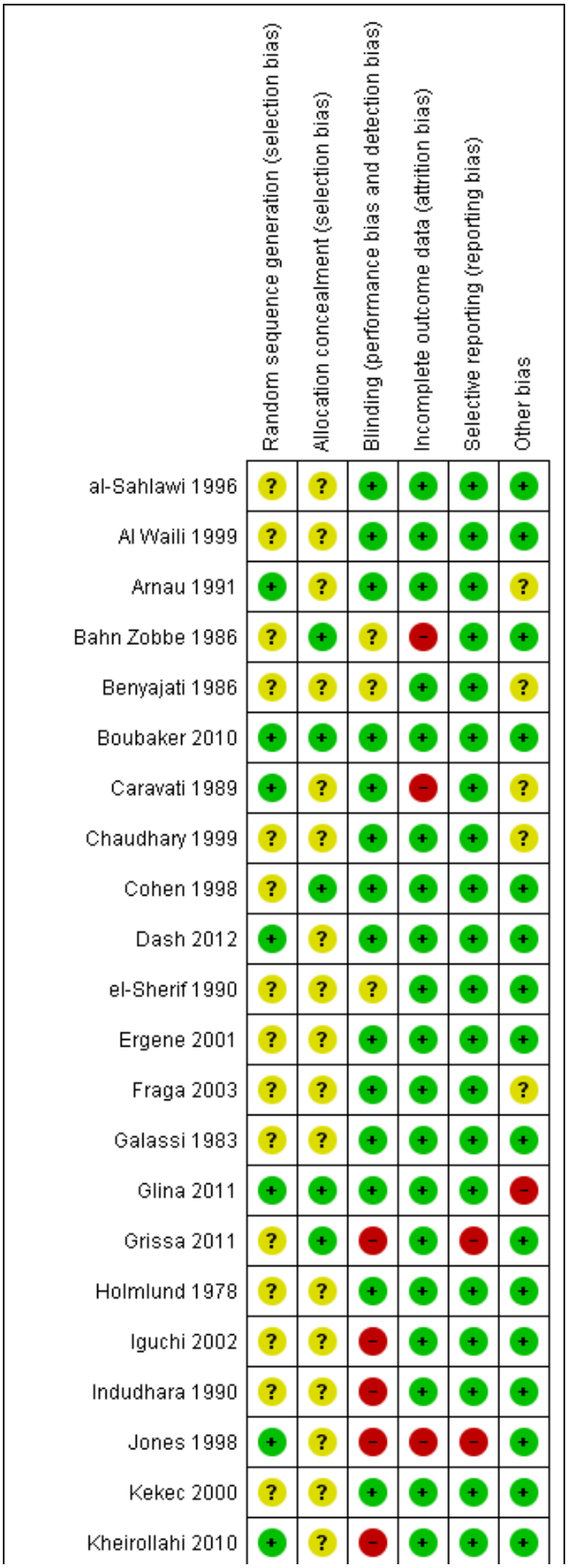


Figure 2. (Continued)

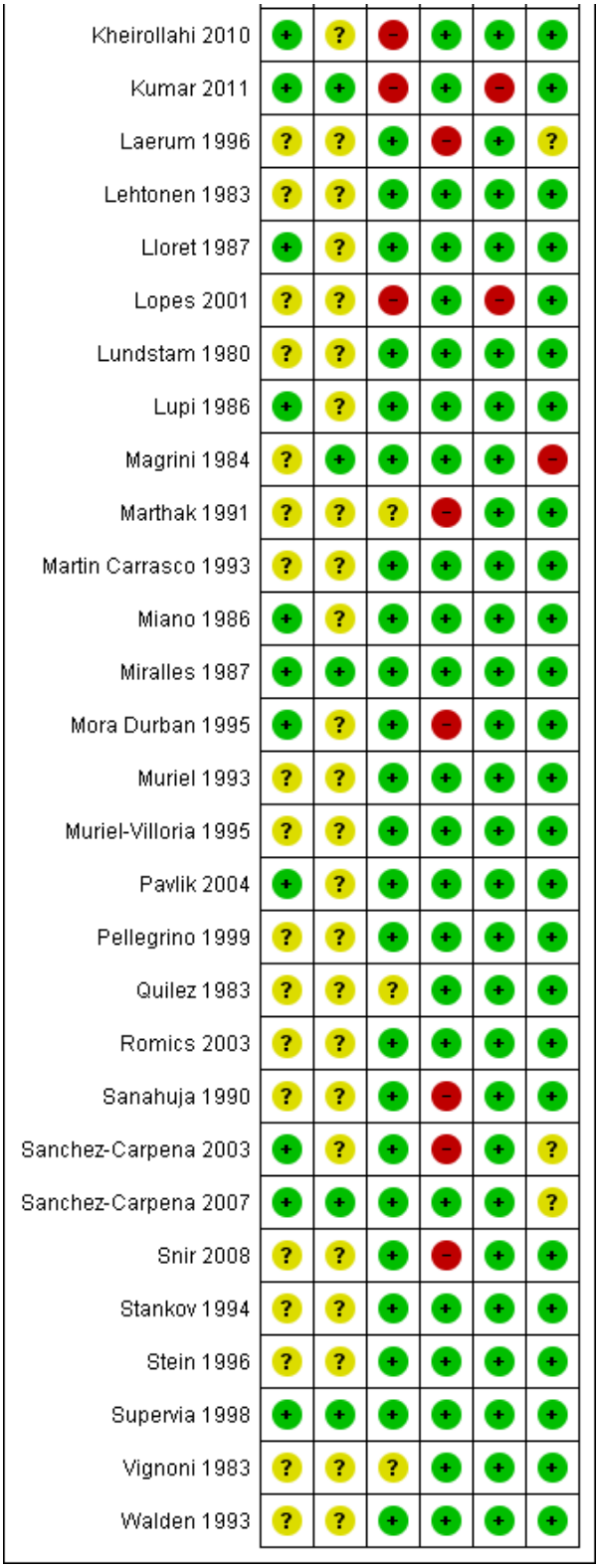
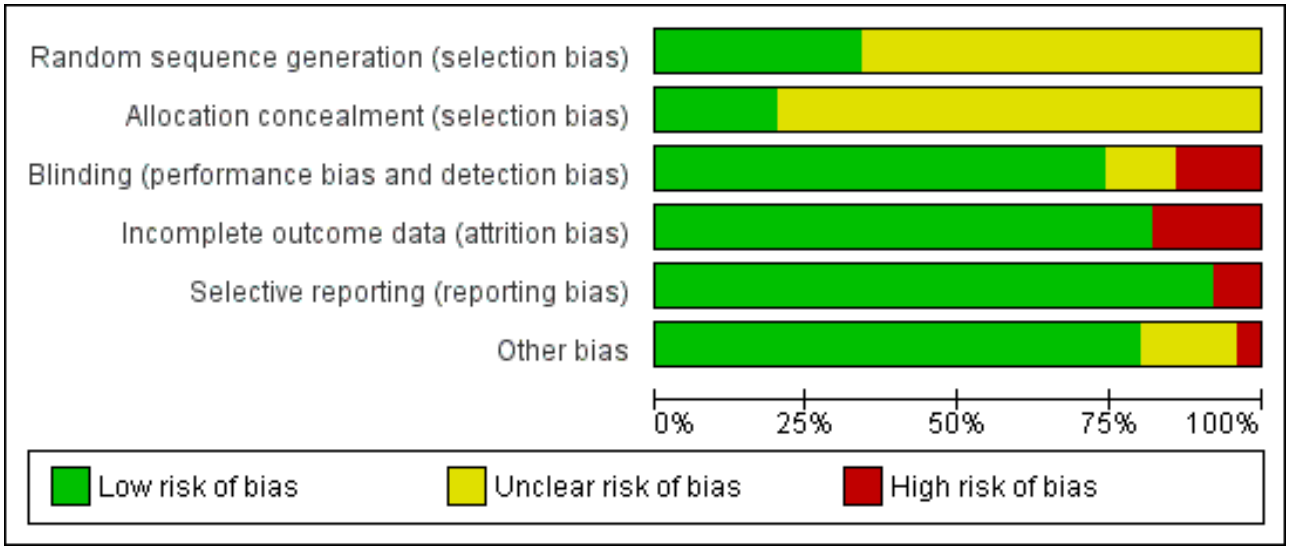


Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Allocation

Sequence generation

Seventeen studies had adequate sequence generation (Arnau 1991; Boubaker 2010; Caravati 1989; Dash 2012; Glina 2011; Jones 1998; Kheirollahi 2010; Kumar 2011; Lloret 1987; Lupi 1986; Miano 1986; Miralles 1987; Mora Durban 1995; Pavlik 2004; Sanchez-Carpena 2003; Sanchez-Carpena 2007; Supervia 1998). The sequence generation was unclear in the remaining 33 studies.

Allocation concealment

Allocation concealment was determined to be adequate in only 10 studies (Bahn Zobbe 1986; Boubaker 2010; Cohen 1998; Glina 2011; Grissa 2011; Kumar 2011; Magrini 1984; Miralles 1987; Sanchez-Carpena 2007; Supervia 1998), allocation concealment was unclear in the remaining 40 studies.

Blinding

Thirty seven studies had adequate blinding (al-Sahlawi 1996; Al Waili 1999; Arnau 1991; Boubaker 2010; Caravati 1989; Chaudhary 1999; Cohen 1998; Dash 2012; Ergene 2001; Fraga 2003; Galassi 1983; Glina 2011; Holmlund 1978; Kekec 2000; Laerum 1996; Lehtonen 1983; Lloret 1987; Lundstam 1980; Lupi 1986; Magrini 1984; Martin Carrasco 1993; Miano 1986; Miralles 1987; Mora Durban 1995; Muriel 1993; Muriel-Villoria 1995; Pavlik 2004; Pellegrino 1999; Romics 2003; Sanahuja 1990; Sanchez-Carpena 2003; Sanchez-Carpena 2007; Snir 2008; Stankov 1994; Stein 1996; Supervia 1998; Walden 1993). Seven studies were not blinded (Grissa 2011; Iguchi 2002; Indudhara 1990; Jones 1998; Kheirollahi 2010; Kumar 2011; Lopes 2001) and six studies did not provide adequate information so it was unclear whether investigators, participants, or outcome assessors were blinded (Bahn Zobbe 1986; Benyajati 1986; el-Sherif 1990; Marthak 1991; Quilez 1983; Vignoni 1983).

Incomplete outcome data

Forty one studies had complete outcome data. Risk for attrition bias was high in nine studies (Bahn Zobbe 1986; Caravati 1989; Jones 1998; Laerum 1996; Marthak 1991; Mora Durban 1995; Sanahuja 1990; Sanchez-Carpena 2003; Snir 2008).

Selective reporting

Forty six studies were free of reporting bias for the primary outcome. The primary outcomes were estimated when the subjects were still in the emergency department. Nevertheless there were issues with incomplete reporting or lack of SD in four studies (Grissa 2011; Jones 1998; Kumar 2011; Lopes 2001).

Other potential sources of bias

Publication bias was evaluated using funnel plots. It seems both negative and positive studies with small sample size are missing. This is evident in all subgroup analyses (Figure 4; Figure 5; Figure 6; Figure 7). Nine studies which were funded by pharmaceutical industries (Arnau 1991; Benyajati 1986; Caravati 1989; Chaudhary 1999; Fraga 2003; Glina 2011; Laerum 1996; Sanchez-Carpena 2003; Sanchez-Carpena 2007) could be considered at risk for bias. Two studies were judge to be at high risk of bias: two authors in Glina 2011 were employees of the funding pharmaceutical company; and the same method of diagnosis was not used in all patients in Magrini 1984. We did not identify any other sources of bias such as extreme imbalance in the groups or stoppage of incomplete study.

Figure 4. Funnel plot of comparison: 1 Pain score: VAS, outcome: 1.2 NSAID versus antispasmodic.

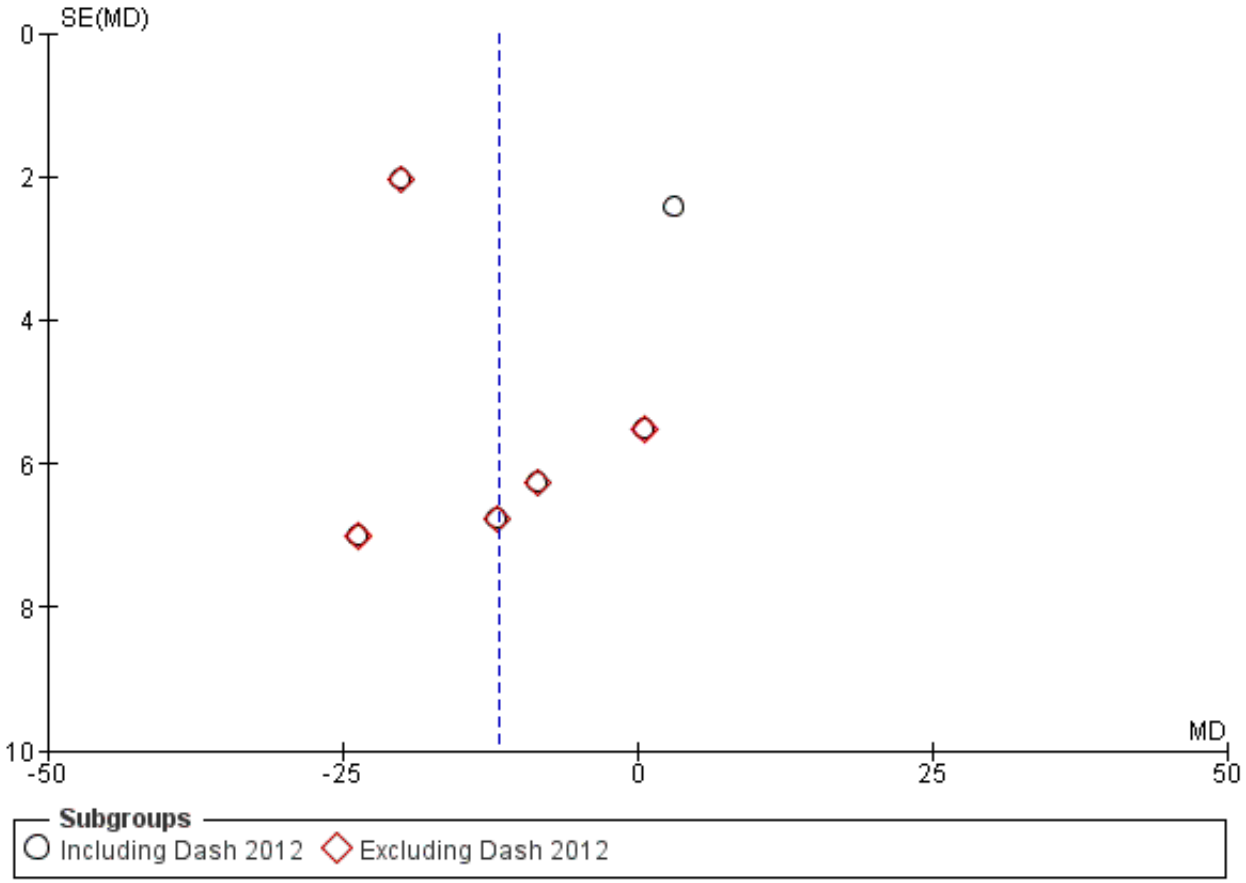


Figure 5. Funnel plot of comparison: 2 50% reduction in pain, outcome: 2.4 NSAID versus other non-opioid.

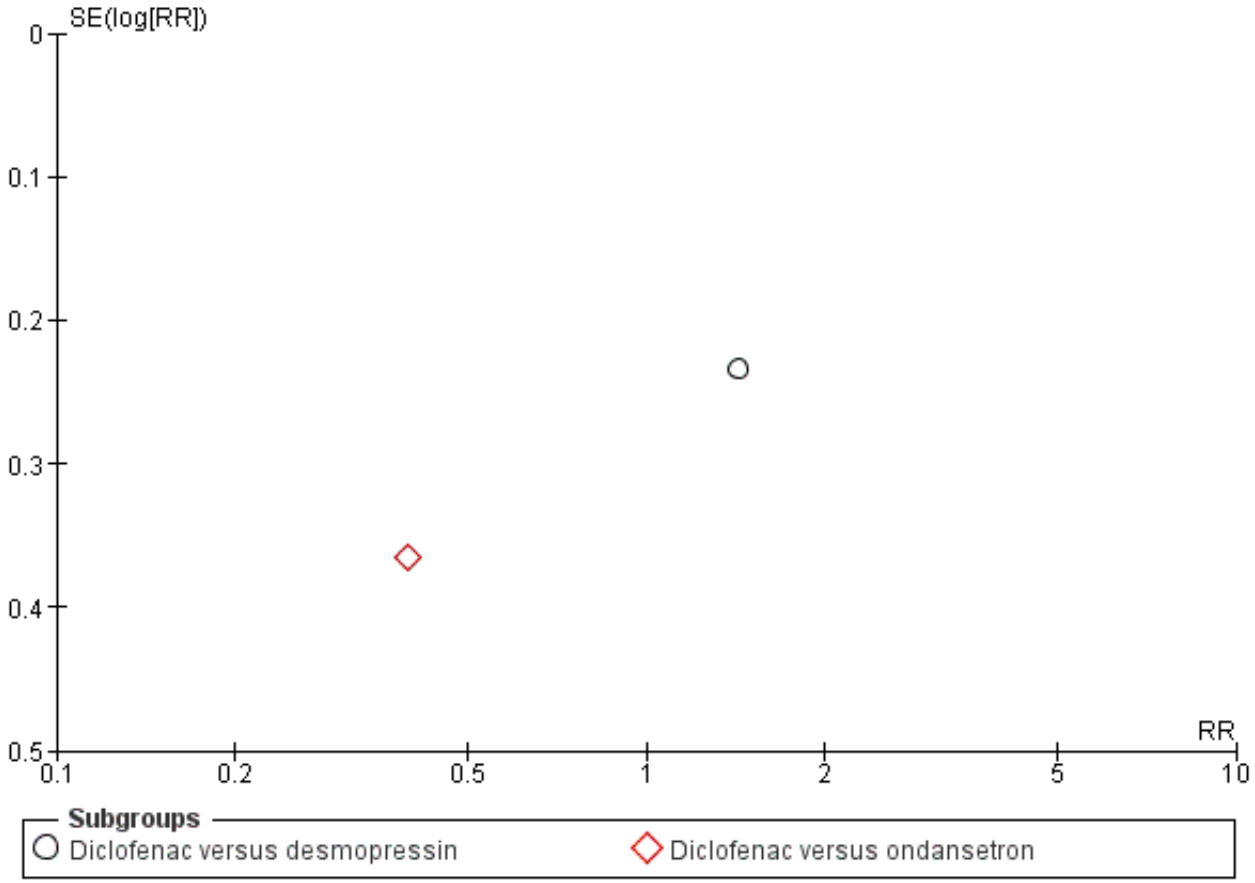


Figure 6. Funnel plot of comparison: 2 50% reduction in pain, outcome: 2.3 NSAID versus antispasmodic.

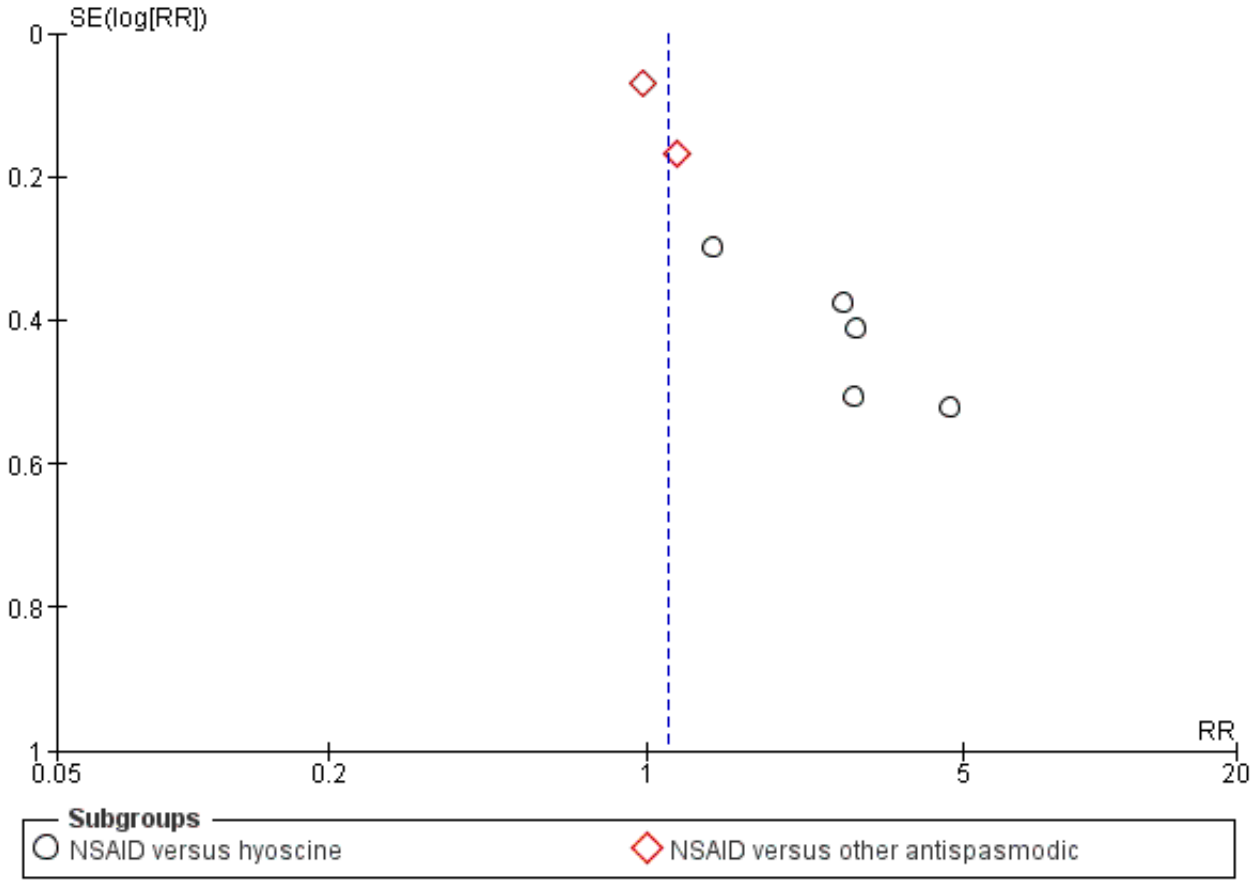
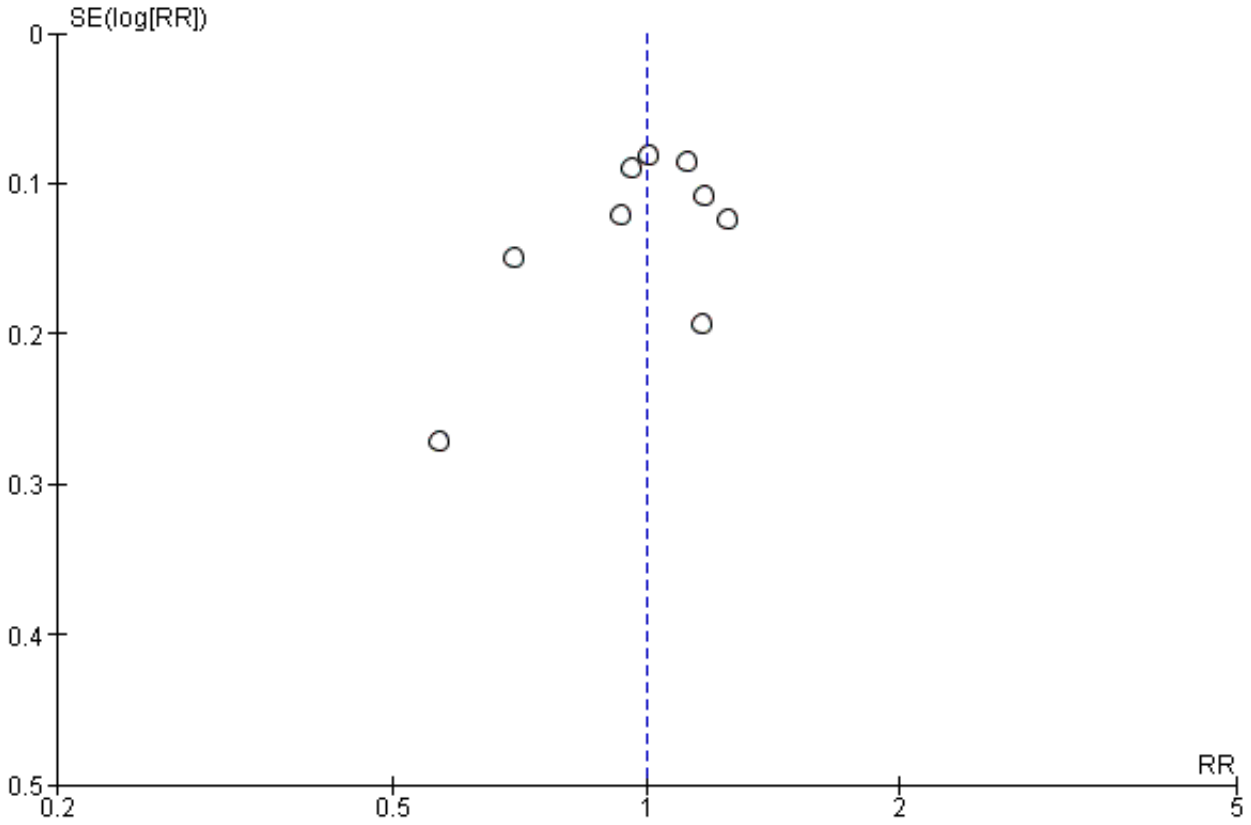


Figure 7. Funnel plot of comparison: 2 50% reduction in pain, outcome: 2.5 NSAID + antispasmodic versus NSAID.



