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Single dose oral ketoprofen and dexketoprofen for acute postoperative pain in adults

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Abstract

Background—Ketoprofen is a non-selective non-steroidal anti-inflammatory drug (NSAID) used to treat acute and chronic painful conditions. Dexketoprofen is the (S)-enantiomer, which is believed to confer analgesia. Theoretically dexketoprofen is expected to provide equivalent analgesia to ketoprofen at half the dose, with a consequent reduction in gastrointestinal adverse events.

Objectives—To assess efficacy, duration of action, and associated adverse events of single dose oral ketoprofen and dexketoprofen in acute postoperative pain in adults.

Search methods—We searched Cochrane CENTRAL, MEDLINE, EMBASE and the Oxford Pain Relief Database for studies to August 2009.

Selection criteria—Randomised, double blind, placebo-controlled trials of single dose orally administered ketoprofen and dexketoprofen in adults with moderate to severe acute postoperative pain.

Data collection and analysis—Two review authors independently assessed trial quality and extracted data. Pain relief or pain intensity data were extracted and converted into the dichotomous outcome of number of participants with at least 50% pain relief over 4 to 6 hours, from which

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CONTRIBUTIONS OF AUTHORS

JB, SD, and RAM carried out searching, data extraction, and analysis, including assessment of study quality. HJM helped with analysis and acted as arbitrator. All review authors contributed to the writing of the protocol and review. SD will be responsible for the update.

DECLARATIONS OF INTEREST

All review authors have received research support from charities, government and industry sources at various times. RAM and HJM have consulted for various pharmaceutical companies. RAM, and HJM have received lecture fees from pharmaceutical companies related to analgesics and other healthcare interventions. JB worked for Pfizer Ltd from 2004 to 2007 and from 2008 to the date of writing. RAM & JB have previously received an unrestricted educational grant from Menarini Group for a review of published and unpublished dexketoprofen trials in acute and chronic painful conditions. Some of the unpublished data provided by Menarini has been included in this review; Menarini had no role in the review, other than being the source of unpublished trial data. No author has any conflict of interest.

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relative risk and number-needed-to-treat-to-benefit (NNT) were calculated. Numbers of participants using rescue medication over specified time periods, and time to use of rescue medication, were sought as additional measures of efficacy. Information on adverse events and withdrawals was collected.

Main results—Fourteen studies compared ketoprofen (968 participants) at mainly 25 mg and 50 mg with placebo (520 participants). Seven studies compared dexketoprofen (681 participants) at mainly 10 mg to 25 mg with placebo (289 participants). Studies were of adequate reporting quality, and participants had pain following dental, orthopaedic, obstetric, gynaecological and general surgery. There was considerable clinical heterogeneity between studies in dental and other types of surgery, particularly bunionectomy, which limited analysis.

Ketoprofen at doses between 12.5 mg and 100 mg produced NNTs for at least 50% pain relief over 4 to 6 hours of 2.4 to 3.3. For dental studies only there was a trend to more efficacy at higher doses, with NNT decreasing from 2.4 at 12.5 mg to 1.6 at 100 mg. Dexketoprofen at doses of 10/12.5 mg and 20/25 mg produced NNTs for at least 50% pain relief over 4 to 6 hours of 3.2 and 3.6, with no obvious dose response. Significantly fewer participants used rescue medication with ketoprofen and dexketoprofen than placebo. The median time to remedication was about 5 hours with ketoprofen and 4 hours with dexketoprofen. The expected equivalent efficacy with a half dose of dexketoprofen compared to ketoprofen was not demonstrated.

Adverse events were uncommon with both drugs, and not significantly different from placebo.

Authors' conclusions—Ketoprofen at doses of 25 mg to 100 mg is an effective analgesic in moderate to severe acute postoperative pain with an NNT for at least 50% pain relief of 3.3 with a 50 mg dose. This is similar to that of commonly used NSAIDs such as ibuprofen (NNT 2.5 for 400 mg dose) and diclofenac (NNT 2.7 at 50 mg dose). Duration of action is about 5 hours. Dexketoprofen is also effective with NNTs of 3.2 to 3.6 in the dose range 10 mg to 25 mg. Both drugs were well tolerated in single doses.

Medical Subject Headings (MeSH)

Acute Disease; Administration, Oral; Analgesics, Non-Narcotic [* administration & dosage]; Anti-Inflammatory Agents, Non-Steroidal [* administration & dosage]; Ketoprofen [* administration & dosage; * analogs & derivatives]; Pain, Postoperative [* drug therapy]; Stereoisomerism

MeSH check words

Adult; Humans

BACKGROUND

Acute pain occurs as a result of tissue damage either accidentally due to an injury or as a result of surgery. Acute postoperative pain is a manifestation of inflammation due to tissue injury. The management of postoperative pain and inflammation is a critical component of patient care. This is one of a series of reviews whose aim is to present evidence for relative analgesic efficacy through indirect comparisons with placebo, in very similar trials performed in a standard manner, with very similar outcomes, and over the same duration.

Such relative analgesic efficacy does not in itself determine choice of drug for any situation or patient, but guides policy-making at the local level.

Recent reviews include well established analgesics such as paracetamol (Toms 2008), naproxen (Derry C 2009), diclofenac (Derry P 2009), and ibuprofen (Derry C 2009a), and newer cyclo-oxygenase-2 selective analgesics, such as lumiracoxib (Roy 2007), celecoxib (Derry 2008), etoricoxib (Clarke 2009) and parecoxib (Lloyd 2009).

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

Clinical trials measuring the efficacy of analgesics in acute pain have been standardised over many years. Trials have to be randomised and double blind. Typically, in the first few hours or days after an operation, patients develop pain that is moderate to severe in intensity, and will then be given the test analgesic or placebo. Pain is measured using standard pain intensity scales immediately before the intervention, and then using pain intensity and pain relief scales over the following 4 to 6 hours for shorter acting drugs, and up to 12 or 24 hours for longer acting drugs. Pain relief of half the maximum possible pain relief or better (at least 50% pain relief) is typically regarded as a clinically useful outcome. For patients given rescue medication it is usual for no additional pain measurements to be made, and for all subsequent measures to be recorded as initial pain intensity or baseline (zero) pain relief (baseline observation carried forward). This process ensures that analgesia from the rescue medication is not wrongly ascribed to the test intervention. In some trials the last observation is carried forward, which gives an inflated response for the test intervention compared to placebo, but the effect has been shown to be negligible over 4 to 6 hours (Moore 2005). Patients usually remain in the hospital or clinic for at least the first 6 hours following the intervention, with measurements supervised, although they may then be allowed home to make their own measurements in trials of longer duration.

Clinicians prescribe non-steroidal anti-inflammatory drugs (NSAIDs) on a routine basis for a range of mild-to-moderate pain. NSAIDs are the most commonly prescribed analgesic medications worldwide, and their efficacy for treating acute pain has been well demonstrated (Moore 2003). They reversibly inhibit cyclooxygenase (prostaglandin endoperoxide synthase), the enzyme mediating production of prostaglandins and thromboxane A2 (FitzGerald 2001). Prostaglandins mediate a variety of physiological functions such as maintenance of the gastric mucosal barrier, regulation of renal blood flow, and regulation of endothelial tone. They also play an important role in inflammatory and no-

ciceptive processes. However, relatively little is known about the mechanism of action of this class of compounds aside from their ability to inhibit cyclooxygenase-dependent prostanoid formation (Hawkey 1999). Since NSAIDs do not depress respiration and do not impair gastro-intestinal motility as do opioids (BNF 2002) they are clinically useful for treating pain after minor surgery and day surgery, and have an opiate-sparing effect after more major surgery (Grahame-Smith 2002).

Ketoprofen, (RS)2-(3-benzoylphenyl)-propionic acid, is one of the propionic acid class of NSAIDs and has analgesic and antipyretic effects. In some countries, the optically pure (S)-enantiomer (dexketoprofen) is available; its trometamol salt is said to be particularly rapidly reabsorbed from the gastrointestinal tract, having a rapid onset of effects. Racemic ketoprofen is used as an analgesic and an anti-inflammatory agent, and is one of the most potent in vitro inhibitors of prostaglandin synthesis, but is also implicated as having an association with higher risk of serious gastrointestinal bleeding events than other NSAIDs (Hernandez-Diaz 2000; Laporte 2004). The analgesic effect is due to the S(+)-enantiomer (dexketoprofen), while the R(−)-enantiomer is devoid of analgesic activity (Barbanoj 2001). Because the R(−)-enantiomer does appear to have ulcerogenic activity, at least in the rat (Barbanoj 2001; Herrero 2003), the implication is that use of dexketoprofen alone should produce equivalent analgesia to double-dose ketoprofen (or the same effect as ketoprofen, but at half the dose), but at lower risk of harm.