Effects of interventions

Effects of intervention will be discussed based on the outcome reports in the studies, including changes in VAS, the proportion of patients with at least 50% reduction in pain within the first hour, and need for rescue medication.

Patient-reported pain score (VAS)

NSAID versus NSAID

Four studies compared NSAID to NSAID, however as the heterogeneity was very high when the studies were pooled (I^2 = 99%), we have reported the individual study results.

- Two studies (Miralles 1987; Muriel 1993) compared patient reported VAS in patients taking IM dipyrone or diclofenac and showed opposite effects.
  - Muriel 1993 reported that dipyrone (both 1g and 2 g doses) was significantly more effective than diclofenac in terms of pain relief in the first 60 minutes of treatment (Analysis 1.1.1 (1 g; 1 study, 84 participants): MD 2.00, 95% CI 0.48 to 3.52), Analysis 1.1.2 (2 g; 1 study, 86 participants): MD 13.00, 95% CI 11.49 to 14.51).
  - Miralles 1987 reported treatment with diclofenac significantly reduced pain in the first 30 minutes compared to 2 g dipyrone (Analysis 1.1.2 (1 study, 50 participants): MD -14.90; 95% CI -26.79 to -3.01).
- Laerum 1996 reported IM diclofenac significantly reduced pain compared to IV indomethacin (Analysis 1.1.3 (1 study, 83 participants): MD -2.00, 95% CI -2.43 to -1.57).
- Fraga 2003 found no significant difference in pain reduction between IM diclofenac sodium compared to IM etofenamate (Analysis 1.1.4 (1 study, 119 participants): MD -7.50, 95%CI -17.06 to 2.06).

NSAIDs versus antispasmodic

Six studies compared NSAIDs to antispasmodics and had adequate data to be included in the meta-analysis (Dash 2012; Ergene 2001; Jones 1998; Pavlik 2004; Snir 2008; Stankov 1994).

- Meta-analysis of these studies showed that NSAIDs were comparable to antispasmodic (Analysis 1.2.1 (6 studies, 403 participants): MD -9.83, 95% CI -20.93 to 1.28; I^2 = 92%). There was very significant heterogeneity. The major source of heterogeneity is likely the wide variety of antispasmodics used in the studies. By removing Dash 2012 which used drotaverine as an antispasmodic, heterogeneity was reduced and the result favours NSAIDs over antispasmodics (Analysis 1.2.2 (5 studies, 303 participants): MD -12.97, 95% CI -21.80 to - 4.14; I^2 = 74%).

NSAID versus non-opioid

Two studies compared 40 mg intranasal desmopressin with 75 mg diclofenac (IM) (Kumar 2011; Lopes 2001) and one study compared IM piroxicam to IV paracetamol (Grissa 2011). Due to the

high heterogeneity when pooled (I^2 = 98%) we have reported the individual study results.

- Kumar 2011 concluded that diclofenac was significantly more effective than intranasal desmopressin in relieving renal colic pain over period of 30 minutes (Analysis 1.3.1 (1 study, 48 participants): MD -32.71, 95% CI -39.38 to -26.04). Lopes 2001 however concluded that desmopressin was an effective analgesic after 10 minutes; but when compared to diclofenac the effect was less prominent after 30 minutes; SDs were not available from this study and could not be included in the meta-analysis.
- Grissa 2011 reported IV paracetamol was found to be more effective than IM piroxicam (Analysis 1.3.2 (1 study, 100 participants): MD 16.00, 95% CI 4.43 to 27.57).

NSAID plus antispasmodic versus NSAID alone

Two studies compared the combination of NSAIDs and antispasmodics to NSAIDs alone (Boubaker 2010; Snir 2008).

- The combination therapy was significantly more effective in pain control (Analysis 1.4 (2 studies, 310 participants): MD -1.99, 95% CI -2.58 to -1.40; I^2 = 0%) but the difference in the VAS was not clinically significant (Gallagher 2001; Todd 1996). Boubaker 2010 reported a very small variance in post treatment scores; therefore, the result of the combined analysis has been swayed toward this larger study.

Non-opioid versus placebo

- Caravati 1989 found no significant difference between nifedipine and placebo in pain control using VAS (Analysis 1.5 (1 study, 56 participants): MD -0.80, 95% CI -2.35 to 0.75).

Non-opioid versus non-opioid

- Miano 1986 used Keele-Dundee Scale with five prefixed degrees to evaluate pain and concluded that IV tiropramide 50 mg was significantly more effective than IV butylscopolamine bromide 20 mg at 60 minutes (P < 0.01).
- Kheirollahi 2010 compared IM hyoscine-N-butylbromide alone and in combination with Intranasal desmopressin showed the combination provided significantly better pain relief at 60 minutes post-treatment (Analysis 1.6 (1 study, 84 participants): MD -3.09, 95% CI --3.82 to -2.36).

50% reduction in pain

NSAID versus placebo

Three studies compared NSAIDs with placebo (Holmlund 1978; Lundstam 1980; Vignoni 1983). Holmlund 1978 compared IV indomethacin to placebo and Lundstam 1980 and Vignoni 1983 compared IM diclofenac to placebo.

- NSAIDs were significantly more effective than placebo in reducing pain by 50% in the first hour (Analysis 2.1 (3 studies, 197 participants): RR 2.28, 95% CI 1.47 to 3.51; I^2 = 15%).

NSAID versus NSAID

Sixteen studies comparing one NSAID to another (al-Sahlawi 1996; Al Waili 1999; Arnau 1991; Cohen 1998; el-Sherif 1990; Glina 2011; Laerum 1996; Lehtonen 1983; Lupi 1986; Muriel 1993; Muriel-Villoria 1995; Stein 1996; Supervia 1998; Sanchez-Carpena 2003; Sanchez-Carpena 2007; Walden 1993).

- Two studies (Arnau 1991;Muriel-Villoria 1995) compared 75 mg diclofenac (IM) with 1g dipyrone (IM). There was no significant difference between diclofenac and dipyrone (Analysis 2.2.1 (2 studies, 335 participants): RR 1.03, 95% CI 0.72 to 1.47; I^2 = 78%).
- Three studies (Arnau 1991;Miralles 1987;Muriel-Villoria 1995) compared 75 mg diclofenac (IM) with 2 g dipyrone (IM). There was no statistically significant difference between diclofenac and dipyrone (Analysis 2.2.2 (3 studies, 366 participants): RR 1.06, 95% CI 0.81 to 1.37; I^2 = 67%).
- Muriel-Villoria 1995 reported 2 g dipyrone (IV) was superior to 75 mg diclofenac (IM) in terms of pain reduction (Analysis 2.2.3 (1 study, 103 participants): RR 0.64, 95% CI 0.49 to 0.84). The authors also concluded that the analgesic effects of dipyrone appeared faster and lasted longer.
- Two studies (Al Waili 1999;Supervia 1998) compared diclofenac to piroxicam. There was no significant difference in 50% pain relief (Analysis 2.2.4 (2 studies, 144 participants): RR 0.94, 95% CI 0.81 to 1.09; I^2 = 0%).
- Walden 1993 reported there was no significance difference observed in pain reduction at 120 minutes post-treatment between diclofenac and ketoprofen (Analysis 2.4.5 (1 study, 86 participants): RR 1.01, 95% C: 0.88 to 1.16).
- Two studies compared dipyrone to dexketoprofen (Sanchez-Carpena 2003; Sanchez-Carpena 2007). Sanchez-Carpena 2003 compared 2 g dipyrone (IM) with two different doses of dexketoprofen (25 and 50 mg; IM) and Sanchez-Carpena 2007 compared the same dose dexketoprofen (IV) with 2 g dipyrone (IV).
  - There were no significant differences between 2 g dipyrone and 25 mg dexketoprofen (Analysis 2.2.6 (2 studies, 405 participants): RR 1.08, 95% CI 0.79 to 1.48; I^2 = 87%).
  - There were no significant differences between 2 g dipyrone and 50 mg dexketoprofen ((Analysis 2.2.7 (2 studies, 405 participants): RR 0.98, 95% CI 0.90 to 1.07; I^2 = 7%).
  - Combined, there was no significant difference between dipyrone and dexketoprofen (Analysis 2.2.8 (2 studies, 610 participants): RR 1.03, 95% CI 0.85 to 1.26; I^2 = 78%).
- Five studies compared indomethacin with other NSAIDs (al-Sahlawi 1996; el-Sherif 1990; Laerum 1996; Lehtonen 1983; Lupi 1986). Overall, indomethacin was found to be comparable to other NSAIDs (RR 1.13, 95% CI 0.83 to 1.54), however there was significant heterogeneity (I^2 = 83%). Subgroup analysis revealed that the source of heterogeneity was Lupi 1986 in which indomethacin (IM) was compared to pirprofen (IM). By removing this study indomethacin was found to be less effective than other NSAIDs (Analysis 2.2.9 (4 studies, 412 participants): RR 1.27, 95% CI 1.01 to 1.60; I^2 = 55%).
  - Lupi 1986 reported pirprofen was significantly more effective than indomethacin in reducing pain by 50% (Analysis 2.2.10 (1 study, 205 participants): RR 0.69, 95% CI 0.55 to 0.88).
- Glina 2011 reported no significant difference between 40 mg parecoxib (IV) and 100 mg ketoprofen (IV) (Analysis 2.2.11, RR 0.91, 95% CI 0.75 to 1.10).
- Two studies compared diclofenac to ketorolac (Cohen 1998;Stein 1996). We were not able to do a meta-analysis on these studies due to differences in data presentation.

NSAID versus antispasmodic

Six studies (seven comparisons) (Benyajati 1986; Dash 2012; Jones 1998; Lloret 1987; Pavlik 2004; Quilez 1983) compared NSAIDs to antispasmodics

- NSAIDs were more effective than antispasmodics in pain reduction (Analysis 2.3 (7 comparisons, 359 participants): RR 1.89, 95% CI 1.12 to 3.19; I^2 = 88%). However there was significant heterogeneity. The source of heterogeneity is likely from the different antispasmodics used in the studies. By pooling the four studies that used hyoscine as the antispasmodic (Benyajati 1986; Jones 1998; Lloret 1987; Quilez 1983) the heterogeneity was markedly reduced (I^2 = 28%). NSAIDs were significantly more effective than hyoscine in pain reduction (Analysis 2.3.1 (5 comparisons, 196 participants): RR 2.44, 95% CI 1.61 to 3.70).

NSAID versus other non-opioid

Two studies compared an NSAID to another on-opioid (Ergene 2001; Lopes 2001).

- Lopes 2001 reported no significant difference between 75 mg diclofenac (IM) and 40 µg intranasal desmopressin (Analysis 2.4.1 (1 study, 30 participants): RR 1.44, 95% CI 0.91 to 2.27).
- Ergene 2001 reported 75 mg diclofenac (IM) was inferior to 8 mg ondansetron (IV) for pain relief (Analysis 2.4.2 (1 study, 64 participants): RR 0.39, 95% CI 0.19 to 0.80).

NSAID plus antispasmodic versus NSAID

Eight studies (nine comparisons) compared NSAIDs with combinations of NSAIDs and antispasmodics (Boubaker 2010; el-Sherif 1990; Indudhara 1990; Lloret 1987; Marthak 1991; Martin Carrasco 1993;, Mora Durban 1995; Sanahuja 1990). There was no significant difference between NSAIDs and combination of NSAIDs and antispasmodics (Analysis 2.5 (9 comparisons, 906 participants): RR 1.00, 95% CI 0.89 to 1.13; I^2 = 59%).

NSAID plus non-opioid versus non-opioid

Lloret 1987 reported dipyrone plus hyoscine was more effective than dipyrone alone for pain reduction (Analysis 2.6 (1 study, 48 participants): RR 3.15, 95% CI 1.69 to 5.88).

Non-opioids versus non-opioids

- Iguchi 2002 reported IV butylscopolamine was less effective in pain control than lidocaine injection to trigger point for complete pain relief at 30 minutes (Analysis 2.7 (1 study, 60 participants): RR 0.39, 95% CI 0.22 to 0.70).

Glucagon versus placebo

Bahn Zobbe 1986 found no significant difference in achieving pain control between a bolus injection of glucagon to placebo (Analysis 2.8 (1 study, 24 participants): RR 0.91, 95% CI 0.71 to 1.15).

Need for rescue medication

The need for rescue analgesia was reported in 18 studies comparing different types, doses and routes of administration of NSAIDs (al-Sahlawi 1996; Al Waili 1999; Arnau 1991; Cohen 1998; el-Sherif 1990; Fraga 2003; Glina 2011; Laerum 1996; Lehtonen 1983; Lloret 1987; Lupi 1986; Magrini 1984; Muriel-Villoria 1995; Sanchez-Carpena 2003; Sanchez-Carpena 2007; Stein 1996; Supervia 1998; Walden 1993).

Eight studies (Dash 2012; Ergene 2001; Kumar 2011; Lloret 1987; Lopes 2001; Pavlik 2004; Snir 2008; Stankov 1994) which compared NSAIDs (given alone or in combination with other non-opioids) to non-opioids reported data on need for rescue analgesics.

NSAID versus placebo

Three studies (four comparisons) compared NSAIDs with placebo (Lundstam 1980; Magrini 1984; Vignoni 1983).

- Patients receiving NSAIDs were significantly less likely to require rescue medicine than those receiving placebo (Analysis 3.1 (4 comparisons, 180 participants): RR 0.35, 95% CI 0.20 to 0.60; I^2 = 24%).

NSAID versus NSAID

Ten studies (Al Waili 1999; Arnau 1991; Cohen 1998; el-Sherif 1990; Fraga 2003; Laerum 1996; Muriel-Villoria 1995; Stein 1996; Supervia 1998; Walden 1993) compared diclofenac with other NSAIDs.

- Pooled analysis of these studies showed that diclofenac is comparable with other NSAIDs (Analysis 3.2.1 (10 studies, 1263 participants) RR 0.78, 95% CI 0.59 to 1.03; I^2 = 0%)

Two studies compared 2 g dipyrone (IM or IV) with 25 mg or 50 mg dexketoprofen (IV or IM) (Sanchez-Carpena 2003; Sanchez-Carpena 2007).

- There was no significant difference in the need for rescue medication between 2 g dipyrone (IM or IV) and either 25 mg dexketoprofen (IM or IV) (Analysis 3.2.2 (2 studies, 405 participants): RR 0.68, 95% CI 0.34 to 1.36; I^2 = 79%) or 50 mg dexketoprofen (IM or IV) (Analysis 3.2.3 (2 studies, 405 participants): RR 0.89, 95% CI 0.46 to 1.73; I^2 = 73%).

Two studies compared different doses of dipyrone (Lloret 1987; Muriel-Villoria 1995). Muriel-Villoria 1995 compared varying doses of dipyrone delivered either IV or IM and Lloret 1987 compared 1g versus 2 g dipyrone (IV).

- IV doses of dipyrone significantly reduced the need for rescue medication compared to IM doses of dipyrone (Analysis 3.2.4 (4 comparisons, 239 participants): RR 0.13, 95% CI 0.04 to 0.45; I^2 = 0%).
- Muriel-Villoria 1995 reported no difference in the need for rescue medication between 1 g or 2 g dipyrone delivered IM (Analysis 3.2.5 (1 study, 138 participants): RR 0.89, 95% CI 0.49 to 1.61).
- There was no significant difference in the need for rescue medication between 1 g and 2 g dipyrone delivered IV (Analysis 3.2.6 (2 studies, 149 participants): RR 5.03, 95% CI 0.86 to 29.25; I^2 = 0%).

Five studies compared indomethacin with other NSAIDs (al-Sahlawi 1996; el-Sherif 1990; Laerum 1996; Lehtonen 1983; Lupi 1986).

- al-Sahlawi 1996 compared 100 mg indomethacin (IV) to 1.8 g lysine acetyl salicylate (IV) and reported a statistically significant reduction in the need for rescue medication in the indomethacin group (Analysis 3.2.7 (1 study, 100 participants): RR 0.15, 95% CI 0.04 to 0.65).
- Pooled analysis of the other four studies showed that patients treated with other NSAIDs needed less rescue medication compared to those who received indomethacin, however

this result was not significant (Analysis 3.2.8 (4 studies, 517 participants): RR 1.36, 95% CI 0.96 to 1.94; I^2 = 14%).

Two studies compared ketoprofen to lysine acetyl salicylate (Magrini 1984) and parecoxib (Glina 2011) and found no significant difference in need for rescue medication (Analysis 3.2.9 (1 study, 20 participants): RR 3.00, 95% CI 0.14 to 65.90), (Analysis 3.2.10 (1 study, 337 participants): RR 1.01, 95% CI 0.61 to 1.68).

NSAID versus antispasmodic

Five studies which compared NSAIDs to antispasmodics (Dash 2012; Lloret 1987; Pavlik 2004; Snir 2008; Stankov 1994).

- There was no significant difference in need for rescue therapy between NSAIDs and antispasmodics (Analysis 3.3.1 (5 studies, 363 participants): RR 0.51, 95% CI 0.17 to 1.48; I^2 = 82%). There was significant heterogeneity. The major source was Pavlik 2004; when this study was removed the heterogeneity was reduced to 65% and the result indicates that patients treated with NSAIDs were significantly less likely to need rescue therapy (Analysis 3.3.2 (4 studies, 299 participants): RR 0.34, 95% CI 0.14 to 0.84; I^2 = 65%).

NSAID versus other non-opioid

Three studies compared NSAIDs with other non-opioids; two compared 75 mg diclofenac (IM) to desmopressin (Kumar 2011; Lopes 2001), and one compared diclofenac to ondansetron (Ergene 2001).

- Combined there was significantly less need for rescue therapy for the NSAID group compared to other non-opioids (Analysis 3.4 (3 studies, 151 participants): RR 0.32, 95% CI 0.13 to 0.78; I^2 = 72%).

NSAID plus antispasmodic versus NSAID

Five studies (seven comparisons) compared combination of NSAIDs and antispasmodics versus NSAIDs (Boubaker 2010; el-Sherif 1990; Lloret 1987; Sanahuja 1990; Snir 2008). There was no significant difference between the two treatment groups (Analysis 3.5 (7 comparisons, 589 participants): RR 0.99, 95% CI 0.62 to 1.57; I^2 = 10%).

NSAID plus non-opioid versus NSAID

Two studies compared the effect of 40 mg intranasal desmopressin to 75 mg diclofenac (IM) (Kumar 2011; Lopes 2001). There was no significant difference between the two treatments (Analysis 3.6 (2 studies, 89 participants): RR 1.74, 95% CI 0.30 to 10.18; I^2 = 60%).

NSAID plus non-opioid versus non-opioid

Lopes 2001 compared Diclofenac plus desmopressin versus desmopressin and reported significantly less need for rescue therapy with the combined treatment (Analysis 3.7.1 (1 study, 42 participants): RR 0.14, 95% CI 0.0 to 0.54).

Non-opioid versus placebo

Romics 2003 reported patients receiving drotaverine were significantly less likely to need rescue therapy than those receiving placebo (Analysis 3.8.1 (1 study, 102 participants): RR 0.64, 95% CI 0.44 to 0.95).

One cross-over study (Caravati 1989) which compared oral nifedipine to placebo showed 77% of the patients receiving both nifedipine and placebo needed further rescue medication, however data presented was non-adequate for further statistical analysis.

Non-opioid versus non-opioid

Iguchi 2002 compared IV butylscopolamine and lidocaine injection to trigger point reported a significantly higher proportion of patients in the butylscopolamine group needed rescue medication (Analysis 3.9.1 (1 study, 60 participants): RR 8.00, 95% CI 1.07 to 60.09).

Pain recurrence

Three studies reported pain recurrence (Al Waili 1999; Boubaker 2010; Grissa 2011).

- Al Waili 1999 reported a higher proportion of patients treated with 75 mg diclofenac (IM) showed pain recurrence in the first 24 hours of follow-up compared to those treated with 40 mg piroxicam (IM) (Analysis 4.1 (1 study, 60 participants): RR 0.05, 95% CI 0.00 to 0.81).
- Boubaker 2010 reported no significant difference in pain recurrence at 72 hours between piroxicam plus phloroglucinol and piroxicam plus placebo groups (Analysis 4.2 (1 study, 253 participants): RR 2.52, 95% CI 0.15 to12.75).
- Grissa 2011 reported no significant difference in pain recurrence within 72 hours of discharge between IM piroxicam and IV paracetamol (Analysis 4.3 (1 study, 82 participants): RR 1.00, 95% CI 0.65 to 1.54).

Adverse effects

Reporting adverse effects was variable. Some studies provided detailed tables and some did not cite any side effects (Table 1). In addition reporting the side effects was further complicated by variation in definitions. No study reported serious adverse effects such as gastro-intestinal bleeding or kidney impairment. Overall, when comparing different NSAIDs, gastrointestinal adverse effects seemed to be a common occurrence (Table 1). In studies which compared NSAIDs with non-NSAIDs, gastro-intestinal and central nervous system adverse effects seemed to be more common among the NSAID groups (Table 2; Table 3).

DISCUSSION

Summary of main results

In this review, our objective was to assess the analgesic efficacy and side effects of different non-opioids including NSAIDs. This proved to be a challenging task due to a multitude of reasons discussed below.

Our systematic search of the literature yielded 53 studies eligible for review. All studies only included adult patients. Some studies required radiologic evidence of a urinary stone as inclusion criteria and others included patients based on clinical findings. This inconsistency in diagnostic criteria is a potential source of heterogeneity. Although one may argue that as a clinician (dealing with a patient requiring urgent analgesics) decision making based on clinical findings is more realistic and practical.

The studies involved many different medications. Among NSAIDs, metamizole, diclofenac and indomethacin were the most

commonly used. Metamizole (dipyrone) is not used in many parts of the world due to the rare but serious hematologic side effect of aplastic anaemia. We have included this medication in our study. Overall NSAIDs were more effective than placebo in alleviating renal colic pain as shown in three relatively old studies. NSAIDs have not been compared to placebo in more recent studies most likely due to ethical issues of using placebo to treat a patient with acute severe pain.

NSAIDs as a group were more efficacious than or comparable to antispasmodics or other non NSAID analgesics. This finding was consistent when proportions of patients with more than 50% reduction in pain or requiring rescue medication or patient reported pain scores were evaluated. In addition, the combination of NSAIDs and antispasmodics was not superior to NSAIDs alone for all assessed outcomes. Patients on combination therapy (NSAID plus antispasmodic) reported lower pain VAS, however the difference was not clinically significant.

Among different types of NSAIDs, higher doses of dipyrone (2 g) seemed to be more efficacious than diclofenac in obtaining long lasting pain relief, and IV doses of dipyrone significantly reduced the need for rescue medication compared to IM doses of dipyrone in one study. Regarding proportion of patients with 50% reduction in pain and need for rescue medication, indomethacin was less effective than other types of NSAIDs.

Overall completeness and applicability of evidence

Data from many studies could not be pooled due to difference in interventions, outcomes measured or presentation of data.

This current review has several limitations common to most systematic reviews. Most of the analyses exhibit significant heterogeneity. Although the presented results are from a random effects model we did not find any significant change when a fixed effect model was used. This points to the fact that the source of heterogeneity is not statistical. There are multiple sources including different inclusion criteria, interventions and outcome measures. For instance, not all NSAIDs may have the same effect on renal colic. Even in the case of the same medication the route of administration and dosing may have been different.