Ketoprofen is available by prescription as 25, 50, 75, 100, 150, and 200 mg capsules in the USA, and as 50, 100, and 200 mg capsules in the UK. Dexketoprofen is available as 25 mg tablets. Injectable, topical, and suppository formulations are also available for ketoprofen, and injectable and topical forms for dexketoprofen. In 2007, in England, there were about 80,000 prescriptions for ketoprofen and 8000 for dexketoprofen in primary care (PACT 2007). Ketoprofen is generally prescribed for arthritis-related inflammatory pains or severe dental pain. It is rarely used for postoperative pain. Dexketoprofen use is less well documented; while it is used in postoperative pain its license typically limits its use to a week or so. Licensed indications vary between countries.

OBJECTIVES

To assess the efficacy and safety of single dose oral ketoprofen and oral dexketoprofen for acute postoperative pain, using methods that permit comparison with other analgesics evaluated in the same way, using criteria of efficacy recommended by an in-depth study at the individual patient level (Moore 2005).

METHODS

Criteria for considering studies for this review

Types of studies—Studies were included if they were full publications of double blind trials of a single dose oral ketoprofen or dexketoprofen against placebo for the treatment of moderate to severe postoperative pain in adults, with at least 10 participants randomly allocated to each treatment group. Multiple dose studies were included if appropriate data

from the first dose were available. Cross-over studies were included provided that data from the first arm were presented separately.

Studies were excluded if they were:

- posters or abstracts not followed up by full publication;
- review articles, case reports, and clinical observations;
- reports of trials concerned with pain other than postoperative pain (including experimental pain);
- studies using healthy volunteers;
- studies where pain relief is assessed only by clinicians, nurses or carers (i.e., not patient-reported);
- studies of less than 4 hours duration or studies that fail to present data over 4 to 6 hours post-dose.

For postpartum pain, studies were included if the pain investigated was due to episiotomy or Caesarean section irrespective of the presence of uterine cramps; studies investigating pain due to uterine cramps alone were excluded.

Types of participants—Studies of adult participants (> 15 years) with established postoperative pain of moderate to severe intensity were included. For studies using a visual analogue scale (VAS), pain of at least moderate intensity was to be equated to greater than 30 mm (Collins 1997). Studies of participants with postpartum pain were included provided the pain investigated resulted from episiotomy or Caesarean section (with or without uterine cramp).

Types of interventions—Ketoprofen, dexketoprofen, or matched placebo administered as a single oral dose for postoperative pain.

Types of outcome measures—Data collected included the following:

- characteristics of participants;
- pain model;
- patient-reported pain at baseline (physician, nurse, or carer reported pain were not included in the analysis);
- patient-reported pain relief and/or pain intensity expressed hourly over 4 to 6 hours using validated pain scales (pain intensity and pain relief in the form of visual analogue scales (VAS) or categorical scales, or both), or reported total pain relief (TOTPAR) or summed pain intensity difference (SPID) at 4 to 6 hours;
- patient-reported global assessment of treatment (PGE), using a standard five-point scale;
- number of participants using rescue medication, and the time of assessment;
- time to use of rescue medication;

- withdrawals: all cause, adverse event;
- adverse events: participants experiencing one or more, and any serious adverse event, and the time of assessment.

Search methods for identification of studies

Electronic searches—The following electronic databases were be searched.

- Cochrane CENTRAL (Issue 3, 2009).
- MEDLINE via Ovid (August 2009).
- EMBASE via Ovid (August 2009).
- Oxford Pain Relief Database (Jadad 1996a).

Please see Appendix 1 for the MEDLINE search strategy, Appendix 2 for the EMBASE search strategy, and Appendix 3 for the CENTRAL search strategy.

Language: No language restriction was applied.

Searching other resources—Additional studies were sought from the reference lists of retrieved articles and reviews.

Unpublished studies: Abstracts, conference proceedings and other grey literature were not searched. Menarini Group provided copies of published and unpublished studies for dexketoprofen; the company markets products containing both ketoprofen and dexketoprofen.

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Data collection and analysis

Selection of studies—Two review authors independently assessed and agreed the search results for studies that might be included in the review. Disagreements were resolved by consensus or referral to a third review author.