We found the outcome measures a challenging issue. Different measures such as VAS, binary or ordinal measures have been used. The time of outcome assessment was quite variable as well. To overcome this problem we grouped studies together that presented the outcomes as a continuous variable. We also estimated the proportion of patients with at least a 50% reduction in pain in the first hour. We elected to use this measure because of the universal availability of pain assessment results in the first hour. In addition we believe this is a relevant clinical outcome. Synthesis of data at times required some degree of judgment from the authors. Some studies allowed a second dose of the protocol medication or opioids in the case of inadequate pain control. In this situation we only pooled data corresponding to the period before administration of the second dose.

Severe adverse effects such as digestive tract bleeding, renal impairment and in the case of metamizole, blood dyscrasia, were not reported. Recent reports from Sweden have suggested a rate of one case of agranulocytosis in 1700 based on six cases in 10,000 prescriptions. The thoroughness and length of follow up for adverse effect is unknown. Therefore underestimation of adverse effects, especially those manifested beyond the short follow up, is quite possible. It seems minor central nervous symptoms such as dizziness, gastro-intestinal complaints such as nausea and injection site erythema formed the majority of the adverse effects. We were not able to pool these data to perform a meaningful meta-analysis. There was insufficient information of adequate quality for any safety analysis. A recent meta-analysis has shown increased risk of cardiovascular event in patients using diclofenac, similar to Cox-2 inhibitors. This has resulted in a European wide adverse event alert for this medication (CNT 2013).

Quality of the evidence

The overall quality of the studies was fair. The main issues were unclear methods of randomisation and concealment. In some studies the outcome assessor was not blinded. Since the outcomes were assessed in the same visit, incomplete follow-up was rare.

Potential biases in the review process

The published protocol was followed to avoid any bias in the review process. Nevertheless, we had to make judgement calls when combining studies and their outcomes. The main challenge in this review is to explain the effects.

Agreements and disagreements with other studies or reviews

Medication used in the treatment of acute renal colic can be categorized in the two broad groups of opioids and non-opioids. The most commonly used non-opioids are NSAIDs. Holdgate 2005a compared NSAIDs to opioids and found: "Single bolus doses of both NSAIDs and opioids provide pain relief to patients with acute renal colic". However, patients receiving NSAIDs achieve greater reduction in pain scores and are less likely to require further analgesia in the short term (Holdgate 2005a). To our knowledge, this is the first review investigating NSAIDs and non-opioids for acute renal colic.

AUTHORS' CONCLUSIONS

Implications for practice

Despite variability in the studies and the evidence not being of the highest quality, we still believe that NSAIDs are an effective treatment for renal colic when compared to placebo or antispasmodics. The addition of antispasmodics to NSAIDs does not result in better pain control. The findings of this review support the use commonly available NSAID such as diclofenac, indomethacin, or ketorolac. We remain uncertain as the effect of metamizole on blood dyscrasia. However, in the presence of other interventions with more certain safety profiles the justification of its use is more difficult, unless there is a remarkable difference in the cost. Data on other types of non-opioid, non-NSAID medication is scarce.

Implications for research

There is lack of studies assessing a combination of different NSAIDs. The optimal dose and route of administration is not clear. More accurate reporting of side effects is required.

ACKNOWLEDGEMENTS

We wish to thank the referees for the comments and feedback during the preparation of this review.

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CHARACTERISTICS OF STUDIES

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

Al Waili 1999

Methods	• Study design: parallel RCT • Study duration: NS • Duration of follow-up: 24 h
Participants	• Country: UAE • Setting: multicentre • Diagnosis based in general urine examination, IV urogram, US and the voiding of a calculus • Number: treatment group 1 (30); treatment group 2 (34) • Mean age (range): 28 years (18 to 42) • Sex (M/F): 52/12 • Exclusion criteria: hepatic or cardiovascular diseases; allergy to NSIADs; received antispasmodics, pethidine, or any other prostaglandin synthesis inhibitors with 2 hours of study
Interventions	Treatment group 1 • Diclofenac: 75 mg (IM) Treatment group 2 • Piroxicam: 40 mg (IM)

Al Waili 1999 *(Continued)*

Outcomes	• VAS-10: 30, 60 min (measured at 15 min intervals for up to 8 h and hourly for 24 h after treatment) • Need for rescue after 1st hour of treatment
Notes	• Source of funding: NS

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) Medication used	Low risk	Double blind, participants and investigators
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	All pre-specified primary and secondary outcomes are reported
Other bias	Low risk	The study appears to be free of other sources of bias

al-Sahlawi 1996

Methods	• Study design: parallel RCT • Study duration: NS • Duration of follow-up: 60 min
Participants	• Country: Kuwait • Setting: single centre • Diagnosis made by history, urinalysis and radiological examination • Number: treatment group 1 (50); treatment group 2 (50); treatment group 3 (50) • Age range: 20 to 60 years • Sex (M/F): treatment group 1 (31/19); treatment group 2 (34/16); treatment group 3 (37/13) • Exclusion criteria: hypersensitivity; pregnancy or lactation; asthma; peptic ulcer disease; renal colic treatment prior to admission
Interventions	Treatment group 1 • Lysine acetyl salicylate: 1.8 (IV) Treatment group 2 • Indomethacin: 100 mg (IV) Treatment group 3 • Pethidine: 100 mg (IV)
Outcomes	• Comparison of drugs in pain relief: 15, 30, 60 min

al-Sahlawi 1996 *(Continued)*

	• Need for rescue medication
Notes	• Source of funding: NS

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) Medication used	Low risk	Participants and investigators
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes are reported
Other bias	Low risk	The study appears to be free of other sources of bias

Arnau 1991

Methods	• Study design: parallel RCT • Study duration: NS • Duration of follow-up: NS
Participants	• Country: Spain • Setting: multicentre (13) • Diagnosis colicky pain in the flank and/or radiating to homolateral hemiabdomen, and/or radiating to genitalia, with or without vegetative symptoms) • Number: treatment group 1 (116); treatment group 2 (101); treatment group 3 (116); treatment group 4 (116) • Mean age ± SD (years): treatment group 1 (41.2 ± 14.7); treatment group 2 (42.9 ± 14); treatment group 3 (40.7 ± 13.9); treatment group 4 (1.4 ± 12.7) • Sex (M/F): treatment group 1 (67/49); treatment group 2 (57/44); treatment group 3 (63/53); treatment group 4 (61/57) • Exclusion criteria: allergy to NSAIDs; GI bleeding; pregnancy or lactation
Interventions	Treatment group 1 • Dipyrone: 1g (IM) Treatment group 2 • Dipyrone: 2g (IM) Treatment group 3 • Diclofenac: 75 mg (IM)

Arnau 1991 *(Continued)*

	Treatment group 4 • Pethidine: 100 mg (IM)
Outcomes	• VAS-10: 15, 30, 45, 60 min • Need for rescue medication
Notes	• Source of funding: Laboratories Europharma, SA and Institut Municipal d'Investigacio Medica, Barcelona for partial financial support

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Coordinating centre; simple randomisation of the therapeutic schedules, pre-established
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) Medication used	Low risk	Observer and participants
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	All pre-specified primary and secondary outcomes are reported
Other bias	Unclear risk	Industry sponsorship could be a source of bias

Bahn Zobbe 1986

Methods	• Study design: parallel RCT • Study duration: September 1982 to September 1984 • Duration of follow-up: NS
Participants	• Country: Denmark • Setting: NS • Acute urethral colic diagnosed clinically and also IVP, and had to be a ureteral calculus and /or acute urostasis on 5 or 10 min urogram • Number: treatment group 1 (18); treatment group 2 (19) • Median age (years): treatment group 1 (51); treatment group 2 (51) • Sex (M/F): NS • Exclusion criteria: calculus > 0.6 mm; acute infection; DM; pheochromocytoma; insulinoma; pregnancy
Interventions	Treatment group • Glucagon: 1 mg IV bolus, followed by continuous infusion of 16 mg of glucagon dissolved in 16 ml of sterile water and further diluted of 0.5 L isotonic saline with rate of 2 mg/h for 8 h Control group

Bahn Zobbe 1986 *(Continued)*

	• Placebo: bolus injection followed by continuous infusion within 8 h
Outcomes	• Pain intensity with 5 scale (worse, no change, moderate relief, relief, painless in admission measured just after bolus injection and then every 2 hours, according to patients or observers • Passing of calculus, recorded by patient, staff, or radiology • Side effects: plasma glucose, nausea, vomiting
Notes	• Source of funding: NS

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The ampoules were randomised in groups of 10 by manufacturer, method was not stated
Allocation concealment (selection bias)	Low risk	The code remained unknown
Blinding (performance bias and detection bias) Medication used	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	37 patients entered but, 8 were excluded due to incomplete registrations and excluded from analysis, data analysis was provided for 29 subjects in total
Selective reporting (reporting bias)	Low risk	All pre-specified primary and secondary outcomes are reported
Other bias	Low risk	The study appears to be free of other sources of bias

Benyajati 1986

Methods	• Study design: parallel RCT • Study duration: NS • Duration of follow-up: 60 min
Participants	• Country: Thailand • Setting: single centre • Patients with abdominal pain, half had renal colic • Number: treatment group 1 (28); treatment group 2 (32) • Mean age ± SD (years): treatment group 1 (27.7 ± 6.6); treatment group 2 (30.6 ± 10.8) • Sex (M/F): treatment group 1 (20/8); treatment group 2 (26/6) • Exclusion criteria: allergy to the two medications; hypotension
Interventions	Treatment group 1 • Baralgan: 2 mg (IV) Treatment group 2 • Hyoscine-N-methyl-bromide: 1 mg (IM)
Outcomes	• VAS: 5, 15, 20, 30, 60 min

Benyajati 1986 *(Continued)*

Notes	• Hoechst Thailand provided samples of the drugs used in this study

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) Medication used	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	All pre-specified primary and secondary outcomes are reported
Other bias	Unclear risk	Industry sponsorship could be a source of bias

Boubaker 2010

Methods	• Study design: parallel RCT • Study duration: January to December 2004 • Duration of follow-up: 60 min
Participants	• Country: Tunisia • Setting: single centre • Patients ≥ 16 y with clinical sign and symptoms of renal colic, diagnosis criteria: history of unilateral colicky acute flank pain + urinalysis or US findings, and those with VAS ≥ 30/100 • Number: treatment group 1 (127); treatment group 2 (126) • Mean age ± SD (years): treatment group 1 (39 ± 14); treatment group 2 (35 ± 13) • Sex (M/F): treatment group 1 (72/55); treatment group 2 (66/60) • Exclusion criteria: previous history of peptic ulcer disease; asthma; bleeding disorder; impaired kidney/hepatic function; hypersensitivity to aspirin, NSAIDs or phloroglucinol; pregnant and breast-feeding women; receiving painkillers within 6 h before presentation
Interventions	Treatment group 1 • Piroxicam: 20 mg (IM) as standard analgesic • Placebo: 20 mL of serum saline (IV) for 20 min Treatment group 2 • Piroxicam: 20 mg (IM) as standard analgesic • Phloroglucinol: 200 mg in 20 mL of serum saline (IV) for 20 min Rescue therapy

Boubaker 2010 *(Continued)*

	• IV morphine titration: if VAS at 60 min > 50% of the initial VAS or if VAS > 50/100 at 2 successive time points
Outcomes	• VAS-100 mm: baseline, 5, 10, 15, 30, 45, 60 min • Heart rate and BP: baseline, 5, 10, 15, 30, 45, 60 min • Presence of adverse events: allergy, vomiting, headache, palpitation • Primary endpoint: pain relief at 60 min, defined as decrease in VAS of ≥ 50% compare to baseline • Secondary endpoint: difference in VAS at any time course, need for rescue therapy, and occurrence of adverse events
Notes	• Source of funding: NS • Definite diagnosis not confirmed by imaging for all subjects

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Sealed random code envelopes were used
Allocation concealment (selection bias)	Low risk	Investigators opened a sealed envelope in numerical order and assigned the patient to that designated group
Blinding (performance bias and detection bias) Medication used	Low risk	It was mentioned that this study is a double-blind study. Patients were blind to the intervention, however other information was not provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	All pre-specified primary and secondary outcomes are reported
Other bias	Low risk	The study appears to be free of other sources of bias

Caravati 1989

Methods	• Study design: cross-over RCT • Study duration: NS • Duration of follow-up: 15 min/phase
Participants	• Country: USA • Setting: multicentre • All patients between 18 and 75 y presenting to the ED with the signs and symptoms of acute renal colic • Number: 35 randomised, 30 analysed • Mean age ± SD: 32 ± 12 years • Sex (M/F): 27/3 • Exclusion criteria: nifedipine hypersensitivity; unstable vital signs; severe aortic stenosis; pregnancy; myocardial infarction
Interventions	Treatment group • Nifedipine:10 mg to 20 mg (oral)

Caravati 1989 *(Continued)*

	Control group • Placebo
Outcomes	• VAS-10 • Vital signs • Need for rescue medication
Notes	• Source of funding: Pfizer Pharmaceuticals

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number table
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) Medication used	Low risk	Patients and clinicians blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	Withdrawn and not crossed over patients did not enter the analysis
Selective reporting (reporting bias)	Low risk	All pre-specified primary and secondary outcomes are reported
Other bias	Unclear risk	Industry sponsorship could be a source of bias

Chaudhary 1999

Methods	• Study design: parallel RCT • Study duration: NS • Duration of follow-up: 120 min
Participants	• Country: India • Setting: Multicentre • Patients with biliary (84), renal (58), and intestinal colic (48) • Number: treatment group 1 (28); treatment group 2 (40); 200 enrolled in total • Age range: 16 to 60 years • Sex (M/F): 112/88 • Exclusion criteria: peptic ulcer disease; glaucoma, hypertension; pregnancy; sensitivity to NSAID
Interventions	Treatment group 1 • Diclofenac (oral) • Pitofenone (oral) • Fenpiverinium (oral) Treatment group 2

Chaudhary 1999 *(Continued)*

	• Metamizole (oral) • Pitofenone (oral) • Fenpiverinium (oral)
Outcomes	• VAS-100: 0, 30, 60, 120 min • Pain intensity pre-post treatment after 2 h
Notes	• Source of funding: Panacea Biotec Ltd

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) Medication used	Low risk	Double blind, participants and investigators
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	All pre-specified primary and secondary outcomes are reported
Other bias	Unclear risk	Industry sponsorship could be a source of bias

Cohen 1998

Methods	• Study design: parallel RCT • Study duration: NS • Duration of follow-up: 6 h
Participants	• Country: Israel • Setting: single centre • Diagnostic criteria were a history of flank pain associated with haematuria, and abdominal ultrasound which excluded extra-renal causes for abdominal pain. Only those patients displaying at least a moderate level of pain on a four-point self-reported VRS participated • Number: treatment group 1 (27); treatment group 2 (30) • Mean age ± SD (years): treatment group 1 (44.0 ± 12.8); treatment group 2 (42.4 ± 13.0) • Sex (males): treatment group 1 (89%); treatment group 2 (77%) • Exclusion criteria: peptic ulcer disease; asthma; bleeding disorder
Interventions	Treatment group 1 • Ketorolac: 30 mg (IM) Treatment group 2 • Diclofenac: 75 mg (IM)

Cohen 1998 *(Continued)*

Outcomes	• Pain VAS-10: 0, 1, 2, 6 h • Sedation: 3 point rating scale • Need for rescue medication
Notes	• Source of funding: NS

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Low risk	Sealed envelopes
Blinding (performance bias and detection bias) Medication used	Low risk	Participants and investigators
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	All pre-specified primary and secondary outcomes are reported
Other bias	Low risk	The study appears to be free of other sources of bias

Dash 2012

Methods	• Study design: parallel RCT • Study duration: January to October 2009 • Duration of follow-up: 60 min
Participants	• Country: India • Setting: single centre • Clinical symptoms and signs of renal colic (history of unilateral colicky pain); standardized screening tools were used to identify patients (urinalysis, X-ray, ultrasound); patients included if they had VAS score ≥ 50/100 at baseline • Number: treatment group 1 (50); treatment group 2 (50) • Mean age ± SD (years): treatment group 1 (38.3 ± 10.2); treatment group 2 (40.8 ± 11.7) • Sex (M/F): treatment group 1 (31/19); treatment group 2 (27/23) • Exclusion criteria: history of peptic ulcer disease; asthma; bleeding disorder; need for immediate surgery or other intervention; suspected hypersensitivity to study medications; antispasmodics or analgesics received within 6 h before presenting; tranquillizing or muscle relaxant therapy used within 3 days; 2 or 3 degree heart block; pregnancy; malignant disease; clinically unstable renal, hepatic, or cardiac insufficiency
Interventions	Treatment group 1 • Drotaverine: 2 ampoules, 80 mg single injection (IM) Treatment group 2

Dash 2012 *(Continued)*

	• Sodium diclofenac: 75 mg single injection 9IM)
Outcomes	• VAS-100: 0, 30, 60 min, and in the next 2 h • MD in VAS score: 0, 30, 60 min • Drug effectiveness defined as number of patients with ≥ 50% decrease in pain intensity 60 min after injection, without exacerbation during following 2 h • Number of patients needing rescue medication at 60 min • Adverse effects
Notes	• Funding: none

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated random list was used
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) Medication used	Low risk	Single blind study, patients were blind to study medication
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	All pre-specified primary and secondary outcomes are reported
Other bias	Low risk	The study appears to be free of other sources of bias

el-Sherif 1990

Methods	• Study design: parallel RCT • Study duration: NS • Duration of follow-up: 30 min
Participants	• Country: Qatar • Setting: single centre • Diagnosis of acute renal colic, based on history, clinical, urinary and radiological examination • Number: treatment group 1 (54); treatment group 2 (44); treatment group 3 (47) • Mean age ± SD (years): treatment group 1 (33.4 ± 9.2); treatment group 2 (35 ± 8.6); treatment group 3 (33.7 ± 8.5) • Sex (M/F): treatment group 1 (48/5); treatment group 2 (41/3); treatment group 3 (42/4) • Exclusion criteria: NS
Interventions	Treatment group 1 • Avafortan: 4 mg (IV) Treatment group 2

el-Sherif 1990 *(Continued)*

	• Indomethacin: 50 mg (IV) Treatment group 3 • Diclofenac:50 mg (IM)
Outcomes	• Pain relief: 10, 20, 30 min • Need for rescue medication
Notes	• Source of funding: NS

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) Medication used	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	All pre-specified primary and secondary outcomes are reported
Other bias	Low risk	The study appears to be free of other sources of bias

Ergene 2001

Methods	• Study design: parallel RCT • Study duration: NS • Duration of follow-up: 60 min
Participants	• Country: Turkey • Setting: single centre • Acute onset of flank pain associated with microscopic or gross haematuria, and who were clinically diagnosed as having ureteral colic • Number: treatment group 1 (33); treatment group 2 (31) • Age range: 18 to 80 years • Sex (M/F): 43/21 • Exclusion criteria: hypersensitivity; lactation; pregnancy; kidney and liver disease; duodenal ulcer; bleeding
Interventions	Treatment group 1 • Ondansetron: 8 mg (IV) Treatment group 2

Ergene 2001 *(Continued)*

	• Diclofenac: 75mg (IM)
Outcomes	• VAS-10: 0, 15, 30, 45, 60 min • Need for rescue medication
Notes	• Source of funding: NS

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) Medication used	Low risk	Participants and Investigators
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	All pre-specified primary and secondary outcomes are reported
Other bias	Low risk	The study appears to be free of other sources of bias

Fraga 2003

Methods	• Study design: parallel RCT • Study duration: NS • Duration of follow-up: 240 min
Participants	• Country: Portugal • Setting: multicentre • Patients with moderate to severe pain suggestive of a clinical diagnosis of acute renal colic, who had not taken any analgesic or antispasmodic drugs in the previous 2 h • Number: treatment group 1 (59); treatment group 2 (60) • Mean age ± SD (years): treatment group 1 (47.4 ± 17); treatment group 2 (45.0 ± 14.2) • Sex (M/F): treatment group 1 (40/19); treatment group 2 (36/24) • Exclusion criteria: pain more than 12 h; drug addiction; pregnancy; lactation
Interventions	Treatment group 1 • Etofenamate: 1000 mg (IM) Treatment group 2 • Diclofenac: 75 mg (IM)
Outcomes	• VAS-100: 0, 30, 60, 120, 240 min • 4-point VRS

Fraga 2003 *(Continued)*

	• Need for rescue medication
Notes	• Patients could get rescued at any time • Source of funding: Bial-Portela & C, SA, Portugal

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) Medication used	Low risk	Single blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	All pre-specified primary and secondary outcomes are reported
Other bias	Unclear risk	Industry sponsorship could be a source of bias

Galassi 1983

Methods	• Study design: parallel RCT • Study duration: NS • Duration of follow-up: 60 min
Participants	• Country: Italy • Setting: NS • Number: treatment group 1 (11); treatment group 2 (14) • Age range: 18 to 72 years • Sex (M/F): NS • Exclusion criteria: NS
Interventions	Treatment group 1 • Indomethacin: 50 mg (IV) Treatment group 2 • Metamizole (Dipyrone): 1000 mg (IV)
Outcomes	• VAS-10: 60 min
Notes	• Source of funding: NS

Risk of bias

Galassi 1983 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) Medication used	Low risk	Double blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	All pre-specified primary and secondary outcomes are reported.
Other bias	Low risk	The study appears to be free of other sources of bias.