Quality assessment—Two review authors independently assessed the included studies for quality using a five-point scale (Jadad 1996b) that considered randomisation, blinding, and study withdrawals and dropouts. The scale used is as follows.

- Is the study randomised? If yes give one point.
- Is the randomisation procedure reported and is it appropriate? If yes add one point, if no deduct one point.
- Is the study double blind? If yes then add one point.
- Is the double blind method reported and is it appropriate? If yes add one point, if no deduct one point.
- Are the reasons for patient withdrawals and dropouts described? If yes add one point.

Data management—Data were extracted by two review authors and recorded on a standard data extraction form. Data suitable for pooling were entered into RevMan 5.0.

Data analysis—QUOROM guidelines were followed (Moher 1999). For efficacy analyses we used the number of participants in each treatment group who were randomised, received medication, and provided at least one post-baseline assessment. For safety analyses we used number of participants who received study medication in each treatment group. Analyses were planned for different doses. Sensitivity analyses were planned for pain model (dental versus other postoperative pain), trial size (39 or fewer versus 40 or more per treatment arm), and quality score (two versus three or more). A minimum of two studies and 200 participants were required for any analysis (Moore 1998).

Primary outcome

Number of participants achieving at least 50% pain relief: For each study, the mean TOTPAR, SPID, VAS TOTPAR or VAS SPID values for active and placebo were converted to %maxTOT-PAR or %maxSPID by division into the calculated maximum value (Cooper 1991). The proportion of participants in each treatment group who achieved at least 50%maxTOTPAR was calculated using verified equations (Moore 1996; Moore 1997a; Moore 1997b). These proportions were then converted into the number of participants achieving at least 50%maxTOTPAR by multiplying by the total number of participants in the treatment group. Information on the number of participants with at least 50%max-TOTPAR for active treatment and placebo was then used to calculate relative benefit (RB) and number needed to treat to benefit (NNT).

Pain measures accepted for the calculation of TOTPAR or SPID were:

- five-point categorical pain relief (PR) scales with comparable wording to “none, slight, moderate, good or complete”;
- four-point categorical pain intensity (PI) scales with comparable wording to “none, mild, moderate, severe”;
- Visual analogue scales (VAS) for pain relief;
- VAS for pain intensity.

If none of these measures were available, numbers of participants reporting “very good or excellent” on a five-point categorical global scale with the wording “poor, fair, good, very good, excellent” were taken as those achieving at least 50% pain relief (Collins 2001). Further details of the scales and derived outcomes are in the glossary (Appendix 4).

Secondary outcomes

1. Use of rescue medication: Numbers of participants requiring rescue medication for treatment and placebo groups were used to calculate relative risk (RR) and numbers needed to treat to prevent (NNTp) use of rescue medication. Median (or mean) time to use of rescue medication was used to calculate the weighted mean of the median (or mean) for the outcome. Weighting was by number of participants.

2. Adverse events: Numbers of participants reporting adverse events for each treatment group were used to calculate RR and numbers needed to treat to harm (NNH) estimates for:

- **i.** any adverse event
- **ii.** any serious adverse event (as reported in the study)
- **iii.** withdrawal due to an adverse event

3. Withdrawals: Withdrawals for reasons other than lack of efficacy (participants using rescue medication - see above) and adverse events were noted, as were exclusions from analysis where data were presented.

RB or relative risk (RR) estimates were calculated with 95% confidence intervals (CI) using a fixed-effect model (Morris 1995). NNT, NNTp and NNH with 95% CI were calculated using the pooled number of events by the method of Cook and Sackett (Cook 1995). A statistically significant difference from control was assumed when the 95% CI of the relative benefit did not include the number one.

Homogeneity of studies was assessed visually (L'Abbè 1987). The z test (Tramèr 1997) was used to determine if there was a significant difference between NNTs for different doses of active treatment, or between groups in the sensitivity analyses.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of studies awaiting classification.

There were 18 included studies; 11 studied ketoprofen only, four dexketoprofen only, and three studied both ketoprofen and dexketoprofen.

Fifteen studies were excluded after reading the full paper (Avila 1991; Bagan 1998; Berti 2000; Gallardo 1982; Giudice 1987; Jimenez-Martinez 2004; Kantor 1984; Letarget 1998; Lobo 1983;Olmedo 2001; Perez 2002; Schreiber 1998; Sunshine 1986; Tufano 1981; Zapata 2000).