Glina 2011

Methods	• Study design: phase IV parallel RCT • Study duration: June 2007 to June 2009 • Duration of follow-up: 2 days
Participants	• Country: international • Setting: multicentre (16) • Subjects aged 18 to 65 y with confirmed diagnosis of renal colic who presented with moderate to severe pain (baseline PI score on a 100 mm VAS > 50) • Number: treatment group 1 (174); treatment group 2 (164) • Mean age ± SD (years): treatment group 1 (38.6 ± 10.3); treatment group 2 (40.1 ± 12.1) • Sex (M/F): treatment group 1 (110/64); treatment group 2 (103/61) • Exclusion criteria: significant renal or hepatic condition; acute pain other than colic; had been a recipient of a kidney allograft; treated for a UTI, pyelonephritis or clinical suspicion of such infection; history of active peptic ulcer disease, active dyspepsia, GI bleeding; an oesophagitis, gastric or duodenal ulcer within 1 month prior to screening
Interventions	Treatment group 1 • Parecoxib: 40 mg (IV) • Placebo Treatment group 2 • Ketoprofen 100 mg (IV) • Placebo
Outcomes	• Mean PID at 30 min assessed by VAS-100 • Baseline pain intensity assessed by VAS score at all time points • PID change from baseline in VAS score at all time points • Mean PID at 120 min • Response in PI (decrease of > 20 mm on the VAS score) at 30 min

Glina 2011 *(Continued)*

	• Pain relief at 30 and 120 min • Sum of time interval weighted PR score through 120 min • Physician's global evaluation of study medication at 30 and 120 min and at day 2 • Need for rescue medication • Time to rescue medication up to 120 min
Notes	• Source of funding: sponsored by Pfizer Inc. Editorial support was provided by L. Prevost, BSc, of PAREXEL, and was funded by Pfizer Inc • Drs Dalia Wajsbrot and Gaston Araya are both currently full-time employees of Pfizer Inc

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A computer generated block randomisation schedule was used
Allocation concealment (selection bias)	Low risk	Sealed envelopes were used to distribute randomisation schedule to the pharmacist
Blinding (performance bias and detection bias) Medication used	Low risk	Double dummy, double blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	All pre-specified primary and secondary outcomes are reported.
Other bias	High risk	The study was funded by a pharmaceutical company. Two of the authors are full-time employees of Pfizer Inc

Grissa 2011

Methods	• Study design: parallel RCT • Study duration: March to August 2006 • Duration of follow-up: 72 h
Participants	• Country: Tunisia • Setting: single centre • Subjects ≥16 y with clinical sign and symptoms of renal colic using standardized screening form to identify eligibility; diagnosis criteria were based on history of unilateral colicky acute flank pain + urinalysis or ultrasonography findings, and those with VAS scores of ≥ 30/100 • Number: treatment group 1 (50); treatment group 2 (50) • Mean age ± SD (years): treatment group 1 (40 ± 14); treatment group 2 (39 ± 13) • Sex (M/F): treatment group 1 (21/29); treatment group 2 (20/30) • Exclusion criteria: history of peptic ulcer; asthma; bleeding disorder; impaired kidney or hepatic function; suspected hypersensitivity to aspirin or NSAID or paracetamol; pregnant and breast-feeding women; received painkiller within 6 h before presentation
Interventions	Treatment group 1 • Paracetamol: 1 g in 100 mL serum saline (IV) in 15 minutes

Grissa 2011 *(Continued)*

	Treatment group 2 • Piroxicam: 20 mg (IM)
Outcomes	• VAS-100: 0, 5, 10, 15, 30, 45, 60, 75, 90 min • Heart rate, BP at above time points • Adverse effects: allergy, vomiting, headache, palpitation • Need for rescue medication • Primary endpoint: pain relief at 90 min (defined as a decrease of VAS of 50% or more as compare to baseline) • Secondary endpoint: VAS difference at any time course, side effects, hospital admission, new visit within 72 h
Notes	• Source of funding: NS

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Random sequence generation not reported
Allocation concealment (selection bias)	Low risk	Sealed random code envelops opened in numerical order
Blinding (performance bias and detection bias) Medication used	High risk	This study was not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomised patients were included in analysis and all outcomes accounted for.
Selective reporting (reporting bias)	High risk	VAS score in 60 minutes and the number of patients needed rescue therapy were not reported
Other bias	Low risk	The study appears to be free of other sources of bias

Holmlund 1978

Methods	• Study design: cross-over RCT • Study duration: NS • Duration of follow-up: NS
Participants	• Country: Sweden • Setting: NS • Number: treatment group 1 (27); control group (20) • Mean age ± SD (years): NS • Sex (M/F): NS • Exclusion criteria: NS
Interventions	Treatment group • Indomethacin: 50 mg (IV)

Holmlund 1978 *(Continued)*

	Control group • Placebo: riboflavin 5 mg because of colour similarities
Outcomes	• Complete pain relief • Vital signs
Notes	• Source of funding: NS

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) Medication used	Low risk	Double blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	All pre-specified primary and secondary outcomes are reported
Other bias	Low risk	The study appears to be free of other sources of bias

Iguchi 2002

Methods	• Study design: parallel RCT • Study duration: started January 1999 • Duration of follow-up: 24 h
Participants	• Country: Japan • Setting: single centre • Patients with renal colic • Number: treatment group 1 (30); treatment group 2 (30) • Mean age ± SD (years): treatment group 1 (43.3 ± 14.8); treatment group 2 (41.3 ± 12.4) • Sex (M/F): treatment group 1 (23/7); treatment group 2 (21/9) • Exclusion criteria: previous history of renal colic treatment; allergy, lower abdominal pain
Interventions	Treatment group 1 • Butylscopolamine: 40 mg (IV) • Sulpyrine: 500 mg (IV) • 5% glucose: 20 mL (IV) Treatment group 2 • 1% lidocaine: 10 to 15 mL to trigger point (local)

Iguchi 2002 *(Continued)*

Outcomes	• VAS-100: 10, 20, 30, 40, 50, 60 min
Notes	• Source of funding: NS

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Only described as simple randomisation
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) Medication used	High risk	Not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	All pre-specified primary and secondary outcomes are reported
Other bias	Low risk	The study appears to be free of other sources of bias

Indudhara 1990

Methods	• Study design: parallel RCT • Study duration: NS • Duration of follow-up: 120 min
Participants	• Country: India • Setting: multicentre • Patents aged 18 to 60 y • Number: treatment group 1 (33); treatment group 2 (30); treatment group 3 (29) • Mean age: 38.5 y • Sex (M/F): NS • Exclusion criteria: history of peptic ulcer; kidney or hepatic dysfunction; allergy

Interventions	Treatment group 1
	• Diclofenac: 150 mg (oral)
	Treatment group 2
	• Baralgan (oral)
	  ◦ Analgin: 500 mg
	  ◦ Benzophenone: 5 mg
	Treatment group 3
	• Pethidine: 50 mg (IM)

Indudhara 1990 *(Continued)*

Outcomes	• VRS-5: 0, 15, 30, 45, 60, 90, 120 min
Notes	• Source of funding: NS

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) Medication used	High risk	Not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	All pre-specified primary and secondary outcomes are reported
Other bias	Low risk	The study appears to be free of other sources of bias

Jones 1998

Methods	• Study design: parallel RCT • Study duration: NS • Duration of follow-up: 30 min
Participants	• Country: USA • Setting: single centre • Patients with signs and symptoms consistent with ureteral colic as determined by a board-certified emergency medicine staff physician • Number: treatment group 1 (25); treatment group 2 (24) • Mean age ± SD (years): treatment group 1 (43.5 ± 2.2); treatment group 2 (43.7 ± 2.8) • Sex (M/F): treatment group 1 (18/7); treatment group 2 (18/6) • Exclusion criteria: allergy; pregnancy; < 18 y; peptic ulcer
Interventions	Treatment group 1 • Ketorolac: 30 mg (IV) Treatment group 2 • Hyoscine: 0.125 mg (sublingual)
Outcomes	• VAS-100: 0, 10, 20, 30 min • Need for rescue medication after 30 min
Notes	• Source of funding: NS

Jones 1998 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated randomisation table
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) Medication used	High risk	Open-label study
Incomplete outcome data (attrition bias) All outcomes	High risk	Only 49/54 patients randomised were reported and included in the analysis. One patient was excluded for incomplete data collection and four were excluded for failure to confirm a ureteral calculi
Selective reporting (reporting bias)	High risk	No data for need for rescue medication reported
Other bias	Low risk	The study appears to be free of other sources of bias

Kekec 2000

Methods	• Study design: parallel RCT • Study duration: NS • Duration of follow-up: 30 min
Participants	• Country: Turkey • Setting: multicentre • Patients presenting with colic • Number: treatment group 1 (25); treatment group 2 (25) • Mean age, range (years): treatment group 1 (35.9, 22 to 52); treatment group 2 (41.9, 18 to 65) • Sex (M/F): 40/10 • Exclusion criteria: allergy; hypertension; infection
Interventions	Treatment group 1 • Tenoxicam: 40 mg (IV) Treatment group 2 • Tenoxicam: 40 mg (IV) • Isosorbide: 5 mg (sublingual)
Outcomes	• VAS-100: 30 min • Heart rate • BP
Notes	• Source of funding: NS
Risk of bias	

Kekec 2000 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) Medication used	Low risk	Participants and investigators
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data reported
Selective reporting (reporting bias)	Low risk	All pre-specified primary and secondary outcomes are reported
Other bias	Low risk	The study appears to be free of other sources of bias

Kheirollahi 2010

Methods	• Study design: open label RCT • Study duration: NS • Study follow-up: 60 min
Participants	• Country: Iran • Setting: single centre • Patients with acute renal colic; aged 18 to 55 y • Number: treatment group 1 (58); treatment group 2 (58) • Mean age ± SD (years): treatment group 1 (31.1 ± 1.1); treatment group 2 (30.3 ± 0.53) • Sex (M/F): treatment group 1 (38/20); treatment group 2 (45/13) • Exclusion criteria: pregnancy; addiction; any history of hypertension; cardiac insufficiency; surgery on kidneys or ureters; receiving any analgesics/IV fluid therapy just before admission; history of any drug reaction to hyoscine-N-butylbromide
Interventions	Treatment group 1 • Hyoscine-N-butylbromide (IM) Treatment group 2 • Hyoscine-N-butylbromide (IM) • Desmopressin (intranasal)
Outcomes	• VAS-100: 0, 30, 60 min
Notes	• Funding: NS

Risk of bias

Bias	Authors' judgement	Support for judgement

Kheirollahi 2010 *(Continued)*

Random sequence generation (selection bias)	Low risk	Simple randomisation method (shuffled deck of cards)
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) Medication used	High risk	No blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only 2 patients dropped out of study due to non-tolerable pain, 1 form each group
Selective reporting (reporting bias)	Low risk	All pre-specified primary and secondary outcomes are reported
Other bias	Low risk	The study appears to be free of other sources of bias

Kumar 2011

Methods	• Study design: parallel RCT • Study duration: NS • Duration of follow-up: 60 min
Participants	• Country: India • Setting: single centre • Presenting with acute renal colic due to stone disease • Number: treatment group 1 (24); treatment group 2 (24); treatment group 3 (24) • Mean age ± SD (years): NS • Sex (M/F): NS • Exclusion criteria: high BP; coronary disease, rhinitis; influenza; peptic ulcer; kidney or liver failure; anticoagulant therapy; pregnant women
Interventions	Treatment group 1 • Desmopressin: 40 µg (intranasally) Treatment group 2 • Diclofenac: 75 mg (IM) Treatment group 3 • Desmopressin: 40 µg (intranasally) • Diclofenac: 75 mg (IM)
Outcomes	• VAS-100: continuous assessed at baseline, 10, 30, 60 min • Adverse reactions • Need for rescue medication
Notes	• Source of funding: NS
Risk of bias	

Kumar 2011 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Block randomisation design
Allocation concealment (selection bias)	Low risk	Block randomisation will result in allocation concealment
Blinding (performance bias and detection bias) Medication used	High risk	Not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	High risk	Adverse effects were not reported
Other bias	Low risk	The study appears to be free of other sources of bias

Laerum 1996

Methods	• Study design: parallel RCT • Study duration: 1990 to 1992 • Duration of follow-up: 8 h
Participants	• Country: Norway • Setting: single centre • Acute unilateral ureteral/renal colic confirmed by radiography • Number: treatment group 1 (41); treatment group 2 (42) • Mean age, 95% CI (years): treatment group 1 (41.6, 37.6 to 45.9); treatment group 2 (45.2, 40.3 to 48.6) • Sex (M/F): treatment group 1 (31/10); treatment group 2 (37/5) • Exclusion criteria: peptic ulcer; asthma; sensitivity to indomethacin; acute rhinitis; pregnancy or lactation
Interventions	Treatment group 1 • Diclofenac: 75 mg (IM) Treatment group 2 • Indomethacin: 50 mg (IV)
Outcomes	• VAS-10: 5, 10, 15, 20, 25, 30, 60,120 min; 4 h, 8h • Need for rescue medication
Notes	• Source of funding: study was supported by CIBA-Geigy Pharma A/S, Oslo

Risk of bias

Bias	Authors' judgement	Support for judgement

Laerum 1996 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) Medication used	Low risk	Single blinded (participants)
Incomplete outcome data (attrition bias) All outcomes	High risk	8 and 9 dropped of each group. It seems that the intention to treat principle was not followed
Selective reporting (reporting bias)	Low risk	All pre-specified primary and secondary outcomes are reported
Other bias	Unclear risk	Industry sponsorship could be a source of bias

Lehtonen 1983

Methods	• Study design: parallel RCT • Study duration: NS • Duration of follow-up: NS
Participants	• Country: Finland • Setting: multicentre • Number: treatment group 1 (93); treatment group 2 (45); treatment group 3 (31) • Mean age (years): treatment group 1 (44.6); treatment group 2 (49.5); treatment group 3 (39.5) • Sex (M/F): treatment group 1 (69/24); treatment group 2 (33/12); treatment group 3 (26/5) • Exclusion criteria: NS
Interventions	Treatment group 1 • Indomethacin: 50 mg (IV) Treatment group 2 • Metamizole (dipyrone): 2.5 g (IV) Treatment group 3 • Pethidine: 50 mg (IV)
Outcomes	• Subjective pain relief: good-moderate-no effect • Side effects • BP • Pulse rate • Need for rescue medication
Notes	• Source of funding: NS

Risk of bias

Bias	Authors' judgement	Support for judgement

Lehtonen 1983 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) Medication used	Low risk	Unclear if participants were blinded, clinician was not blinded, outcome assessor was blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	All pre-specified primary and secondary outcomes are reported
Other bias	Low risk	The study appears to be free of other sources of bias

Lloret 1987

Methods	• Study design: parallel RCT • Study duration: NS • Duration of follow-up: 30 min
Participants	• Country: Spain • Setting: multicentre • Number: treatment group 1 (25); treatment group 2 (25); treatment group 3 (23); treatment group 4 (23) • Mean age ± SD (years): treatment group 1 (38.6 ± 14.9); treatment group 2 (42.9 ± 19.9); treatment group 3 (43.8 ± 14.5); treatment group 4 (36.9 ± 15.3) • Sex (M/F): NS • Exclusion criteria: pregnancy; glaucoma; hypertension; cardiac failure; megacolon; hepato cellular
Interventions	Treatment group 1 • Dipyrone: 2.5 g Treatment group 2 • Dipyrone: 2.5 mg • Hyoscine: 20 mg Treatment group 3 • Dipyrone: 1 g Treatment group 4 • Hyoscine: 20 mg
Outcomes	• VAS-100: 10, 20, 30 min • Need for rescue medication
Notes	• Source of funding: NS

Lloret 1987 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation list
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) Medication used	Low risk	Double blind; patient and observer
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	All pre-specified primary and secondary outcomes are reported
Other bias	Low risk	The study appears to be free of other sources of bias

Lopes 2001

Methods	• Study design: parallel RCT • Study duration: June 1996 to May 1997 • Duration of follow-up: 30 min
Participants	• Country: Portugal • Setting: single centre • Patients admitted with renal colic caused by stones • Number: treatment group 1 (20); treatment group 2 (19); treatment group 3 (22) • Mean age: 48.3 y • Sex (M/F): 38/23 • Exclusion criteria: high BP; rhinitis; peptic ulcer; liver or kidney disease; influenza
Interventions	Treatment group 1 • Desmopressin: 40 µg (intranasal) Treatment group 2 • Diclofenac: 75 mg (IM) Treatment group 3 • Desmopressin: 40 µg (intranasal) • Diclofenac: 75 mg (IM)
Outcomes	• VAS-10: 0, 10, 20, 30 min • Vital signs • Need for rescue medication
Notes	• Source of funding: NS

Lopes 2001 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	not reported
Allocation concealment (selection bias)	Unclear risk	not reported
Blinding (performance bias and detection bias) Medication used	High risk	Not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	High risk	All pre-specified primary and secondary outcomes are reported; however data could not be meta-analysed as the SDs were missing
Other bias	Low risk	The study appears to be free of other sources of bias

Lundstam 1980

Methods	• Study design: parallel RCT • Study duration: NS • Duration of follow-up: 25 min
Participants	• Country: Sweden • Setting: single centre • Number: treatment group (9); control group (10) • Age range: 24 to 69 y • Sex (M/F): NS • Exclusion criteria: NS
Interventions	Treatment group • Diclofenac: 25 mg (IM) Control group • Placebo
Outcomes	• VAS-100: 15, 25 min • Patient reported pain scale
Notes	• Source of funding: NS

Risk of bias

Bias	Authors' judgement	Support for judgement

Lundstam 1980 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) Medication used	Low risk	Participants and clinician
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	All pre-specified primary and secondary outcomes are reported
Other bias	Low risk	The study appears to be free of other sources of bias

Lupi 1986

Methods	• Study design: parallel RCT • Study duration: NS • Duration of follow-up: NS
Participants	• Country: Italy • Setting: NS • Patients with ureteral colic aged 18 to 70 y • Number: treatment group 1 (104); treatment group 2 (101) • Mean age ± SD (years): treatment group 1 (41.03 ± 14.38); treatment group 2 (41.05 ± 14.11) • Sex (M/F): treatment group 1 (65/39); treatment group 2 (72/29) • Exclusion criteria: taken analgesic in the 4 h proceeding examination; diagnostic investigations did not confirm the initial diagnosis
Interventions	Treatment group 1 • Pirprofen: 400 mg/4 mL (IM) Treatment group 2 • Meglumine indomethacin: 77.2 mg/2 mL (IM)
Outcomes	• Pain intensity measured by ACCS-100 mm (Analogue Chromatic Continuous Scale) at baseline, 15, 30, 60 min, and 30 min after the second injection • Need for rescue medication
Notes	• Source of funding: NS

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation list was used

Lupi 1986 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) Medication used	Low risk	Double blind; patients and observers were blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	All pre-specified primary and secondary outcomes are reported
Other bias	Low risk	The study appears to be free of other sources of bias

Magrini 1984

Methods	• Study design: parallel RCT • Study duration: NS • Duration of follow-up: 180 min
Participants	• Country: Italy • Setting: single centre • Patients aged 30 to 75 y; presence of severe or very severe pain; verbal consent • Number: treatment group 1 (10); treatment group 2 (10); control group (10) • Median age, range (years): treatment group 1 (48.5, 30 to 69); treatment group 2 (50.5, 42 to 60); control group (42.5, 32 to 75) • Sex (M/F): NS • Exclusion criteria: history of haemorrhagic disorders or peptic ulcer; severe hepatic, kidney, respiratory, or cardiac insufficiency; obesity; diabetes mellitus; severely debilitated patients, narcotics addicts; known hypersensitivity to ketoprofen or ASA; previously received analgesics; unlikely to cooperate or to give reliable answers
Interventions	Treatment group 1 • Ketoprofen: 200 mg (IV) Treatment group 2 • Lysine acetyl salicylate: 1 g (IV) Control group • Placebo: IV bolus injection
Outcomes	• 5 scale pain intensity score: 0, 15, 30, 60, 120, 180 min after injection • VAS-10: (after last interview ˜180 minutes or before injecting second dose) (no relief = 0, complete relief = 10) • Peak pain intensity difference • Sum of pain Intensity difference • Developing adverse effects • Heart rate, BP • Need for rescue medication

Magrini 1984 *(Continued)*

Notes	• Source of funding: NS • Renal colic diagnosis was based on history and clinical examination and was confirmed in most cases by roentgenographic examination and urinalysis (not done for all subjects)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Low risk	Subjects randomly were allocated from identically numbered and coded ampoules
Blinding (performance bias and detection bias) Medication used	Low risk	Not discussed however the author mentions that it is a double-blind study
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	All pre-specified primary and secondary outcomes are reported
Other bias	High risk	Same method of diagnosis was not used in all patients

Marthak 1991

Methods	• Study design: parallel RCT • Study duration: NS • Duration of follow-up: 60 min
Participants	• Country: India • Setting: multicentre • History and signs or symptoms of moderate the severe renal or ureteric colic • Number: treatment group 1 (75); treatment group 2 (78) • Mean age, range (years): treatment group 1 (32.3, 18 to 68); treatment group 2 (32.8, 18 to 71) • Sex (M/F): treatment group 1 (65/10); treatment group 2 (66/11) • Exclusion criteria: asthma, urticaria or rhinitis precipitated by aspirin or other prostaglandin synthetase inhibiting drugs; pregnancy; severe cardiac, kidney or hepatic insufficiency; peptic ulcer; know hypersensitivity to study drugs; pregnant; use of strong analgesics in 3 h preceding trial drug administration
Interventions	Treatment group 1 • Diclofenac: 75 mg (IM) treatment group 2 • Dipyrone: 1g (IM) • Pitofenone: 4 mg (IM) • Fenpiverinium: 0.04 mg (IM)
Outcomes	• VAS-10: degree of pain relief

Marthak 1991 *(Continued)*

	• BP and pulse rate
Notes	• Source of funding: NS

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) Medication used	Unclear risk	Single blinded, method not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	14 patients were excluded after randomisation due to wrong diagnosis. Intention-to-treat analysis was not employed
Selective reporting (reporting bias)	Low risk	All pre-specified primary and secondary outcomes are reported
Other bias	Low risk	The study appears to be free of other sources of bias

Martin Carrasco 1993

Methods	• Study design: parallel RCT • Study duration: NS • Duration of follow-up: 60 min
Participants	• Country: Spain • Setting: multicentre • Number: 34 • Mean age ± SD (years): treatment group 1 (41.3 ± 13.9); treatment group 2 (40.8 ± 14.9) • Sex (M/F): NS • Exclusion criteria: NS
Interventions	Treatment group 1 • Ketorolac: 30 mg (IV) Treatment group 2 • Dipyrone: 2.5 g (IV) • Antispasmodic (IV)
Outcomes	• VAS-100: 0, 30, 60 min
Notes	• Source of funding: NS

Risk of bias

Martin Carrasco 1993 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Sequences generation only described as a random list
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) Medication used	Low risk	Double blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	All pre-specified primary and secondary outcomes are reported
Other bias	Low risk	The study appears to be free of other sources of bias

Miano 1986

Methods	• Study design: parallel RCT • Study duration: NS • Duration of follow-up: 120 min
Participants	• Country: Italy • Setting: multicentre • Number: treatment group 1 (103); treatment group 2 (96) • Mean age (range): 44 years (17 to 78) • Sex (M/F): NS • Exclusion criteria: NS
Interventions	Treatment group 1 • Tiropramide: 50 mg (IV) Treatment group 2 • Butylscopolamine: 20 mg (IV)
Outcomes	• Dundee Scale-5: 0, 15, 30, 60, 120 min
Notes	• Source of funding: NS

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Predefined random sequence
Allocation concealment (selection bias)	Unclear risk	Not reported

Miano 1986 *(Continued)*

Blinding (performance bias and detection bias) Medication used	Low risk	Participants and outcomes assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	All pre-specified primary and secondary outcomes are reported; data could not be included in our meta-analyses
Other bias	Low risk	The study appears to be free of other sources of bias

Miralles 1987

Methods	• Study design: parallel RCT • Study duration: NS • Duration of follow-up: 30 min
Participants	• Country: Spain • Setting: NS • Number: treatment group 1 (27); treatment group 2 (23) • Mean age (range): 43.2 years (17 to 72) • Sex (M/F): NS • Exclusion criteria: allergy; peptic ulcer disease; haematological disorders; pregnancy; analgesics 6 h prior to admission
Interventions	Treatment group 1 • Diclofenac: 75 mg (IM) Treatment group 2 • Dipyrone: 2 g (IM)
Outcomes	• VAS-100: 30 min
Notes	• Source of funding: NS

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation list was used
Allocation concealment (selection bias)	Low risk	Randomly numbered closed envelops were used and the dose was given in the absence of the physicians
Blinding (performance bias and detection bias) Medication used	Low risk	Patient and investigator blinded
Incomplete outcome data (attrition bias)	Low risk	No missing outcome data

Miralles 1987 *(Continued)*

All outcomes

Selective reporting (reporting bias)	Low risk	All pre-specified primary and secondary outcomes are reported
Other bias	Low risk	The study appears to be free of other sources of bias

Mora Durban 1995

Methods	• Study design: parallel RCT • Study duration: NS • Duration of follow-up: 60 min
Participants	• Country: Spain • Setting: multicentre • Patients aged 18 to 75 y with intense or very intense renal colic pain, diagnosis was confirmed by plain abdominal radiography + urine analysis for all patients • Number: treatment group 1 (67); treatment group 2 (68) • Mean age ± SD (years): treatment group 1 (40.3 ± 12.9); treatment group 2 (36.6 ± 11.2) • Sex (M/F): treatment group 1 (42/25); treatment group 2 (41/27) • Exclusion criteria: temperature > 37.5°C; pregnant and breastfeeding women; receiving treatment within 8 h prior to admission; receiving analgesic, antispasmodics and calcium channel blockers; history of ulcer; GI bleeding; hepatic/kidney failure; blood dyscrasias; asthma or allergy to any of the study medication
Interventions	Treatment group 1 (single dose injection) • Flurbiprofen: 150 mg (IM) Treatment group 2 (single dose injection) • Dipyrone: 2 g (IM) • Hyoscine-N-butylbromide: 20 mg (IM)
Outcomes	• Pain intensity assessed by VRS of five point (0 to 4): baseline, 5, 10, 20, 30, 45, 60 min • VAS-10 • Global evaluation of treatment by patients and investigators base on "excellent, good, regular and none" scale
Notes	• Source of funding: NS

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A randomisation list was used separately for each hospital and blocked randomisation was employed by a computer program
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) Medication used	Low risk	Patients and investigators

Mora Durban 1995 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	High risk	135 subjects entered, however 128 were entered for analysis (7 were excluded from efficacy analysis), so ITT was not used
Selective reporting (reporting bias)	Low risk	All pre-specified primary and secondary outcomes are reported.
Other bias	Low risk	The study appears to be free of other sources of bias

Muriel 1993

Methods	• Study design: parallel RCT • Study duration: NS • Duration of follow-up: 6 h
Participants	• Country: Spain • Setting: multicentre • Number: treatment group 1 (43); treatment group 2 (45); treatment group 3 (41) • Mean age ± SD (years): treatment group 1 (47 ± 2); treatment group 2 (48 ± 2); treatment group 3 (48 ± 2) • Sex (M/F): NS • Exclusion criteria: NS
Interventions	Treatment group 1 • Dipyrone: 1g (IM) Treatment group 2 • Dipyrone: 2g (IM) Treatment group 3 • Diclofenac: 75 mg (IM)
Outcomes	• VAS-100: 10, 20, 30, 60 min and 6 h
Notes	• Source of funding: NS

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) Medication used	Low risk	Participants and Investigator
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data

Muriel 1993 *(Continued)*

Selective reporting (reporting bias)	Low risk	All pre-specified primary and secondary outcomes are reported
Other bias	Low risk	The study appears to be free of other sources of bias