One further study was identified after peer review and has been added to "awaiting classification" (Akural 2009), together with two studies for which we have been unable to obtain copies of the full text (Balzanelli 1996; Yatomi 1979).

Details of individual studies are in the 'Characteristics of included studies', 'Characteristics of excluded studies' and 'Studies awaiting classification' tables.

Ketoprofen—Fourteen studies fulfilled the inclusion criteria (Arnold 1990; Cooper 1984; Cooper 1988; McGurk 1998; Mehlisch 1984; Olson 1999; Olson 2001; Schreiber 1996; Seymour 1996; Seymour 2000; Sunshine 1993; Sunshine 1998; Turek 1988; Vidal 1999). In the 14 included studies the total number of participants was 2510, of whom 968 were treated with ketoprofen (dose range 6.25 mg to 150 mg) and 542 with placebo.

Dose: Ketoprofen 6.25 mg was given to 35 participants in one treatment arm (Sunshine 1998), 12.5 mg to 138 participants in three treatment arms (Seymour 1996; Seymour 2000; Sunshine 1998), 25 mg to 281 participants in eight treatment arms (Arnold 1990; Cooper 1984; Cooper 1988; Mehlisch 1984; Olson 1999; Olson 2001; Seymour 1996; Sunshine 1998), 50 mg to 314 participants in eight treatment arms (Cooper 1984; McGurk 1998;Mehlisch 1984; Olson 1999; Schreiber 1996; Sunshine 1993;Turek 1988; Vidal 1999), 100 mg to 161 participants in five treatment arms (Arnold 1990; Cooper 1984; Cooper 1988; Mehlisch 1984; Sunshine 1993) and 150 mg to 39 participants in one treatment arm (Turek 1988).

Formulation: One study (Olson 1999) administered ketoprofen in liquid formulation. All other studies administered ketoprofen as a capsule or tablet.

Type of surgery: Eight studies (Cooper 1984; Cooper 1988; McGurk 1998;Mehlisch 1984; Olson 2001; Seymour 1996; Seymour 2000; Sunshine 1998) enrolled participants with dental pain following extraction of at least one impacted third molar, and six studies enrolled participants with pain following other types of surgery (general surgery Arnold 1990; postepisiotomy pain Olson 1999; knee/ankle surgery Schreiber 1996; Caesarean section Sunshine 1993; elective surgery Turek 1988; hallux valgus surgery (bunionectomy)Vidal 1999).

Study duration: Study duration was 6 hours in eleven studies (Arnold 1990; Cooper 1984; Cooper 1988; McGurk 1998; Mehlisch 1984;Olson 1999; Olson 2001; Seymour 1996; Seymour 2000;Sunshine 1998; Turek 1988), 24 hours in one (Vidal 1999), three days in one Schreiber 1996), and up to seven days in one (Sunshine 1993). These latter three studies included multiple dose phases, but reported results for the first dose separately for at least some relevant outcomes (Schreiber 1996; Sunshine 1993; Vidal 1999). One study in hallux valgus surgery (Vidal 1999) used patient-controlled (PCA) rescue analgesia; the device was programmed to deliver a bolus of 2 mg morphine with a 15 minute lockout. Any patient taking rescue morphine within the first hour was withdrawn from the study; for patients remedicating thereafter, pain intensity was assessed as that of the last observation carried forward and pain relief rated as ‘none’ in later assessments. As the Vidal 1999 study matched all the study inclusion criteria and used morphine as a rescue treatment in the same way as other studies use oral rescue analgesia, it was included. Sensitivity analyses were planned to evaluate any impact of potential study differences on overall estimates, and because bunion surgery is an uncommon pain model without the proven sensitivity of third molar extraction (Bulley 2009).

Dexketoprofen—Seven studies using dexketoprofen fulfilled the inclusion criteria (Cooper 1998; Gay 1996; Harrison 1996; Jackson 2004; McGurk 1998; Schreiber 1996; Vidal 1999). In the seven included studies the total number of participants was 1275, of whom 681 were treated with dexketoprofen (dose range 5 mg to 100 mg) and 289 with placebo.