Muriel-Villoria 1995

Methods	• Study design: parallel RCT • Study duration: December 1988 to March 1991 • Duration of follow-up: 6 h
Participants	• Country: Spain • Setting: multicentre • Diagnosed as having acute renal colic on the basis of presenting symptoms (colicky pain in the flank and/or radiating to homolateral hemiabdomen, and/or radiating to genitalia, with or without vegetative symptoms • Number: treatment group 1 (71); treatment group 2 (30); treatment group 3 (67); treatment group 4 (71); treatment group 5 (32); treatment group 6 (22) • Mean age ± SD (years): treatment group 1 (49 ± 13); treatment group 2 (47 ± 13); treatment group 3 (47 ± 13); treatment group 4 (45 ± 15); treatment group 5 (46 ± 14); treatment group 6 (52 ± 6) • Sex (% males): treatment group 1 (55); treatment group 2 (50); treatment group 3 (49); treatment group 4 (48); treatment group 5 (56); treatment group 6 (36) • Exclusion criteria: allergy; Lactation; pregnancy; underlying disease
Interventions	Treatment group 1 • Dipyrone: 1 g (IM) Treatment group 2 • Dipyrone: 1 g (IV) Treatment group 3 • Dipyrone 2 g (IM) Treatment group 4 • Dipyrone: 2 g (IV) Treatment group 5 • Diclofenac: 75 mg (IM) Treatment group 6 • Diclofenac: 75 mg (IV)
Outcomes	• VAS-100: 10, 20, 30, 60 min; 2, 4, 6 h • Vital signs: BP and pulse rate • Need for rescue medication
Notes	• Source of funding: NS

Risk of bias

Bias	Authors' judgement	Support for judgement

Muriel-Villoria 1995 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) Medication used	Low risk	Participants and Investigators; double dummy
Incomplete outcome data (attrition bias) All outcomes	Low risk	20 eligible patients excluded for different reasons. All outcomes accounted for the rest of the patients
Selective reporting (reporting bias)	Low risk	All pre-specified primary and secondary outcomes are reported.
Other bias	Low risk	The study appears to be free of other sources of bias

Pavlik 2004

Methods	• Study design: parallel RCT • Study duration: October 2000 to February 2001 • Duration of follow-up: 6 h
Participants	• Country: Czech Republic • Setting: multicentre • Patients aged between 18 and 65 y with haematuria and moderate to severe pain (> 50 mm on a 100-mm VAS) due to suspected renal colic starting within the 24 h before presentation • Number: treatment group 1 (31); treatment group 2 (32) • Mean age ± SD (years): treatment group 1 (45.84 ± 12.29); treatment group 2 (42.63 ± 12.27) • Sex (M/F): treatment group 1 (22/9); treatment group 2 (27/5) • Exclusion criteria: pregnancy or breast feeding; antispasmodic agent or prostaglandin synthesis inhibitor 2 h before presentation, kidney or hepatic dysfunction, severe or malignant hypertension; severe kidney disease
Interventions	Treatment group 1 • Cizolirtine: 350 mg (IV) Treatment group 2 • Metamizole: 2500 mg (IV, slow single dose)
Outcomes	• VAS-100: every 30 min to 360 min • Need for rescue medication
Notes	• Source of funding: NS

Risk of bias

Bias	Authors' judgement	Support for judgement

Pavlik 2004 *(Continued)*

Random sequence generation (selection bias)	Low risk	Pre-established random list
Allocation concealment (selection bias)	Unclear risk	Consecutive allocation based on the random list but not clear if the investigator were able to identify allocation group.
Blinding (performance bias and detection bias) Medication used	Low risk	Participants and investigators
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only one patient excluded due to need for surgery
Selective reporting (reporting bias)	Low risk	All pre-specified primary and secondary outcomes are reported
Other bias	Low risk	The study appears to be free of other sources of bias

Pellegrino 1999

Methods	• Study design: parallel RCT • Study duration: NS • Duration of follow-up: 120 min
Participants	• Country: Argentina • Setting: NS • Number: treatment group 1 (29); treatment group 2 (31) • Mean age ± SD (years): treatment group 1 (46.68 ± 12.59); treatment group 2 (41.83 ± 11.76) • Sex (M/F): treatment group 1 (17/12); treatment group 2 (21/10) • Exclusion criteria: NS
Interventions	Treatment group 1 • Diclofenac: 75 mg (IV) Treatment group 2 • Lysine clonixinate: 200 mg (IV)
Outcomes	• VAS-10: 20, 60, 120 min
Notes	• Source of funding: NS

Risk of bias

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

Pellegrino 1999 *(Continued)*

Blinding (performance bias and detection bias) Medication used	Low risk	Double blind
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	All pre-specified primary and secondary outcomes are reported
Other bias	Low risk	The study appears to be free of other sources of bias

Quilez 1983

Methods	• Study design: parallel RCT • Study duration: NS • Duration of follow-up: 30 min
Participants	• Country: Spain • Setting: NS • Number: treatment group 1 (23); treatment group 2 (24); treatment group 3 (14) • Mean age ± SD (years): treatment group 1 (50.91 ± 14.89); treatment group 2 (43.70 ± 14.23); treatment group 3 (44.85 ± 14.03) • Sex (M/F): treatment group 1 (14/9); treatment group 2 (14/10); treatment group 3 (8/6) • Exclusion criteria: NS
Interventions	Treatment group 1 • Hyoscine-N-butylbromide: 20 mg (IM) Treatment group 2 • Diclofenac: 75 mg (IM) Treatment group 3 • Pentazocine: 30 mg (IM)
Outcomes	• Pain assessment at 30 min, 3 categories (totally, partially, no change)
Notes	• Source of funding: NS

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias)	Unclear risk	Not reported

Quilez 1983 *(Continued)*

Medication used		
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	All pre-specified primary and secondary outcomes are reported
Other bias	Low risk	The study appears to be free of other sources of bias

Romics 2003

Methods	• Study design: parallel RCT • Study duration: June 1999 to June 2000 • Duration of follow-up: 40 min
Participants	• Country: international (Croatia, Estonia, Hungary, Latvia) • Setting: multicentre (11) • Patients with renal spasm, typical physical complaints; a pain intensity of ≥ 50% on a 10 cm VAS marked by the patient; a ureteric or kidney stone verified by ultrasonography and/or native abdominal X-ray • Number: treatment group (48); control group (54) • Mean age ± SD (years): treatment group (42.5 ± 11.25); control group (41.7 ± 10.79) • Sex (M/F): NS • Exclusion criteria: allergy to drotaverine; need for surgery; muscle relaxant within 3 d; pregnancy; unstable kidney or hepatic disease; cardiac disease
Interventions	Treatment group • Drotaverine: 40 mg (IV) Control group • Placebo
Outcomes	• VAS-100: 40 min • Four grade pain intensity scale: 40 min • Need for rescue medication
Notes	• No NSAIDs • Source of funding: NS

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias)	Low risk	Participants and investigator

Romics 2003 *(Continued)*

Medication used		
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	All pre-specified primary and secondary outcomes are reported
Other bias	Low risk	The study appears to be free of other sources of bias

Sanahuja 1990

Methods	• Study design: parallel RCT • Study duration: NS • Duration of follow-up: NS
Participants	• Country: Spain • Setting: multicentre • Number: treatment group 1 (29); treatment group 2 (28) • Mean age ± SD (years): treatment group 1 (44.5 ± 14.3); treatment group 2 (42.4 ± 11.0) • Sex (M/F): NS • Exclusion criteria: UTI; initial diagnosis was changed; pregnancy; allergy to study drugs
Interventions	Treatment group 1 • Diclofenac: 75 mg (IM) Treatment group 2 • Baralgan: 5 ml (IV, slow infusion)
Outcomes	• Algometric descriptive scale (0, 1, 2) for pain intensity • Need for rescue medication
Notes	• Source of funding: NS

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) Medication used	Low risk	Patients and investigator
Incomplete outcome data (attrition bias) All outcomes	High risk	4 patients excluded after randomisation not included in the analysis

Sanahuja 1990 *(Continued)*

Selective reporting (reporting bias)	Low risk	All pre-specified primary and secondary outcomes are reported
Other bias	Low risk	The study appears to be free of other sources of bias

Sanchez-Carpena 2003

Methods	• Study design: parallel RCT • Study duration: June 1998 to September 1999 • Duration of follow-up: 6 h
Participants	• Country: international (Spain, Sweden, Finland) • Setting: multicentre (18) • Diagnosis of renal colic • Number: treatment group 1 (112); treatment group 2 (113); treatment group 3 (108) • Mean age ± SD (years): treatment group 1 (42.1 ± 12.4); treatment group 2 (41.7 ± 13.4); treatment group 3 (39.7 ± 13.0) • Sex (M/F): treatment group 1 (70/42); treatment group 2 (70/43); treatment group 3 (68/40) • Exclusion criteria: complicated renal colic, ureteronephrosis, pyelonephritis or acute kidney failure; allergy; pregnancy and lactation; history of alcohol or drug addiction
Interventions	Treatment group 1 • Dexketoprofen: 25 mg (IM) Treatment group 2 • Dexketoprofen: 50 mg (IM) Treatment group 3 • Dipyrone: 2g (IM)
Outcomes	• VAS-100: 15, 30, 45 min; 1, 2, 4, 6 h • VRS: 15, 30, 45 min; 1, 2, 4, 6 h • Need for rescue medication
Notes	• Source of funding: Menarini Group

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated randomisation
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) Medication used	Low risk	Observers and patients blinded
Incomplete outcome data (attrition bias)	High risk	38 patients were excluded after randomisation and did not enter the analysis

Sanchez-Carpena 2003 *(Continued)*

All outcomes

Selective reporting (reporting bias)	Low risk	All pre-specified primary and secondary outcomes are reported
Other bias	Unclear risk	Industry sponsorship could be a source of bias

Sanchez-Carpena 2007

Methods	• Study design: parallel RCT • Study duration: May 2001 to April 2002 • Duration of follow-up: 1 week
Participants	• Country: Spain • Setting: multicentre (17) • Diagnosis was initially based upon colicky pain in the flank and/or radiating to the homolateral hemiabdomen and/or genitalia with or without vegetative symptoms. • Number: treatment group 1 (101); treatment group 2 (104); treatment group 3 (103) • Mean age ± SD (years): treatment group 1 (37.6 ± 11.7); treatment group 2 (39.9 ± 12.4); treatment group 3 (39.1 ± 11.0) • Sex (M/F): treatment group 1 (61/40); treatment group 2 (68/36); treatment group 3 (65/38) • Exclusion criteria: hypersensitivity to study drugs; history of serious medical conditions; pregnancy or lactation; alcohol or drug addiction; hydronephrosis; pyelonephritis
Interventions	Treatment group 1 • Dexketoprofen: 25 mg (IV) Treatment group 2 • Dexketoprofen: 50 mg (IV) Treatment group 3 • Dipyrone: 2 g (IV)
Outcomes	• Decrease in pain severity measured with VAS-100 • VRS • Sum of pain intensity differences • Sum of analogue pain intensity differences • Need for rescue medication
Notes	• Source of funding: by Menarini group

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation
Allocation concealment (selection bias)	Low risk	Sealed envelop
Blinding (performance bias and detection bias)	Low risk	Observer and patients (double dummy)

Sanchez-Carpena 2007 *(Continued)*

Medication used

Incomplete outcome data (attrition bias) All outcomes	Low risk	According to intention to treat principle: all randomised patients entered the analysis, although 31 were excluded from the study
Selective reporting (reporting bias)	Low risk	All pre-specified primary and secondary outcomes are reported.
Other bias	Unclear risk	Industry sponsorship could be a source of bias

Snir 2008

Methods	• Study design: parallel RCT • Study duration: NS • Duration of follow-up: 40 min
Participants	• Country: Israel • Setting: multicentre (2) • Patients with clear clinical presentation or renal colic supported by urinalysis and/or imaging findings • Number: treatment group 1 (29); treatment group 2 (30); treatment group 3 (27) • Mean age (years): treatment group 1 (46.2); treatment group 2 (44.1); treatment group 3 (43.9) • Sex (M/F): treatment group 1 (22/7); treatment group 2 (26/4); treatment group 3 (20/7) • Exclusion criteria: complete arteriovenous block; peptic ulcer disease; asthma; known allergy to papaverine hydrochloride or sodium diclofenac; children; breast-feeding women; patients who received analgesics within 4 h before admission
Interventions	Treatment group 1 • Papaverine hydrochloride: 120 mg (IV) Treatment group 2 • Sodium diclofenac: 75 mg (IM) Treatment group 3 • Papaverine hydrochloride: 120 mg (IV) • Sodium diclofenac: 75 mg (IM)
Outcomes	• VAS-10: 0, 20, 40 min • Recorded adverse reactions • BP • Need for rescue medication
Notes	• Source of funding: NS

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported

Snir 2008 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) Medication used	Low risk	It was mentioned that it was a single-blinded study and the treating physicians were not blinded. Patients were blind to the intervention
Incomplete outcome data (attrition bias) All outcomes	High risk	90 subjects randomised, 4 were excluded due to incomplete data. All outcomes accounted for the rest
Selective reporting (reporting bias)	Low risk	All pre-specified primary and secondary outcomes are reported
Other bias	Low risk	The study appears to be free of other sources of bias

Stankov 1994

Methods	• Study design: parallel RCT • Study duration: NS • Duration of follow-up: 120 min
Participants	• Country: Germany • Setting: multicentre (8) • Patients with acute renal colic • Number: treatment group 1 (36); treatment group 2 (33); treatment group 3 (35) • Mean age ± SD: 46.4 ± 16.2 years • Sex (M/F): (71/33) • Exclusion criteria: pretreatment with analgesics or antispasmodics last 24 h; Intolerance to study drugs; Narrow-angle glaucoma; megacolon; acute pulmonary oedema; bronchial asthma; analgesic-inducible asthma; chronic respiratory tract infection; tachyarrhythmia; circulatory instability; systolic BP < 100 mm Hg; damaged haematopoiesis; intoxication with alcohol or other drugs; pregnant or nursing women
Interventions	Treatment group 1 • Dipyrone: 2.5 g (IV) Treatment group 2 • Butylscopolamine: 20 mg (IV) Treatment group 3 • Tramadol: 100 mg (IV)
Outcomes	• VAS-100: 10, 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120 min • 5-point scale • Need for rescue medication
Notes	• Source of funding: NS

Risk of bias

Bias	Authors' judgement	Support for judgement

Stankov 1994 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) Medication used	Low risk	Observer and patients blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only 2 patients excluded after randomisation, one lost to follow-up
Selective reporting (reporting bias)	Low risk	All pre-specified primary and secondary outcomes are reported.
Other bias	Low risk	The study appears to be free of other sources of bias

Stein 1996

Methods	• Study design: parallel RCT • Study duration: NS • Duration of follow-up: 120 min
Participants	• Country: Israel • Setting: NS • Patients with acute onset of flank pain along with macrohaematuria or microhaematuria and who were diagnosed as having moderate to severe renal colic were eligible; roentgenographic evidence of kidney or ureteral stone or obstruction was not mandatory • Number: treatment group 1 (27); treatment group 2 (30) • Mean age, range (years): treatment group 1 (39.1, 18 to 44); treatment group 2 (41.4, 22 to 65) • Sex (M/F): treatment group 1 (24/3); treatment group 2 (21/9) • Exclusion criteria: history of gastric or duodenal ulcer; pregnancy or lactation; severely impaired kidney or liver function; bleeding disorders; known hypersensitivity to NSAIDs
Interventions	Treatment group 1 • Ketorolac: 60 mg (IM) Treatment group 2 • Diclofenac: 75 mg (IM)
Outcomes	• 4 point VAS: 60, 120 min • Need for rescue medication
Notes	• Source of funding: NS

Risk of bias

Bias	Authors' judgement	Support for judgement

Stein 1996 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding (performance bias and detection bias) Medication used	Low risk	Participants and investigators
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	All pre-specified primary and secondary outcomes are reported
Other bias	Low risk	The study appears to be free of other sources of bias

Supervia 1998

Methods	• Study design: parallel RCT • Study duration: 10-month study period • Duration of follow-up: 30 min
Participants	• Country: Spain • Setting: multicentre • Patients with acute renal colic, confirmed by clinical signs and symptoms, urine analysis or visualisation of the calculus by abdominal radiology or ultrasonography • Number: treatment group 1 (40); treatment group 2 (40) • Mean age ± SD (years): treatment group 1 (36.5 ± 14.1); treatment group 2 (41.5 ± 15.2) • Sex (M/F): treatment group 1 (23/17); treatment group 2 (31/9) • Exclusion criteria: allergy to salicylates or NSAID; oral mucosal lesions; anticoagulation therapy; pregnant or lactation; peptic ulcer; impaired kidney function; GI bleeding' haematological disorders
Interventions	Treatment group 1 • Piroxicam: 20 mg (sublingual) • Placebo: IM Treatment group 2 • Diclofenac: 75 mg (IM) • Placebo: sublingual
Outcomes	• VAS-10: 30 min • Need for rescue medication
Notes	• Source of funding: NS

Risk of bias

Bias	Authors' judgement	Support for judgement

Supervia 1998 *(Continued)*

Random sequence generation (selection bias)	Low risk	Random number
Allocation concealment (selection bias)	Low risk	Closed envelope
Blinding (performance bias and detection bias) Medication used	Low risk	Observer blinded, patients cannot be blinded because of different mode of administration
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	All pre-specified primary and secondary outcomes are reported
Other bias	Low risk	The study appears to be free of other sources of bias

Vignoni 1983

Methods	• Study design: parallel RCT • Study duration: NS • Duration of follow-up: 25 min
Participants	• Country: Italy • Setting: single centre • Number: treatment group (63); control group (68) • Mean age ± SD (years): treatment group (39.2 ± 14.47); control group (37.6 ± 11.69) • Sex (M/F): NS • Exclusion criteria: renal colic not confirmed by urine analysis, IV urography or voiding of a calculus
Interventions	Treatment group • Diclofenac: 75 mg (IM) Control group • Placebo
Outcomes	• VAS-100: every 5 min up to 25 min • Need for rescue medication
Notes	• Source of funding: NS

Risk of bias

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

Vignoni 1983 *(Continued)*

Blinding (performance bias and detection bias) Medication used	Unclear risk	Double blind according to the study title; no details provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	All pre-specified primary and secondary outcomes are reported
Other bias	Low risk	The study appears to be free of other sources of bias

Walden 1993

Methods	• Study design: parallel RCT • Study duration: February 1986 to March 1988 • Duration of follow-up: 120 min
Participants	• Country: Sweden • Setting: multicentre • Patients aged > 18 y with moderate and severe pain (VAS > 50 mm) and also confirmed diagnosis of ureteral colic by urine analysis and IV urography or voiding calculus • Number: treatment group 1 (41); treatment group 2 (45) • Age range: 22 to 78 years • Sex (M/F): 60/26 • Exclusion criteria: gastroduodenal ulcer; severe cardiopulmonary disease; pregnancy; hypersensitivity to NSAID or aspirin; asthmatic bronchitis; treatment with strong analgesic before entering study
Interventions	Treatment group 1 • Ketoprofen: 100 mg (IM) Treatment group 2 • Diclofenac: 50 mg (IM)
Outcomes	• VAS-100: 10, 30, 60, 120 min post injection • VRS by patients (1: complete, 2: partial, 3: none pain relief) at 120 min • 5 scale score by the nurse • Need for rescue medication
Notes	• Source of funding: NS

Risk of bias

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

Walden 1993 *(Continued)*

Blinding (performance bias and detection bias) Medication used	Low risk	Not reported, only authors mention that the study was a double-blinded study
Incomplete outcome data (attrition bias) All outcomes	Low risk	Withdrawals were entered in the analysis, using the last obtained data prior to dropping out
Selective reporting (reporting bias)	Low risk	All pre-specified primary and secondary outcomes are reported
Other bias	Low risk	The study appears to be free of other sources of bias

BP - blood pressure; GI - gastrointestinal; IM - intramuscular; IV - intravenous; MD - mean difference; NSAIDs - nonsteroidal anti-inflammatory drugs; PID - pain intensity difference; PR - pain reduction; RCT - randomised controlled trial; US - ultrasound; VAS - visual analogue scale; VRS - verbal rating scale

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

Study	Reason for exclusion
Al-Faddagh 1996	Study report was not available
Al-Obadi 1997	Not RCT
Altay 2007	Piroxicam (IM versus sublingual)
Ayan 2013	Aromatherapy with rose essential oil as an additive intervention to conventional therapy (no medication)
Bach 1983	Stone expulsion, not treatment of renal colic
Basar 1991	Not RCT
Bergus 1996	Narcotic
Bilora 2000	No baseline VAS
Breijo 2007	Inadequate data
Catano 2004	No data on VAS or severity of pain change
Cole 1989	Prophylaxis not treatment
Cordell 1996	Narcotic
Curry 1995	Narcotic
Dellabella 2003	Stone expulsion, not treatment of renal colic
Dellabella 2005	Stone expulsion, not treatment of renal colic
El-Sherif 1995	Not RCT
Elliott 1979	Narcotic

Study	Reason for exclusion
Engelstein 1992	Treatment of stones, not renal colic
Galassi 1985	Outcome was assessed on baseline, 1 day and 10 days
Godoy 2000	Only 4 patients in renal colic group
Grenabo 1984	No VAS reported, number of patients who had recurrence of pain requiring readmission during 7 days after admission is reported
Hazhir 2010	Narcotic
Henry 1987	Narcotic
Ho 2004	Compared IM diclofenac sodium versus oral diclofenac potassium
Holdgate 2005	All participants both in treatment and control groups received morphine
Julian 1992	No data on VAS or severity of pain change
Kapoor 1989	All participants (treatment and placebo arms) received narcotic (meperidine)
Khalifa 1986	Narcotic
Laerum 1995	Recurrent renal colic study
Lishner 1985	Narcotic
Lundstam 1982	Narcotic
Mortelmans 2006	Inadequate data
Muller 1990	Treatment of stones, not renal colic; narcotic
NCT00646061	Narcotic
NCT01339624	Narcotic
Nissen1990	IV versus rectal indomethacin
Ohkawa 1997	Outcomes were evaluated before treatment, 1, 3 and 7 days after treatment
Oosterlinck 1982	Narcotic
Pardo 1984	No standard pain scale; Number of patients in each subgroup are not included to calculate RR
Persson 1985	Narcotic
Phillips 2009	No data on VAS within the first hour
Porpiglia 2000	Stone expulsion as outcome
Porpiglia 2004	Stone expulsion as outcome
Primus 1989	Narcotic

Study	Reason for exclusion
Roshani 2010	Sample size in each arm was not reported
Ruiz 1988	Not RCT
Sala-Mateus 1989	Inappropriate use of VAS
Soleimanpour 2012	Compares lidocaine to morphine (narcotic)
Timbal 1981	Detail of VAS score not provided
Viksmoen 1986	Narcotic
Wandschneider 1973	Anti-inflammatory study in urological procedures
Yencilek 2008	All patient received NSAID + antispasmodic and those who didn't respond in 60 minutes were randomised, contaminated data
Yilmaz 2005	Stone expulsion, not renal colic

RCT - randomised controlled trial

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

Tanko 1996

Methods	Unknown
Participants	Unknown
Interventions	Diclofenac sodium
Outcomes	Unknown
Notes	Unable to translate

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

NCT01543165

Trial name or title	Efficacy of nefopam and morphine in balanced analgesia for acute ureteric colic
Methods	Parallel randomised control study
Participants	18-55 year old with renal colic
Interventions	Group 1 • Sequential IV administration of ketorolac and nefopam Group 2 • Sequential IV administration of ketorolac and morphine Group 3

NCT01543165 *(Continued)*	• IV administration of ketorolac
Outcomes	VAS
Starting date	December 2012
Contact information	Kyuseok Kim, MD dremkks@snubh.org
Notes	No results available

DATA AND ANALYSES

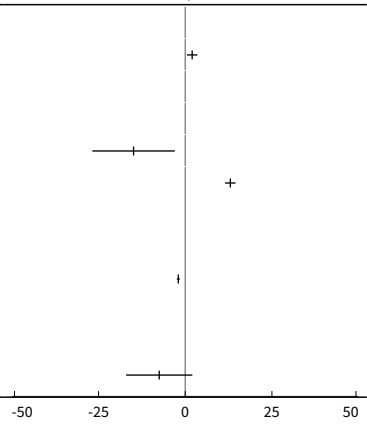
Comparison 1. Pain score: VAS

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 NSAID versus NSAID	4		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.1 Diclofenac (IM) versus dipyrone (IM) (1 g)	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
1.2 Diclofenac (IM) versus dipyrone (IM) (2 g)	2		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
1.3 Diclofenac versus indomethacin	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
1.4 Diclofenac versus etofenamate	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
2 NSAID versus antispasmodic	6		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.1 Including Dash 2012	6	403	Mean Difference (IV, Random, 95% CI)	-9.83 [-20.93, 1.28]
2.2 Excluding Dash 2012	5	303	Mean Difference (IV, Random, 95% CI)	-12.97 [-21.80, -4.14]
3 NSAID versus non-opioid	2		Mean Difference (IV, Random, 95% CI)	Totals not selected
3.1 Diclofenac versus intranasal desmopressin	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
3.2 Piroxicam versus paracetamol	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
4 NSAID + antispasmodic versus NSAID	2	310	Mean Difference (IV, Random, 95% CI)	-1.99 [-2.58, -1.40]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5 Non-opioid versus placebo	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
6 Non-opioid versus non-opioid	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
6.1 Hyoscine-N-butylbromide (IM) versus hyoscine-N-butylbromide + intranasal desmopressin	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]

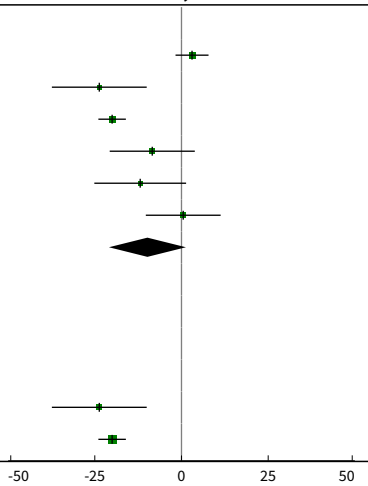
Analysis 1.1. Comparison 1 Pain score: VAS, Outcome 1 NSAID versus NSAID.

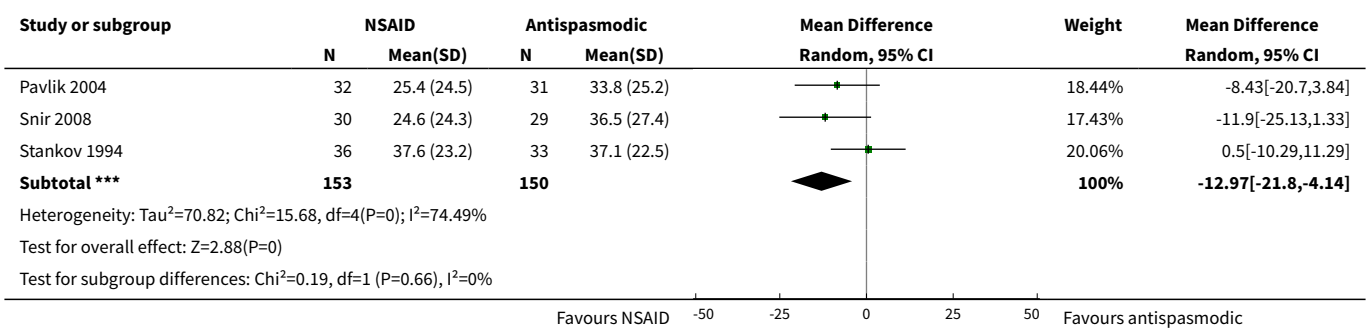
Study or subgroup	Diclofenac N	Diclofenac Mean(SD)	NSAID 2 N	NSAID 2 Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
1.1.1 Diclofenac (IM) versus dipyrone (IM) (1 g)						
Muriel 1993	41	28 (4)	43	26 (3)		2[0.48,3.52]
1.1.2 Diclofenac (IM) versus dipyrone (IM) (2 g)						
Miralles 1987	27	17.4 (19.3)	23	32.3 (23)		-14.9[-26.79,-3.01]
Muriel 1993	41	28 (4)	45	15 (3)		13[11.49,14.51]
1.1.3 Diclofenac versus indomethacin						
Laerum 1996	41	21 (1)	42	23 (1)		-2[-2.43,-1.57]
1.1.4 Diclofenac versus etofenamate						
Fraga 2003	60	33.2 (25.3)	59	40.7 (27.8)		-7.5[-17.06,2.06]



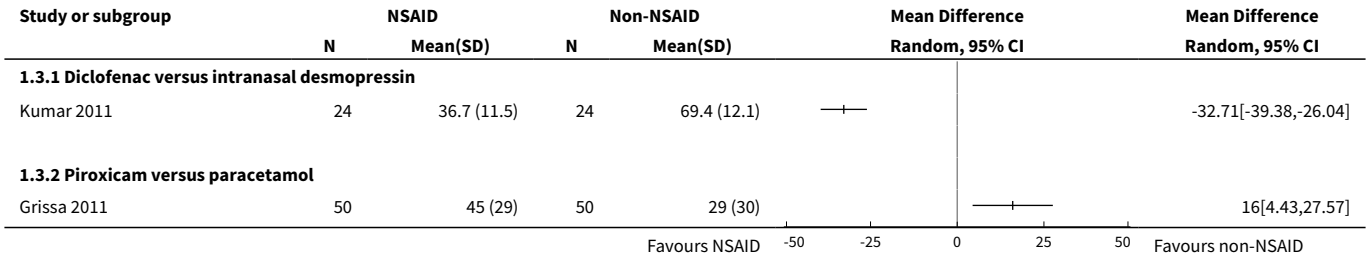
Analysis 1.2. Comparison 1 Pain score: VAS, Outcome 2 NSAID versus antispasmodic.

Study or subgroup	NSAID N	NSAID Mean(SD)	Antispasmodic N	Antispasmodic Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.2.1 Including Dash 2012							
Dash 2012	50	40.9 (11)	50	37.8 (13.2)		18.74%	3.04[-1.72,7.8]
Ergene 2001	31	38.4 (27.3)	33	62.1 (28.5)		15%	-23.7[-37.37,-10.03]
Jones 1998	24	42 (7)	24	62 (7)		18.94%	-20[-23.96,-16.04]
Pavlik 2004	32	25.4 (24.5)	31	33.8 (25.2)		15.69%	-8.43[-20.7,3.84]
Snir 2008	30	24.6 (24.3)	29	36.5 (27.4)		15.22%	-11.9[-25.13,1.33]
Stankov 1994	36	37.6 (23.2)	33	37.1 (22.5)		16.41%	0.5[-10.29,11.29]
Subtotal * **	**203**		**200**			**100%**	**-9.83[-20.93,1.28]**
Heterogeneity: Tau²=165.31; Chi²=60.93, df=5(P<0.0001); I²=91.79%							
Test for overall effect: Z=1.73(P=0.08)							
1.2.2 Excluding Dash 2012							
Ergene 2001	31	38.4 (27.3)	33	62.1 (28.5)		16.98%	-23.7[-37.37,-10.03]
Jones 1998	24	42 (7)	24	62 (7)		27.08%	-20[-23.96,-16.04]

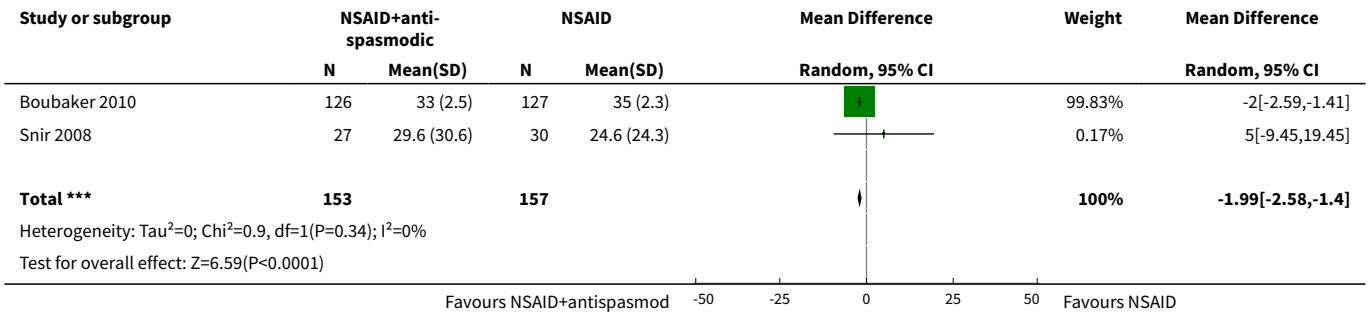




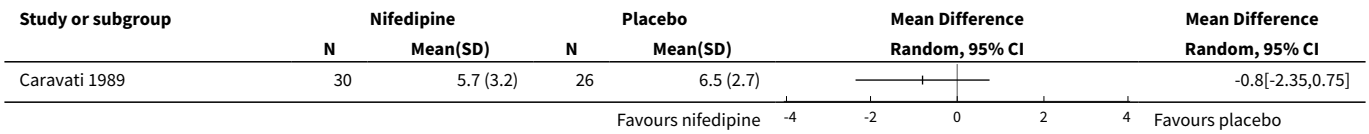
Analysis 1.3. Comparison 1 Pain score: VAS, Outcome 3 NSAID versus non-opioid.



Analysis 1.4. Comparison 1 Pain score: VAS, Outcome 4 NSAID + antispasmodic versus NSAID.

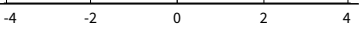


Analysis 1.5. Comparison 1 Pain score: VAS, Outcome 5 Non-opioid versus placebo.



Analysis 1.6. Comparison 1 Pain score: VAS, Outcome 6 Non-opioid versus non-opioid.

Study or subgroup	Non-opioid 1 N	Non-opioid 1 Mean(SD)	Non-opioid 2 N	Non-opioid 2 Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
1.6.1 Hyoscine-N-butylbromide (IM) versus hyoscine-N-butylbromide + intranasal desmopressin						
Kheirollahi 2010	57	3.7 (2.2)	57	6.8 (1.8)		-3.09[-3.82,-2.36]

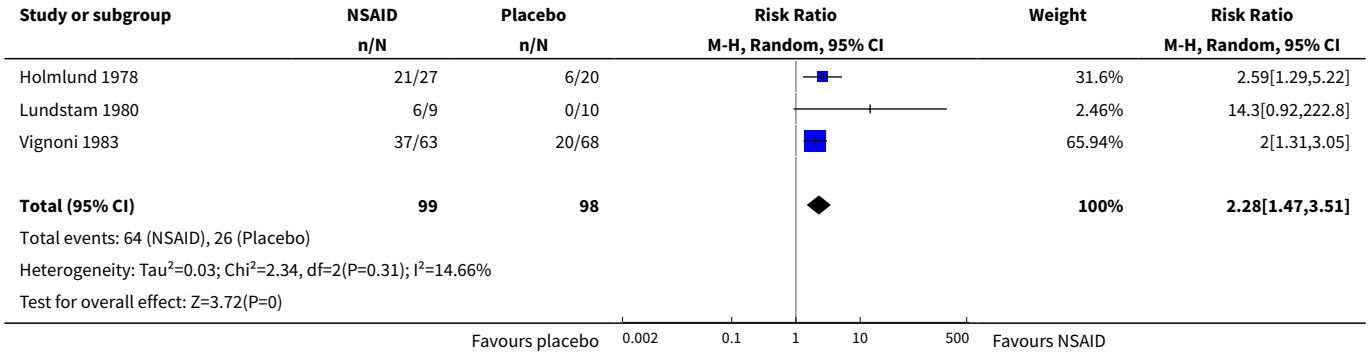


Comparison 2. 50% reduction in pain

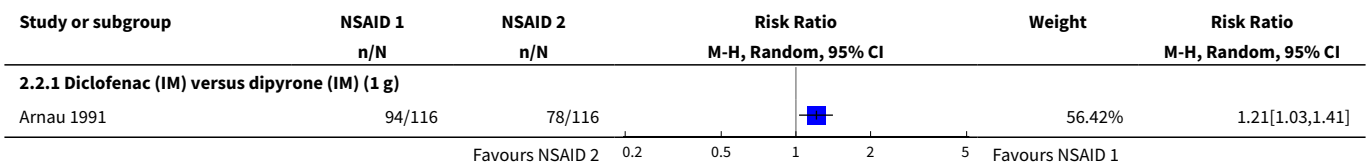
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 NSAID versus placebo	3	197	Risk Ratio (M-H, Random, 95% CI)	2.28 [1.47, 3.51]
2 NSAID versus NSAID	14		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Diclofenac (IM) versus dipyrone (IM) (1 g)	2	335	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.72, 1.47]
2.2 Diclofenac (IM) versus dipyrone (IM) (2 g)	3	366	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.81, 1.37]
2.3 Diclofenac (IM) versus dipyrone (IV) (2 g)	1	103	Risk Ratio (M-H, Random, 95% CI)	0.64 [0.49, 0.84]
2.4 Diclofenac versus piroxicam	2	144	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.81, 1.09]
2.5 Diclofenac versus ketoprofen	1	86	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.88, 1.16]
2.6 Dipyrone (2 g) versus dexketoprofen (25 mg)	2	405	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.79, 1.48]
2.7 Dipyrone (2 g) versus dexketoprofen (50 mg)	2	405	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.90, 1.07]
2.8 Dipyrone (2 g) versus dexketoprofen (25 and 50 mg)	2	610	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.85, 1.26]
2.9 Indomethacin versus other NSAID	4	412	Risk Ratio (M-H, Random, 95% CI)	1.27 [1.01, 1.60]
2.10 Indomethacin versus pirprofen	1	205	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.55, 0.88]
2.11 Ketoprofen versus parecoxib	1	297	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.75, 1.10]
3 NSAID versus antispasmodic	6		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

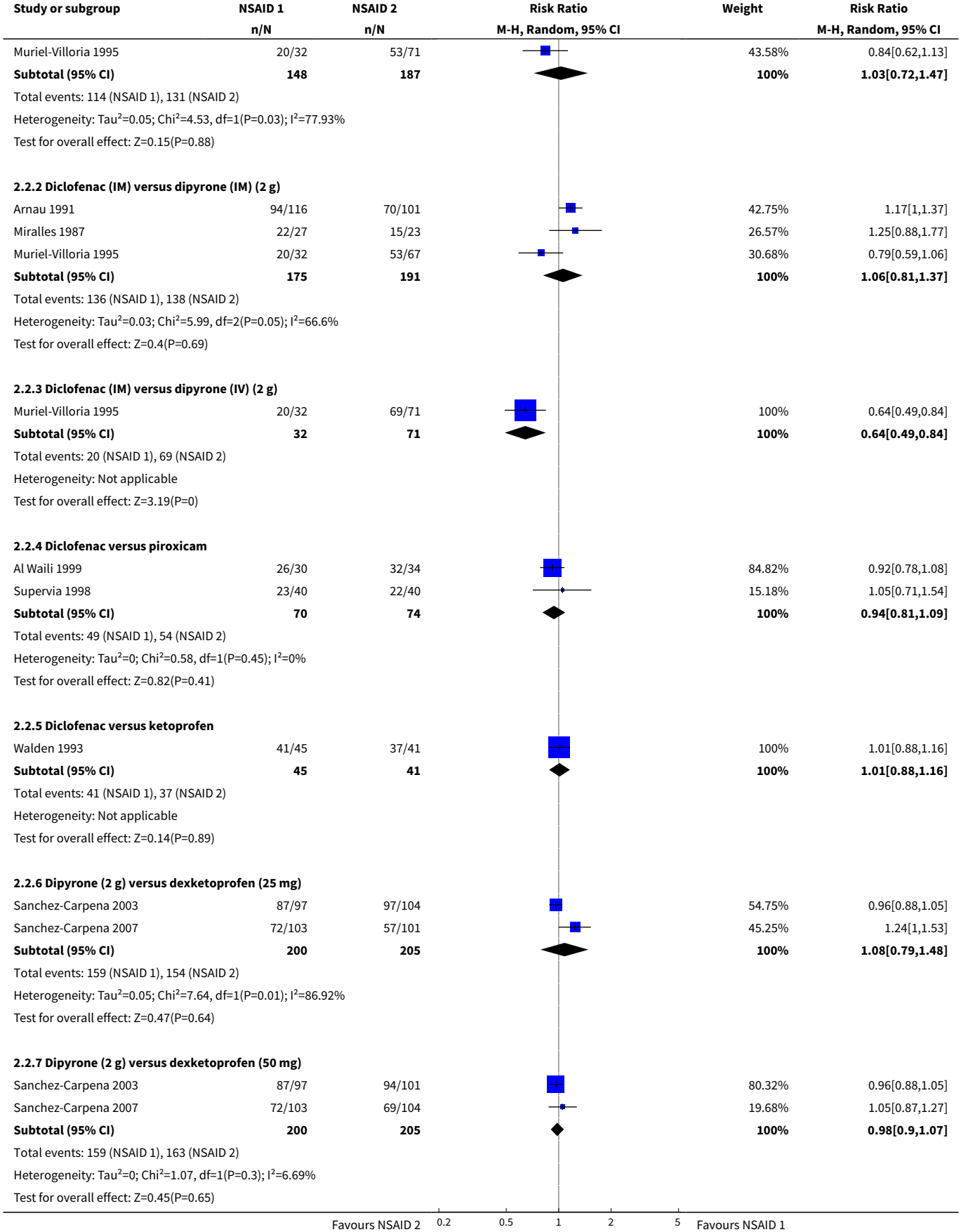
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 NSAID versus hyoscine	4	196	Risk Ratio (M-H, Random, 95% CI)	2.44 [1.61, 3.70]
3.2 NSAID versus other antispasmodic	2	163	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.87, 1.17]
4 NSAID versus other non-opioid	2		Risk Ratio (IV, Random, 95% CI)	Totals not selected
4.1 Diclofenac versus desmopressin	1		Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
4.2 Diclofenac versus ondansetron	1		Risk Ratio (IV, Random, 95% CI)	0.0 [0.0, 0.0]
5 NSAID + antispasmodic versus NSAID	8	906	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.89, 1.13]
6 NSAID + non-opioid versus non-opioid	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
7 Non-opioid versus non-opioid	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
8 Glucagon versus placebo	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

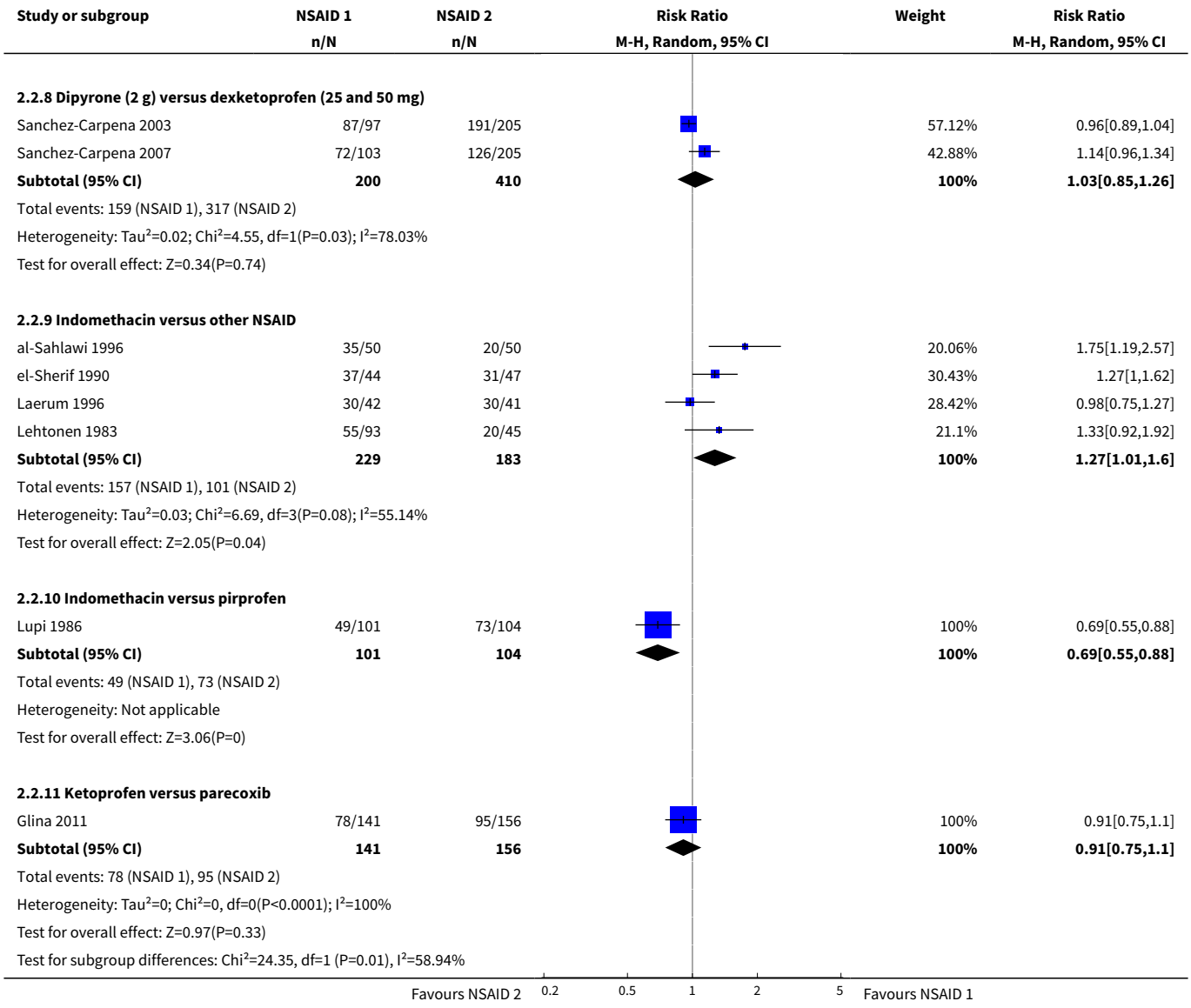
Analysis 2.1. Comparison 2 50% reduction in pain, Outcome 1 NSAID versus placebo.



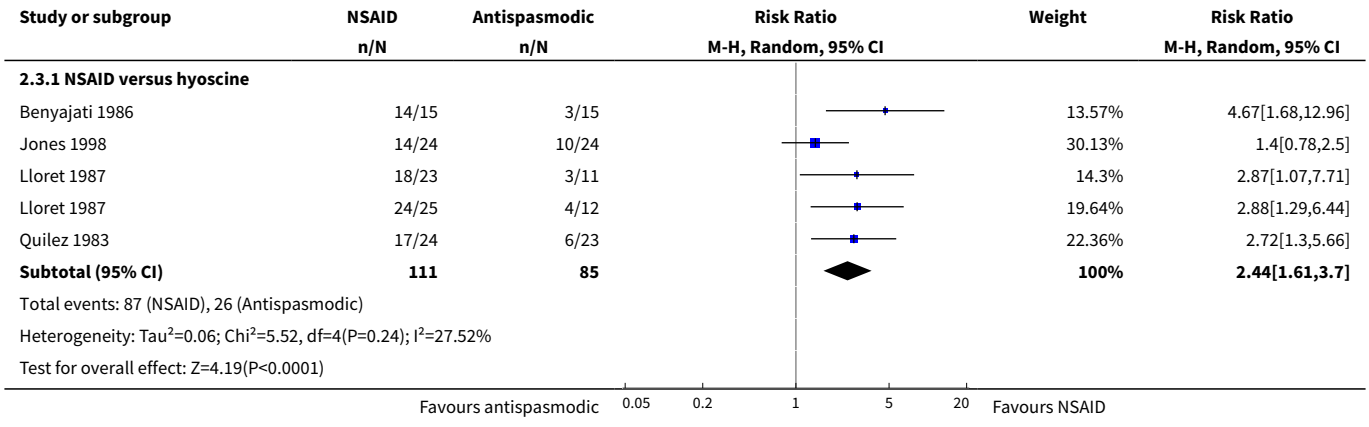
Analysis 2.2. Comparison 2 50% reduction in pain, Outcome 2 NSAID versus NSAID.

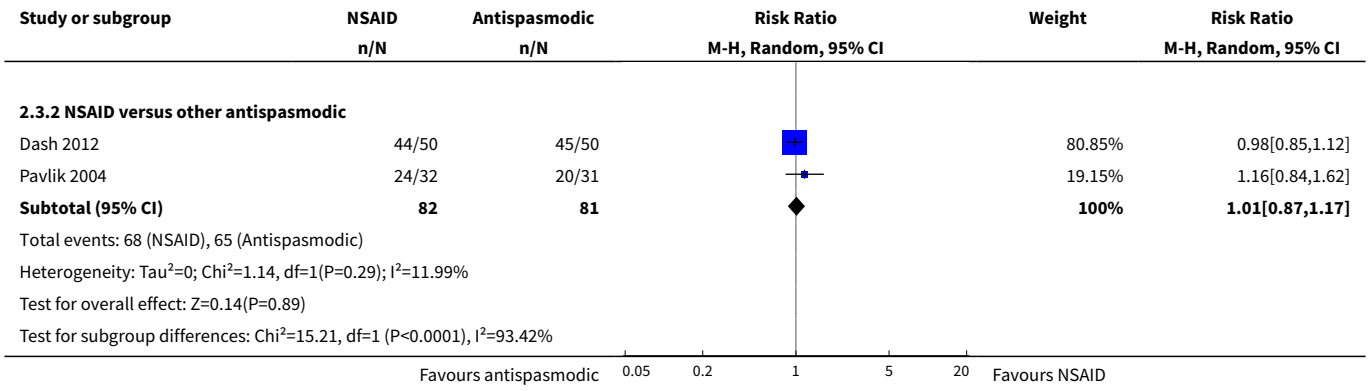




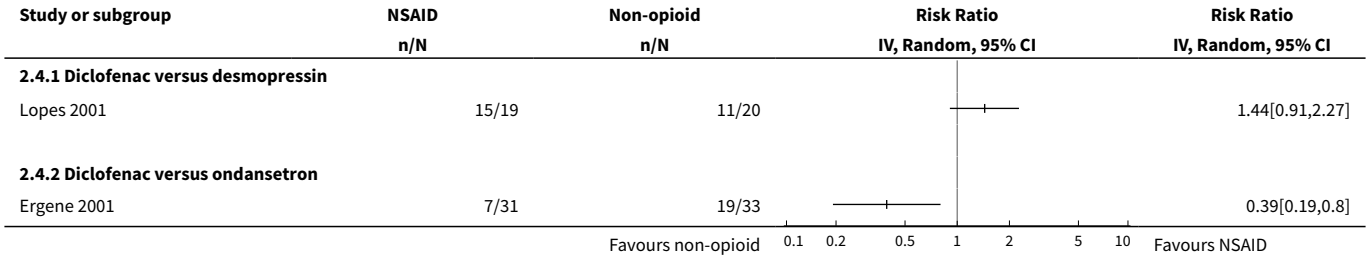


Analysis 2.3. Comparison 2 50% reduction in pain, Outcome 3 NSAID versus antispasmodic.