Dose: Dexketoprofen 5 mg was given to 41 participants in one treatment arm (Gay 1996), 10 mg to 42 participants in one treatment arm (Gay 1996), 12.5 mg to 188 participants in

four treatment arms (Harrison 1996; McGurk 1998; Schreiber 1996; Vidal 1999), 20 mg to 41 participants in one treatment arm (Gay 1996), 25 mg to 276 participants in six treatment arms (Cooper 1988; Harrison 1996; Jackson 2004; McGurk 1998; Schreiber 1996; Vidal 1999), 50 mg to 42 participants in one treatment arm (McGurk 1998), and 100 mg to 51 participants in one treatment arm (Cooper 1988). For the purposes of analysis, data for 10 mg and 12.5 mg, and for 20 mg and 25 mg were combined as the small differences in dose were unlikely to have a clinically significant impact on results.

Study duration: Study duration was 6 hours in four studies (Cooper 1998; Gay 1996; Harrison 1996; McGurk 1998), and 24 hours in two studies (Jackson 2004; Vidal 1999), and three days in one study (Schreiber 1996). Two studies included multiple dose phases (Schreiber 1996; Vidal 1999), but reported results for the first dose separately for at least some relevant outcomes.

Type of surgery: Five studies (Cooper 1988; Gay 1996; Harrison 1996; Jackson 2004; McGurk 1998) enrolled participants with dental pain following extraction of at least one impacted third molar, and two studies enrolled participants with pain following hallux valgus surgery (bunionectomy) (Vidal 1999, see Ketoprofen above, and knee or ankle surgery, Schreiber 1996).

Studies included small numbers of participants treated in active comparator arms with licensed doses of other analgesics (ibuprofen 200 mg, 400 mg; aspirin 650 mg; paracetamol 500 mg, 650 mg, 1000 mg; rofecoxib 50 mg; codeine 90 mg; dipyrone 500 mg; paracetamol +oxycodone 650/10 mg). These participants are not evaluated in this review.

Risk of bias in included studies

Methodological quality of included studies: All included studies were both randomised and double blind.

Ketoprofen: Four studies were given a quality score of five (McGurk 1998;Olson 2001; Schreiber 1996; Vidal 1999) seven a score of four (Cooper 1984; Cooper 1988; Seymour 1996; Seymour 2000;Sunshine 1993; Sunshine 1998; Turek 1988), and three a score of three (Arnold 1990; Mehlisch 1984; Olson 1999).

Dexketoprofen: Four studies were given a quality score of five (Harrison 1996;McGurk 1998; Schreiber 1996; Vidal 1999), and three a score of four (Cooper 1998; Gay 1996; Jackson 2004).

Details are reported in the ‘Characteristics of included studies’ table.

Effects of interventions

Number of patients achieving at least 50% pain relief with ketoprofen

Ketoprofen 6.25 mg versus placebo: Only one study, with 70 participants in the comparison, provided data (Sunshine 1998) and no analyses were undertaken.

Ketoprofen 12.5 mg versus placebo: Three studies with 274 participants provided data (Seymour 1996; Seymour 2000; Sunshine 1998) (Analysis 1.1).

- The proportion of participants experiencing at least 50% pain relief over 4 to 6 hours with ketoprofen 12.5 mg was 56% (77/138).
- The proportion of participants experiencing at least 50% pain relief over 4 to 6 hours with placebo was 13% (18/136).
- The relative benefit of treatment compared with placebo 4.2 (2.7 to 6.6).
- The NNT for at least 50% pain relief over 4 to 6 hours was 2.4 (1.9 to 3.1).

Ketoprofen 25 mg versus placebo: Eight studies with 535 participants provided data (Arnold 1990; Cooper 1984; Cooper 1988; Mehlisch 1984; Olson 1999; Olson 2001; Seymour 1996; Sunshine 1998) (Analysis 2.1 see total).

- The proportion of participants experiencing at least 50% pain relief over 4 to 6 hours with ketoprofen 25 mg was 62% (175/281).
- The proportion of participants experiencing at least 50% pain relief over 4 to 6 hours with placebo was 12% (31/254).
- The relative benefit of treatment compared with placebo was 4.9 (3.5 to 6.9).
- The NNT for at least 50% pain relief over 4 to 6 hours was 2.0 (1.8 to 2.3).

Ketoprofen 50 mg versus placebo: Eight studies with 624 participants provided data (Cooper 1984; McGurk 1998; Mehlisch 1984; Olson 1999; Schreiber 1996; Sunshine 1993; Turek 1988; Vidal 1999) (Analysis 3.1; Figure 1, see total).