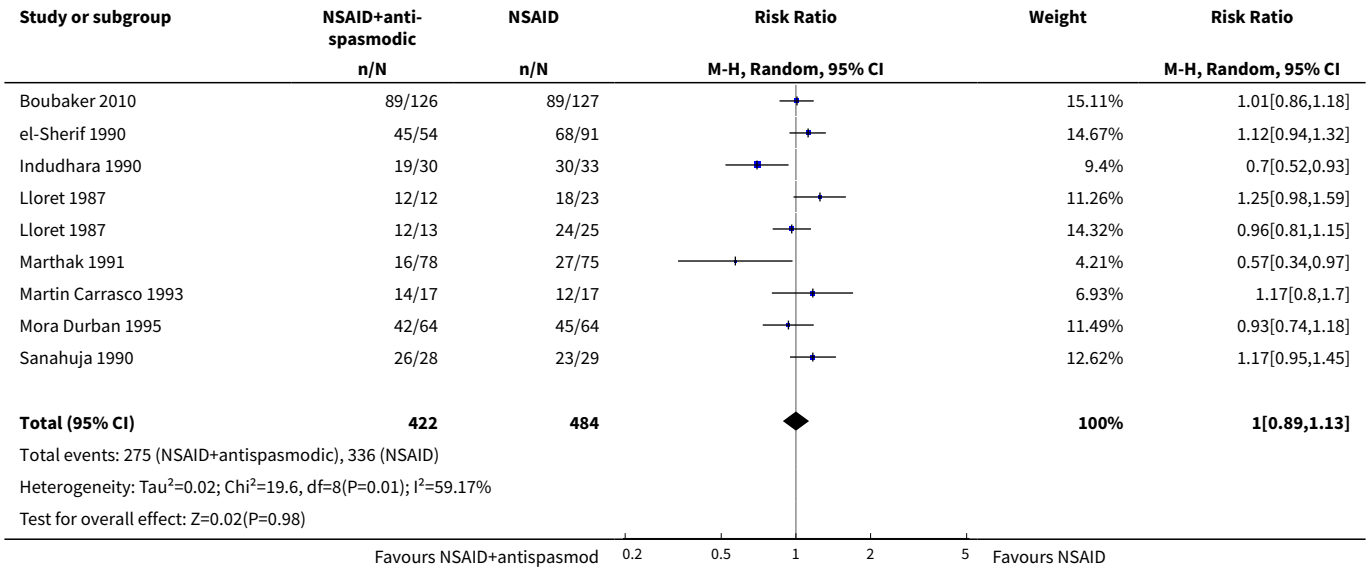




Analysis 2.4. Comparison 2 50% reduction in pain, Outcome 4 NSAID versus other non-opioid.

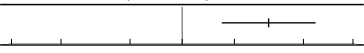


Analysis 2.5. Comparison 2 50% reduction in pain, Outcome 5 NSAID + antispasmodic versus NSAID.



Analysis 2.6. Comparison 2 50% reduction in pain, Outcome 6 NSAID + non-opioid versus non-opioid.

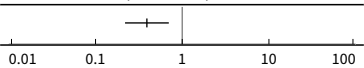
Study or subgroup	NSAIDs+non-opioid n/N	Non-opioid n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Lloret 1987	24/25	7/23		3.15[1.69,5.88]



Favours no-opioid | Favours NSAID+non-opioid

Analysis 2.7. Comparison 2 50% reduction in pain, Outcome 7 Non-opioid versus non-opioid.

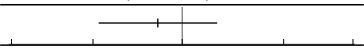
Study or subgroup	Non-opioid 1 n/N	Non-opioid 2 n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Iguchi 2002	9/30	23/30		0.39[0.22,0.7]



Favours non-opioid 2 | Favours non-opioid 1

Analysis 2.8. Comparison 2 50% reduction in pain, Outcome 8 Glucagon versus placebo.

Study or subgroup	Glucagon n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Bahn Zobbe 1986	10/11	13/13		0.91[0.72,1.15]



Favours placebo | Favours glucagon

Comparison 3. Rescue medication

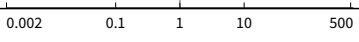
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 NSAID versus placebo	3	180	Risk Ratio (M-H, Random, 95% CI)	0.35 [0.20, 0.60]
1.1 Diclofenac versus saline	2	150	Risk Ratio (M-H, Random, 95% CI)	0.44 [0.29, 0.65]
1.2 Ketoprofen versus placebo	1	15	Risk Ratio (M-H, Random, 95% CI)	0.15 [0.03, 0.67]
1.3 Lysine acetyl salicylate versus placebo	1	15	Risk Ratio (M-H, Random, 95% CI)	0.06 [0.00, 0.95]
2 NSAID versus NSAID	18		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Diclofenac versus other NSAID	10	1263	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.59, 1.03]
2.2 Dipyrone (2 g) versus dexketoprofen (25 mg)	2	405	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.34, 1.36]
2.3 Dipyrone (2 g) versus dexketoprofen (50 mg)	2	405	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.46, 1.73]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.4 Dipyrone (IV) versus dipyrone (IM)	1	239	Risk Ratio (M-H, Random, 95% CI)	0.13 [0.04, 0.45]
2.5 Dipyrone (1 g) IM versus dipyrone (2 g) IM	1	138	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.49, 1.61]
2.6 Dipyrone (1 g) IV versus dipyrone (2 g) IV	2	149	Risk Ratio (M-H, Random, 95% CI)	5.03 [0.86, 29.25]
2.7 Indomethacin versus lysine acetyl salicylate	1	100	Risk Ratio (M-H, Random, 95% CI)	0.15 [0.04, 0.65]
2.8 Indomethacin versus other NSAID	4	517	Risk Ratio (M-H, Random, 95% CI)	1.36 [0.96, 1.94]
2.9 Ketoprofen versus lysine acetyl salicylate	1	20	Risk Ratio (M-H, Random, 95% CI)	3.0 [0.14, 65.90]
2.10 Ketoprofen versus parecoxib	1	337	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.61, 1.68]
3 NSAID versus antispasmodic	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 Including Pavlik 2004	5	363	Risk Ratio (M-H, Random, 95% CI)	0.51 [0.17, 1.48]
3.2 Excluding Pavlik 2004	4	299	Risk Ratio (M-H, Random, 95% CI)	0.34 [0.14, 0.84]
4 NSAID versus other non-opioid	3	151	Risk Ratio (M-H, Random, 95% CI)	0.32 [0.13, 0.78]
4.1 Diclofenac (75 mg) IM versus desmopressin	2	87	Risk Ratio (M-H, Random, 95% CI)	0.25 [0.04, 1.64]
4.2 Diclofenac versus ondansetron	1	64	Risk Ratio (M-H, Random, 95% CI)	0.39 [0.19, 0.80]
5 NSAID + antispasmodic versus NSAID	5	589	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.62, 1.57]
6 NSAID + non-opioid versus NSAID	2	89	Risk Ratio (M-H, Random, 95% CI)	1.74 [0.30, 10.18]
7 NSAID + non-opioid versus non-opioid	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
7.1 Diclofenac + desmopressin versus desmopressin	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
8 Non-opioid versus placebo	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.1 Drotaverine versus placebo	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
9 Non-opioid versus non-opioid	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
9.1 Butylscopolamine IV versus lidocaine	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

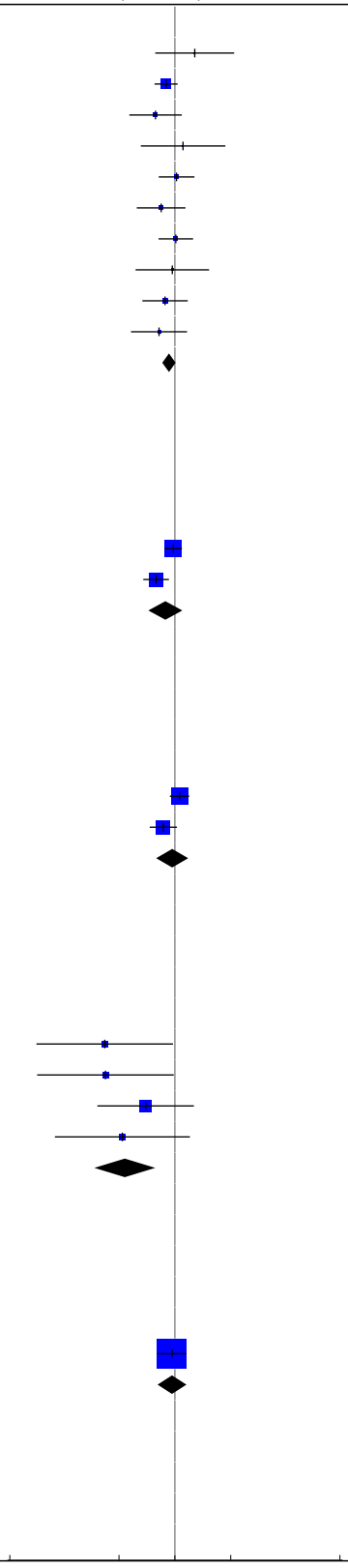
Analysis 3.1. Comparison 3 Rescue medication, Outcome 1 NSAID versus placebo.

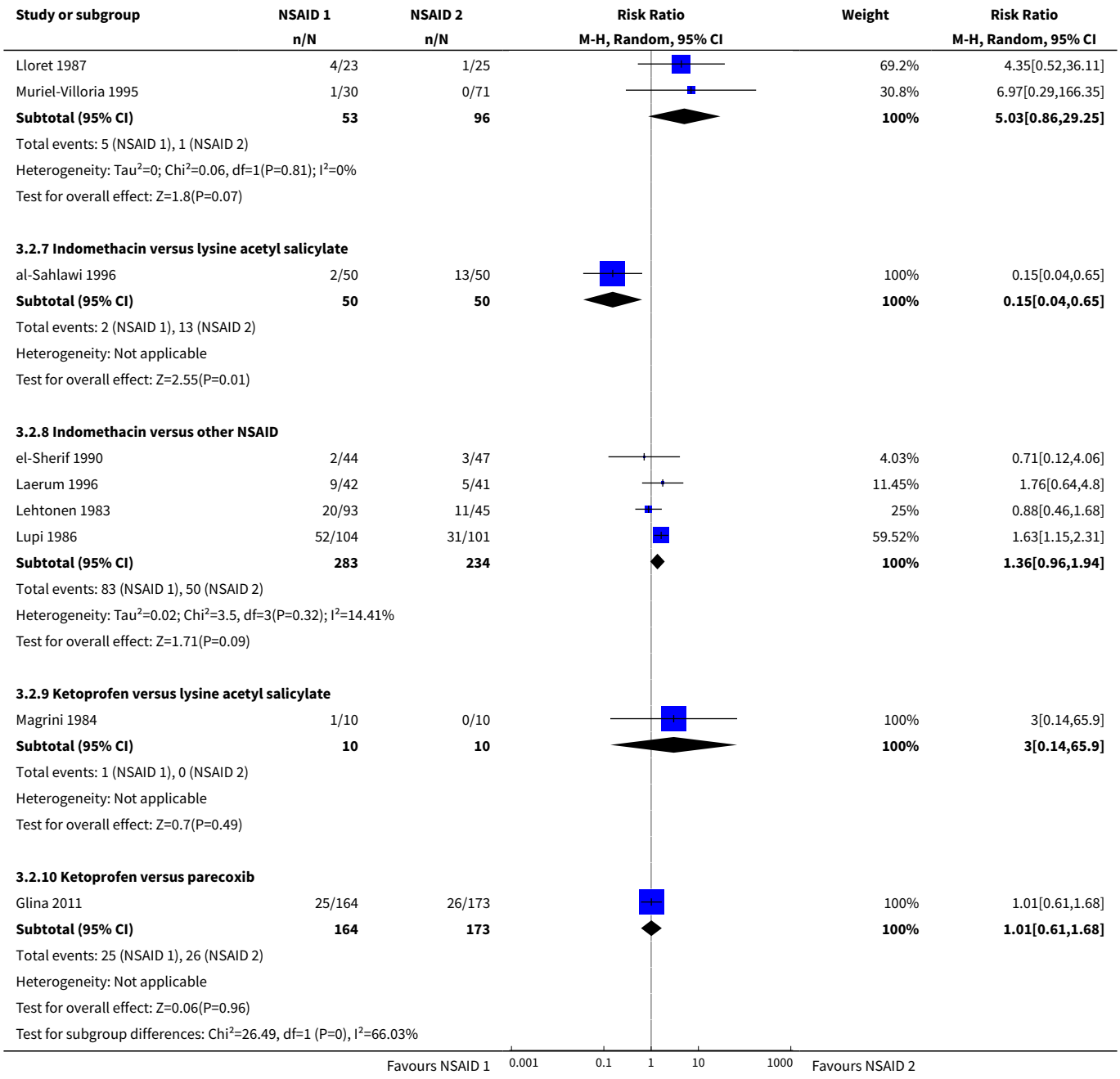
Study or subgroup	NSAID n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
3.1.1 Diclofenac versus saline					
Lundstam 1980	3/9	10/10		28.12%	0.37[0.16,0.86]
Vignoni 1983	17/63	40/68		56.83%	0.46[0.29,0.72]
Subtotal (95% CI)	**72**	**78**		**84.94%**	**0.44[0.29,0.65]**
Total events: 20 (NSAID), 50 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.21, df=1(P=0.65); I^2=0%					
Test for overall effect: Z=4.06(P<0.0001)					
3.1.2 Ketoprofen versus placebo					
Magrini 1984	1/10	5/5		11.33%	0.15[0.03,0.67]
Subtotal (95% CI)	**10**	**5**		**11.33%**	**0.15[0.03,0.67]**
Total events: 1 (NSAID), 5 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.48(P=0.01)					
3.1.3 Lysine acetyl salicylate versus placebo					
Magrini 1984	0/10	4/5		3.72%	0.06[0,0.95]
Subtotal (95% CI)	**10**	**5**		**3.72%**	**0.06[0,0.95]**
Total events: 0 (NSAID), 4 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2(P=0.05)					
Total (95% CI)	**92**	**88**		**100%**	**0.35[0.2,0.6]**
Total events: 21 (NSAID), 59 (Placebo)					
Heterogeneity: Tau^2=0.08; Chi^2=3.94, df=3(P=0.27); I^2=23.83%					
Test for overall effect: Z=3.79(P=0)					
Test for subgroup differences: Chi^2=3.64, df=1 (P=0.16), I^2=45.12%					



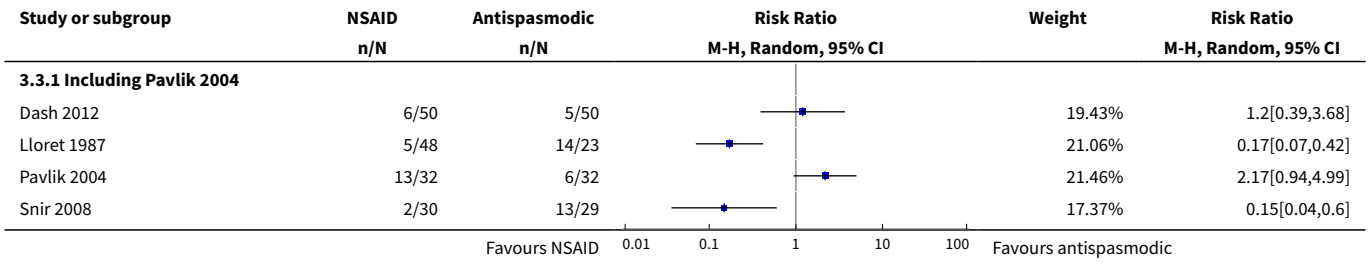
Analysis 3.2. Comparison 3 Rescue medication, Outcome 2 NSAID versus NSAID.

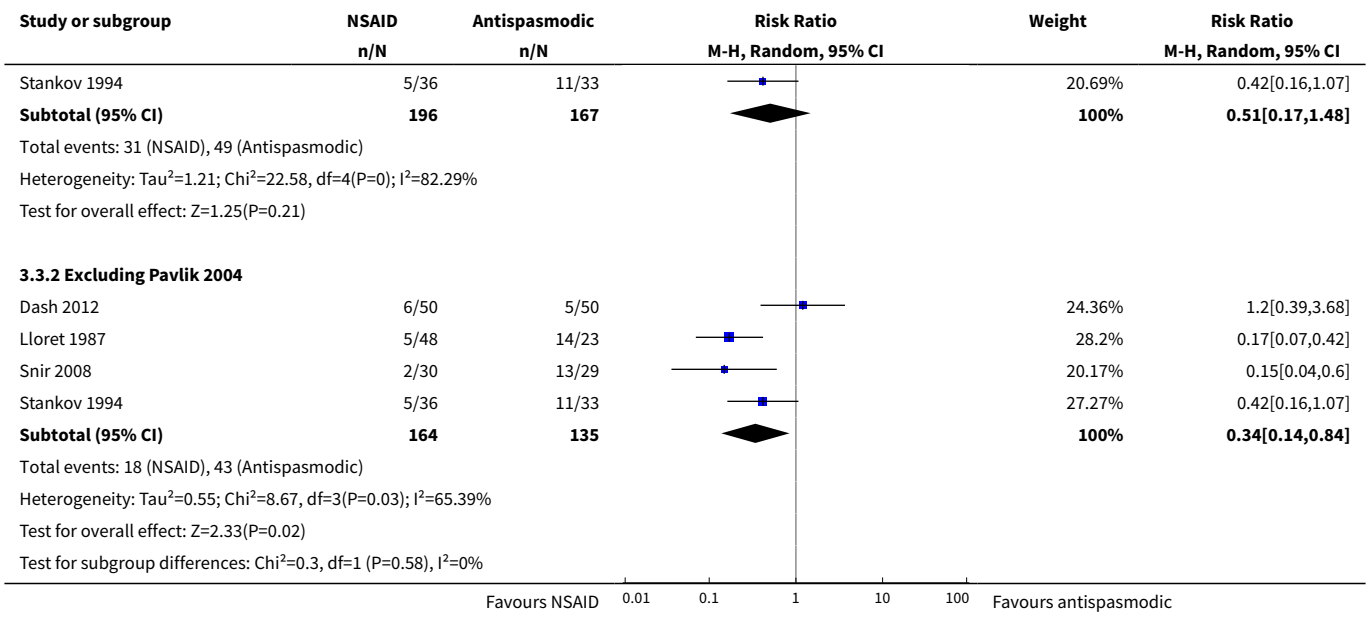
Study or subgroup	NSAID 1 n/N	NSAID 2 n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
3.2.1 Diclofenac versus other NSAID					
Al Waili 1999	4/30	2/34		2.89%	2.27[0.45,11.51]
Arnau 1991	19/116	51/217		33.61%	0.7[0.43,1.12]
Cohen 1998	4/30	8/27		6.51%	0.45[0.15,1.33]
el-Sherif 1990	3/47	2/44		2.51%	1.4[0.25,8.01]
Fraga 2003	12/60	11/59		14.11%	1.07[0.51,2.24]
Laerum 1996	5/41	9/42		7.54%	0.57[0.21,1.55]
Muriel-Villoria 1995	8/54	34/239		15.06%	1.04[0.51,2.12]
Stein 1996	3/30	3/27		3.33%	0.9[0.2,4.09]
Supervia 1998	6/40	9/40		8.71%	0.67[0.26,1.7]
Walden 1993	4/45	7/41		5.73%	0.52[0.16,1.65]
Subtotal (95% CI)	**493**	**770**		**100%**	**0.78[0.59,1.03]**
Total events: 68 (NSAID 1), 136 (NSAID 2)					
Heterogeneity: Tau^2=0; Chi^2=5.65, df=9(P=0.77); I^2=0%					
Test for overall effect: Z=1.73(P=0.08)					
3.2.2 Dipyrone (2 g) versus dexketoprofen (25 mg)					
Sanchez-Carpena 2003	35/97	40/104		53.76%	0.94[0.65,1.34]
Sanchez-Carpena 2007	16/103	34/101		46.24%	0.46[0.27,0.78]
Subtotal (95% CI)	**200**	**205**		**100%**	**0.68[0.34,1.36]**
Total events: 51 (NSAID 1), 74 (NSAID 2)					
Heterogeneity: Tau^2=0.2; Chi^2=4.85, df=1(P=0.03); I^2=79.39%					
Test for overall effect: Z=1.1(P=0.27)					
3.2.3 Dipyrone (2 g) versus dexketoprofen (50 mg)					
Sanchez-Carpena 2003	35/97	30/101		54.4%	1.21[0.81,1.81]
Sanchez-Carpena 2007	16/103	26/104		45.6%	0.62[0.35,1.09]
Subtotal (95% CI)	**200**	**205**		**100%**	**0.89[0.46,1.73]**
Total events: 51 (NSAID 1), 56 (NSAID 2)					
Heterogeneity: Tau^2=0.17; Chi^2=3.68, df=1(P=0.05); I^2=72.85%					
Test for overall effect: Z=0.33(P=0.74)					
3.2.4 Dipyrone (IV) versus dipyrone (IM)					
Muriel-Villoria 1995	0/35	8/33		19.92%	0.06[0,0.93]
Muriel-Villoria 1995	0/36	8/35		19.89%	0.06[0,0.96]
Muriel-Villoria 1995	1/15	8/36		39.82%	0.3[0.04,2.19]
Muriel-Villoria 1995	0/15	9/34		20.37%	0.12[0.01,1.86]
Subtotal (95% CI)	**101**	**138**		**100%**	**0.13[0.04,0.45]**
Total events: 1 (NSAID 1), 33 (NSAID 2)					
Heterogeneity: Tau^2=0; Chi^2=1.41, df=3(P=0.7); I^2=0%					
Test for overall effect: Z=3.22(P=0)					
3.2.5 Dipyrone (1 g) IM versus dipyrone (2 g) IM					
Muriel-Villoria 1995	16/71	17/67		100%	0.89[0.49,1.61]
Subtotal (95% CI)	**71**	**67**		**100%**	**0.89[0.49,1.61]**
Total events: 16 (NSAID 1), 17 (NSAID 2)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.39(P=0.7)					
3.2.6 Dipyrone (1 g) IV versus dipyrone (2 g) IV					



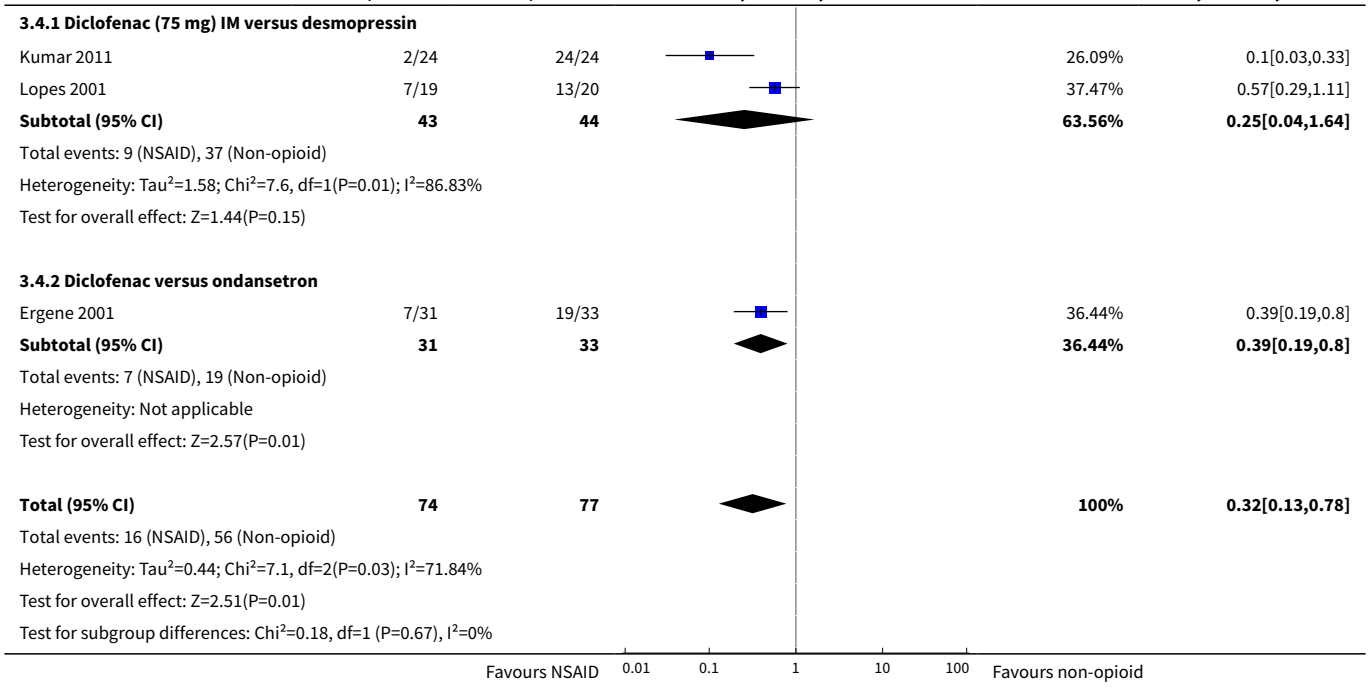


Analysis 3.3. Comparison 3 Rescue medication, Outcome 3 NSAID versus antispasmodic.





Analysis 3.4. Comparison 3 Rescue medication, Outcome 4 NSAID versus other non-opioid.



Analysis 3.5. Comparison 3 Rescue medication, Outcome 5 NSAID + antispasmodic versus NSAID.

Study or subgroup	NSAID+anti-spasmodic n/N	NSAID n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Boubaker 2010	37/126	38/127		61.92%	0.98[0.67,1.43]
el-Sherif 1990	2/27	2/44		5.62%	1.63[0.24,10.9]
el-Sherif 1990	2/27	3/47		6.75%	1.16[0.21,6.52]
Lloret 1987	0/13	1/25		2.14%	0.62[0.03,14.22]
Lloret 1987	0/12	4/23		2.59%	0.21[0.01,3.52]
Sanahuja 1990	3/31	7/30		12.05%	0.41[0.12,1.46]
Snir 2008	7/27	2/30		8.93%	3.89[0.88,17.13]
Total (95% CI)	**263**	**326**		**100%**	**0.99[0.62,1.57]**
Total events: 51 (NSAID+antispasmodic), 57 (NSAID)					
Heterogeneity: Tau^2=0.05; Chi^2=6.68, df=6(P=0.35); I^2=10.12%					
Test for overall effect: Z=0.04(P=0.97)					

Favours NSAID+antispasmod — Favours NSAIDs

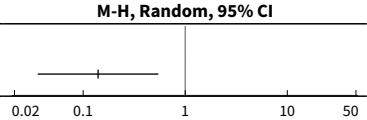
Analysis 3.6. Comparison 3 Rescue medication, Outcome 6 NSAID + non-opioid versus NSAID.

Study or subgroup	NSAID n/N	NSAID +non-opioid n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Kumar 2011	2/24	3/24		46.85%	0.67[0.12,3.64]
Lopes 2001	7/19	2/22		53.15%	4.05[0.95,17.22]
Total (95% CI)	**43**	**46**		**100%**	**1.74[0.3,10.18]**
Total events: 9 (NSAID), 5 (NSAID+non-opioid)					
Heterogeneity: Tau^2=0.98; Chi^2=2.52, df=1(P=0.11); I^2=60.31%					
Test for overall effect: Z=0.61(P=0.54)					

Favours NSAID — Favours NSAID+non-opioid

Analysis 3.7. Comparison 3 Rescue medication, Outcome 7 NSAID + non-opioid versus non-opioid.

Study or subgroup	NSAID+non-opioid n/N	Non-opioid n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
3.7.1 Diclofenac + desmopressin versus desmopressin				
Lopes 2001	2/22	13/20		0.14[0.04,0.54]



Favours NSAID+non-opioid — Favours non-opioid

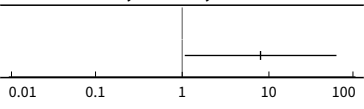
Analysis 3.8. Comparison 3 Rescue medication, Outcome 8 Non-opioid versus placebo.

Study or subgroup	Non-opioid n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
3.8.1 Drotaverine versus placebo				
Romics 2003	20/48	35/54		0.64[0.44,0.95]

Favours non-opioid — Favours placebo

Analysis 3.9. Comparison 3 Rescue medication, Outcome 9 Non-opioid versus non-opioid.

Study or subgroup	Non-opioid 1 n/N	Non-opioid 2 n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
3.9.1 Butylscopolamine IV versus lidocaine				
Iguchi 2002	8/30	1/30		8[1.07,60.09]

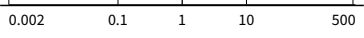


Comparison 4. Pain recurrence

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 NSAID versus NSAID	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 NSAID + antispasmodic versus NSAID	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3 NSAID versus non-opioid	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

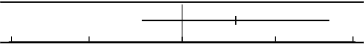
Analysis 4.1. Comparison 4 Pain recurrence, Outcome 1 NSAID versus NSAID.

Study or subgroup	NSAID 1 n/N	NSAID 2 n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Al Waili 1999	0/32	9/30		0.05[0,0.81]



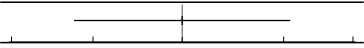
Analysis 4.2. Comparison 4 Pain recurrence, Outcome 2 NSAID + antispasmodic versus NSAID.

Study or subgroup	NSAID+antispasmodic n/N	NSAID n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Boubaker 2010	5/126	2/127		2.52[0.5,12.75]



Analysis 4.3. Comparison 4 Pain recurrence, Outcome 3 NSAID versus non-opioid.

Study or subgroup	NSAID n/N	Non-opioid n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Grissa 2011	21/42	20/40		1[0.65,1.54]



ADDITIONAL TABLES

Table 1. Adverse effects for NSAIDs versus NSAIDs

Study	Comparison		GI		CNS		Injection site		Other	
	NSAID (1)	NSAID (2)	NSAID (1)	NSAID (2)	NSAID (1)	NSAID (2)	NSAID (1)	NSAID (2)	NSAID (1)	NSAID (2)
Sanchez-Carpena 2003	Dexketoprofen	Dipyrone	2/225	7/108	6	4	10	7	3	2
Sanchez-Carpena 2007	Dexketoprofen	Dipyrone	39/205	22/103	4	3	19	0	6	0
Sanahuja 1990	Diclofenac	Baralgan	0/29	0/28	0	0	0	0	1	1
Indudhara 1990	Diclofenac	Baralgan	2/33	6/30	0	0	0	0	0	0
Miralles 1987	Diclofenac	Dipyrone	Adverse effects not reported							
Muriel-Villoria 1995	Diclofenac	Dipyrone	24/55	18/239	104	134	1	4	--	--
Muriel 1993	Diclofenac	Dipyrone	6/41	11/88	59	85	1	2	--	--
Arnau 1991	Diclofenac	Dipyrone	26/116	45/227	65	157	13	32	11	37
Marthak 1991	Diclofenac	Dipyrone + anti-spasmodic	5/82	8/85	0	2	1	0	1	1
Fraga 2003	Diclofenac	Etofenamate	4/60	0/59	1	1	0	1	0	0
el-Sherif 1990	Diclofenac	Indomethacin	3/47	3/44	0	1	0	0	0	1
Laerum 1996	Diclofenac	Indomethacin	3/41	6/42	1	2	1	1	--	--
Walden 1993	Diclofenac	Ketoprofen	Total adverse effects: NSAID 1 (7/45); NSAID 2 (10/41)							
Stein 1996	Diclofenac	Ketorolac	0/30	0/27	0	2	0	0	0	0
Cohen 1998	Diclofenac	Ketorolac	0	0	0	0	0	0	0	0
Al Waili 1999	Diclofenac	Piroxicam	0	0	0	0	0	0	0	0
Supervia 1998	Diclofenac	Piroxicam	0	0	1/40	0	0	0	0	0

Table 1. Adverse effects for NSAIDs versus NSAIDs *(Continued)*

Mora Durban 1995	Flurbiprofen	Dipyrone + hyoscine	0	0	--	--	33/67	43/68	--	--
al-Sahlawi 1996	Indomethacin	Lysine acetyl salicylate	Adverse effects not reported							
Lehtonen 1983	Indomethacin	Metamizole	12	7	12	3	0	0	0	1
Galassi 1983	Indomethacin	Metamizole	14/18	0/14	5	0	0	0	12	0
Lupi 1986	Indomethacin	Pirprofen	2							
Glina 2011	Ketoprofen	Parecoxib	14/164	11/174	6	10	--	--	--	--
Martin Carrasco 1993	Ketorolac	Dipyrone + antispasmodic	1							
Boubaker 2010	Piroxicam	Piroxicam + phloroglucinol	9/127	10/126	3	7	4	3	--	--
Kekec 2000	Tenoxicam	Tenoxicam + isosorbide	0	0	0	0	0	0	0	0

CNS - central nervous system; GI - gastrointestinal; NSAID - nonsteroidal anti-inflammatory drug

Table 2. Adverse effects for NSAIDs versus non-opioids

Study	Comparison		GI		CNS		Injection site		Other	
	NSAID	Non-NSAID	NSAID	Non-NSAID	NSAID	Non-NSAID	NSAID	Non-NSAID	NSAID	Non-NSAID
Benyajati 1986	Baralgan	Hyoscine	0	0	0	0	0	0	0	0
Kumar 2011	Diclofenac	Desmopressin	Adverse effects not reported							
Lopes 2001	Diclofenac	Desmopressin	1/19	0/20	0	0	0	0	0	1
Dash 2012	Diclofenac	Drotaverine	8/50	0/50	3	7	0	0	0	1
Quilez 1983	Diclofenac	N-butyl hyoscine	No serious side effects were observed							

Table 2. Adverse effects for NSAIDs versus non-opioids *(Continued)*

Ergene 2001	Diclofenac	Ondansetron	0	0	0	0	0	0	0	0
Snir 2008	Diclofenac	Papaverine	0/30	0	0	4/29	0	0	0	0
Vignoni 1983	Diclofenac	Placebo	No adverse effects were observed							
Lundstam 1980	Diclofenac	Placebo	No adverse effects were observed							
Stankov 1994	Dipyrone	Butylscopolamine	1/36	1/33	--	1	--	--	1	--
Lloret 1987	Dipyrone	Hyoscine	0	0	24/48	12/23	18	1	13	11
Holmlund 1978	Indomethacin	Placebo	No adverse effects were observed							
Jones 1998	Ketorolac	Hyoscyamine	No adverse effects were observed							
Pavlik 2004	Metamizole	Cizolirtine	2/32	2/31	0	0	0	0	1	0
Grissa 2011	Piroxicam	Paracetamol	--	1	--	--	--	--	1	--

CNS - central nervous system; GI - gastrointestinal; NSAID - nonsteroidal anti-inflammatory drug

Table 3. Adverse effects for other comparisons

Study	Comparison		GI		CNS		Injection site		Other	
	Drug 1	Drug 2	Drug 1	Drug 2	Drug 1	Drug 2	Drug 1	Drug 2	Drug 1	Drug 2
Iguchi 2002	Butylscopolamine	Lidocaine	No adverse effects were observed							
Romics 2003	Drotaverine	Placebo	20 patients in drotaverine, 4 in placebo had mild adverse effects							
Bahn Zobbe 1986	Glucagon	Placebo	11/18	1/19	0	0	0	0	3	0
Caravati 1989	Nifedipine	Placebo	1/13	0	0	0	0	0	2	0
Miano 1986	Tyropramide	Butylscopo-lamine	3/103	4/96	7	6	0	0	2	8

CNS - central nervous system; GI - gastrointestinal

APPENDICES

Appendix 1. Electronic search strategies

Database	Search terms
CENTRAL	1. aminopyrine* or amodiaquine* or ampyrone* or apazone* or aspirin* in All Fields in CENTRAL 2. bromelain* or clofazimine* or clonixin* or curcumin* in All Fields in CENTRAL 3. dapsone* or diclofenac* or diflunisal* or dipyrone* in All Fields in CENTRAL 4. epirizole* or etodolac* or fenoprofen* or flurbiprofen* in All Fields in CENTRAL 5. glycyrrhizic acid* or ibuprofen* or indomethacin* or ketoprofen* in All Fields in all products 6. ketorolac* or meclofenamic acid* or mefenamic acid* or mesalamine* or naproxen* or niflumic acid* or oxyphenbutazone* in All Fields in all products 7. pentosan* or phenylbutazone* or piroxicam* or prenazone* in All Fields in CENTRAL 8. salicyate* sulfasalazine* or sulindac* or suprofen* in All Fields in CENTRAL 9. tolemetin* or tenoxicam* or meclofenamate* or nabumetone* in All Fields in CENTRAL 10.nsaid* in All Fields in CENTRAL 11.non steroid* antiinflammatory agent* in All Fields in CENTRAL 12.non steroid* anti inflammatory agent* in All Fields in CENTRAL 13.MeSH descriptor Cyclooxygenase Inhibitors explode all trees in MeSH products 14.nordihydroguaiaretic acid* in All Fields in CENTRAL 15.MeSH descriptor Indomethacin explode all trees in MeSH products 16.MeSH descriptor Parasympatholytics explode all trees in MeSH products 17.atropine* or benactyzine* or biperiden* or butylscopolammonium* or cromakalim* or cyclopentolate* in All Fields in CENTRAL 18.dexetimide* or dicyclomine* or emepronium* or flavoxate* or hymecromone* in All Fields in CENTRAL 19.n-methyscopolamine* or nafronyl* or orpenadrine* or oxyphonium* or phloroglucinol* or trimebutine* anti spasmodics* in All Fields in CENTRAL 20.antospasmodic* or vagolytic* in All Fields in CENTRAL 21.MeSH descriptor Calcium Channel Blockers explode all trees in MeSH products 22.amlodipin* or amrinone* or bencyclan* orbepridil* or cinnarizin* or conotoxin* or diltiazem* or felodipine* or fendiline* or flunarizine* or gallopamil* or isradipine* in All Fields in CENTRAL 23.lidoflazine* or magnesium sulphate* or magnesium sulfate* or mibefradil* or nicardipine* in All Fields in CENTRAL 24.nifedipine* or nimodipine* or nisoldipine* or nitrendipine* orperhexiline* or prenylamine* or verapamil* in All Fields in CENTRAL 25.omega agatoxin* or omega conotoxin* or demopressin* or ddavp* in All Fields in CENTRAL 26.MeSH descriptor Vasopressins explode all trees in MeSH products 27.vasopressin* or pinaverium* or propanthelin* or pinaverium* or tolteridine* in All Fields in CENTRAL 28.MeSH descriptor Propantheline, this term only in MeSH products 29.MeSH descriptor Dicyclomine, this term only in MeSH products 30.MeSH descriptor Cholinergic Antagonists explode all trees in MeSH products 31.MeSH descriptor Scopolamine, this term only in MeSH products 32.MeSH descriptor Analgesics, Non-Narcotic explode all trees in MeSH products 33.anticholingeric* or anti cholinergic* in All Fields in CENTRAL 34.oxybutinin* or scopolamine* or hyosine* or celecoxib* or refoxocib* or refcoxib* or analgesic* or tamsulosin* in All Fields in CENTRAL 35.MeSH descriptor Anti-Inflammatory Agents, Non-Steroidal explode all trees

(Continued)

36.(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35)
37.MeSH descriptor Renal Colic, this term only
38.MeSH descriptor Ureteral Obstruction, this term only
39.(urolithiasis):ti,ab,kw or (nephrolithiasis):ti,ab,kw in Clinical Trials
40.(ureteral colic):ti,ab,kw or (ureteric colic):ti,ab,kw in Clinical Trials
41.(renal colic):ti,ab,kw or (kidney colic):ti,ab,kw in Clinical Trials
42.MeSH descriptor Urolithiasis explode all trees
43.(#37 OR #38 OR #39 OR #40 OR #41 OR #42)
44.(#36 AND #43)

MEDLINE

1. Renal Colic/
2. exp Urolithiasis/
3. Ureteral Obstruction/
4. urolithiasis.tw.
5. nephrolithiasis.tw.
6. (ureter$ and (stone$ or calcul$ or colic)).tw.
7. (kidney$ and (stone$ or calcul$ or colic)).tw.
8. (renal$ and (stone$ or calcul$ or colic)).tw.
9. (urin$ and (stone$ or calcul$ or colic)).tw.
10. or/1-9
11. exp Anti-Inflammatory Agents, Non-Steroidal/
12. (aminopyrine$ or amodiaquine$ or ampyrone$ or antipyrine$ or apazone$ or aspirin$).tw.
13. (bromelain$ or clofazimine$ or clonixin$ or curcumin$).tw.
14. (dapsone$ or diclofenac$ or diflunisal$ or dipyrone$).tw.
15. (epirizole$ or etodolac$).tw.
16. (flurbiprofen$ or fenoprofen$ or glycyrrhizic acid$).tw.
17. (ibuprofen$ or indomethacin).tw.
18. (ketoprofen$ or ketorolac$).tw.
19. (meclofenamic acid$ or mefenamic acid$ or mesalamine$ or naproxen$ or niflumic acid$).tw.
20. (oxyphenbutazone$ or pentosan$ or phenylbutazone$ or piroxicam$ or prenazone$).tw.
21. (sulfasalazine$ or sulfasalazine$ or sulindac$ or suprofen$ or tolmetin$ or tenoxicam$ or meclofenamate$ or nabumetone$).tw.
22. (non steroid$ antiinflammatory agent$ or non steroid$ anti inflammatory agent$ or nsaid$).tw.
23. exp Cyclooxygenase Inhibitors/
24. nordihydroguaiaretic acid.tw.
25. exp Indomethacin/
26. Piroxicam/
27. prostaglandin inhibitor$.tw.
28. exp Parasympatholytics/
29. (atropine$ or benactyzine$ or biperiden$ or butylscopolammonium bromide$).tw.
30. (cromakalim$ or cyclopentolate$ or dexetimide$ or dicyclomine$ or emepronium$ or flavoxate$).tw.
31. (n-methylscopolamine$ or hymecromone$ or orphenadrine$ or phloroglucinol or trimebutine$).tw.
32. (anti spasmodic$ or antispasmodic$).tw.
33. vagolytic$.tw.
34. exp Calcium Channel Blockers/
35. demopressin$.tw.
36. exp Vasopressins/
37. vasopressin$.tw.

(Continued)

	38.Propantheline/ 39.propanthelin$.tw. 40.DICYCLOMINE/ 41.exp Cholinergic Antagonists/ 42.(anticholinergic$ or anti cholinergic$).tw. 43.(oxybutinin$ or trimebutine$).tw. 44.exp SCOPOLAMINE/ 45.scopolamine$.tw. 46.celecoxib$.tw. 47.exp Analgesics, Non-Narcotic/ 48.analgesic$.tw. 49.exp Adrenergic alpha antagonists/ 50.tamsulosin$.tw. 51.or/11-50 52.and/10,51
EMBASE	1. exp Urolithiasis/ 2. (urolithiasis or nephrolithiasis).tw. 3. (ureter$ and (stone$ or calcul$ or colic)).tw. 4. (kidney$ and (stone$ or calcul$ or colic)).tw. 5. (renal$ and (stone$ or calcul$ or colic)).tw. 6. (urin$ and (stone$ or calcul$ or colic)).tw. 7. Kidney Colic/ 8. (renal colic or kidney colic or ureteric colic or ureteral colic).tw. 9. or/1-8 10.Prostaglandin Inhibitor/ 11.Prostaglandin Inhibit$.tw. 12.antiprostaglandin$.tw. 13.exp Nonsteroid Antiinflammatory Agent/ 14.(non steroid$ antiinflammatory agent$ or non steroid$ anti inflammatory agent$).tw. nsaid$.tw. 15.exp Prostaglandin Synthase Inhibitor/ 16.exp Cholinergic Receptor Blocking Agent/ 17.exp Calcium Channel Blocking Agent/ 18.exp VASOPRESSIN/ 19.exp Analgesic Agent/ 20.exp Spasmolytic Agent/ 21.exp Analgesic Agent/ 22.Rofecoxib/ 23.Desmopressin/ 24.Nifedipine/ 25.exp Cyclooxygenase 2 Inhibitor/ 26.or/10-26 27.and/9,27

Appendix 2. Risk of bias assessment tool

Potential source of bias	Assessment criteria

(Continued)

Random sequence generation Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence	*Low risk of bias:* Random number table; computer random number generator; coin tossing; shuffling cards or envelopes; throwing dice; drawing of lots; minimization (minimization may be implemented without a random element, and this is considered to be equivalent to being random).
	High risk of bias: Sequence generated by odd or even date of birth; date (or day) of admission; sequence generated by hospital or clinic record number; allocation by judgement of the clinician; by preference of the participant; based on the results of a laboratory test or a series of tests; by availability of the intervention.
	Unclear: Insufficient information about the sequence generation process to permit judgement.
Allocation concealment Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment	*Low risk of bias:* Randomisation method described that would not allow investigator/participant to know or influence intervention group before eligible participant entered in the study (e.g. central allocation, including telephone, web-based, and pharmacy-controlled, randomisation; sequentially numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes).
	High risk of bias: Using an open random allocation schedule (e.g. a list of random numbers); assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or non-opaque or not sequentially numbered); alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure.
	Unclear: Randomisation stated but no information on method used is available.
Blinding of participants and personnel Performance bias due to knowledge of the allocated interventions by participants and personnel during the study	*Low risk of bias*: No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding; blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken.
	High risk of bias: No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding; blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding.
	Unclear: Insufficient information to permit judgement
Blinding of outcome assessment Detection bias due to knowledge of the allocated interventions by outcome assessors.	*Low risk of bias:* No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding; blinding of outcome assessment ensured, and unlikely that the blinding could have been broken.
	High risk of bias: No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding; blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding.
	Unclear: Insufficient information to permit judgement
Incomplete outcome data Attrition bias due to amount, nature or handling of incomplete outcome data.	*Low risk of bias:* No missing outcome data; reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; missing data have been imputed using appropriate methods.
	High risk of bias: Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; 'as-treated' analysis done with

(Continued)

	substantial departure of the intervention received from that assigned at randomisation; potentially inappropriate application of simple imputation.
	Unclear: Insufficient information to permit judgement
Selective reporting Reporting bias due to selective outcome reporting	*Low risk of bias:* The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way; the study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon).
	High risk of bias: Not all of the study's pre-specified primary outcomes have been reported; one or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified; one or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); one or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; the study report fails to include results for a key outcome that would be expected to have been reported for such a study.
	Unclear: Insufficient information to permit judgement
Other bias Bias due to problems not covered elsewhere in the table	*Low risk of bias:* The study appears to be free of other sources of bias.
	High risk of bias: Had a potential source of bias related to the specific study design used; stopped early due to some data-dependent process (including a formal-stopping rule); had extreme baseline imbalance; has been claimed to have been fraudulent; had some other problem.
	Unclear: Insufficient information to assess whether an important risk of bias exists; insufficient rationale or evidence that an identified problem will introduce bias.

CONTRIBUTIONS OF AUTHORS

- Literature search review: KA, AE, AJM
- Review of the abstracts: KA, AE, AJM
- Review of the studies for inclusion: KA, AEM, AJM
- Arbiter: SJ
- Assessment of quality: KA, AEM, SJ
- Statistical analysis: KA, SJ
- Writing the manuscript: KA, AEM

DECLARATIONS OF INTEREST

None known

SOURCES OF SUPPORT

Internal sources

- Department of Urologic Sciences, University of British Columbia, Canada.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Risk of bias assessment tool has replaced the quality assessment checklist.

INDEX TERMS

Medical Subject Headings (MeSH)

Acute Disease; Analgesics, Non-Narcotic [*therapeutic use]; Anti-Inflammatory Agents, Non-Steroidal [*therapeutic use]; Diclofenac [therapeutic use]; Indomethacin [therapeutic use]; Parasympatholytics [*therapeutic use]; Randomized Controlled Trials as Topic; Renal Colic [*drug therapy]; Scopolamine [therapeutic use]

MeSH check words

Humans