- The proportion of participants experiencing at least 50% pain relief over 4 to 6 hours with ketoprofen 50 mg was 48% (151/314).
- The proportion of participants experiencing at least 50% pain relief over 4 to 6 hours with placebo was 18% (56/310).
- The relative benefit of treatment compared with placebo was 2.7 (2.0 to 3.5).
- The NNT for at least 50% pain relief over 4 to 6 hours was 3.3 (2.7 to 4.3).

Ketoprofen 100 mg versus placebo: Five studies with 321 participants provided data (Arnold 1990; Cooper 1984; Cooper 1988; Mehlisch 1984; Sunshine 1993) (Analysis 4.1 see total).

- The proportion of participants experiencing at least 50% pain relief over 4 to 6 hours with ketoprofen 100 mg was 66% (106/161).
- The proportion of participants experiencing at least 50% pain relief over 4 to 6 hours with placebo was 18% (28/160).
- The relative benefit of treatment compared with placebo was 3.6 (2.5 to 5.1).
- The NNT for at least 50% pain relief over 4 to 6 hours was 2.1 (1.7 to 2.6).

Ketoprofen 150 mg versus placebo: Only one study, with 81 participants in the comparison, provided data (Turek 1988), and no analyses were undertaken.

Summary of results A: Number of participants with ≥ 50% pain relief over 4 to 6 hours with ketoprofen					
Dose	**Studies**	**Participants**	**Ketoprofen (%)**	**Placebo (%)**	**NNT (95%CI)**
12.5 mg	3	274	56	13	2.4 (1.9 to 3.1)
25 mg	8	535	62	12	2.0(1.8 to 2.3)
50 mg	8	624	48	18	3.3 (2.7 to 4.3)
100 mg	5	321	66	18	2.1 (1.7 to 2.6)

Sensitivity analysis of primary outcome

Trial size: There were insufficient data for any dose of ketoprofen to compare results of studies where both treatment arms had fewer than 40 participants with those having 40 or more participants. Individual treatment arms ranged in size from 14 to 67 participants.

Quality score: All studies scored three or more so no analysis was carried out.

Pain model: There were sufficient data to compare dental and other types of surgery for ketoprofen 50 mg only. (Analysis 3.1; Figure 1)

- Three studies (190 participants) used ketoprofen 50 mg in dental surgery (Cooper 1984; McGurk 1998; Mehlisch 1984). Overall 62% (61/98) of participants achieved 50% pain relief with ketoprofen and 6% (6/92) with placebo. The relative benefit for treatment compared with placebo was 9.0 (4.2 to 19), giving an NNT for at least 50% pain relief over 4 to 6 hours of 1.8 (1.5 to 2.2).
- Five studies (434 participants) used ketoprofen 50 mg in other types of surgery (Olson 1999; Schreiber 1996; Sunshine 1993; Turek 1988; Vidal 1999). Overall 42% (90/216) of participants achieved 50% pain relief with ketoprofen and 23% (50/218) with placebo. The relative benefit for treatment compared with placebo was 1.8 (1.4 to 2.4), giving an NNT for at least 50% pain relief over 4 to 6 hours of 5.3 (3.7 to 9.9).

The difference between the NNTs was statistically significant ($z = 5.23$, $P < 0.00006$), but based on small numbers, particularly for the dental studies. The extent of clinical heterogeneity between these studies is illustrated in Figure 1.

Post hoc analysis of dental studies only shows a dose response trend, based on limited data, particularly for the higher doses. (Summary of results B).

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Summary of results B: Number of participants with ≥50% pain relief over 4 to 6 hours with ketoprofen in dental studies

Dose	Studies	Participants	Ketoprofen (%)	Placebo (%)	NNT (95%CI)
12.5 mg	3	274	56	13	2.4 (1.9 to 3.1)
25 mg	6	452	64	12	2.0 (1.7 to 2.3)
50 mg	3	190	62	7	1.8 (1.5 to 2.2)
100 mg	3	195	72	10	1.6(1.4 to 2.0)

Formulation: One study used a liquid formulation of ketoprofen (Olson 1999) in participants with episiotomy pain. Although this study did have lower NNTs for both 25 mg and 50 mg doses than other studies in non-dental pain, 95% CIs were wide, and there were insufficient data to draw any conclusions about differences in efficacy.

Study with PCA rescue analgesia: One study, in hallux valgus surgery (bunionectomy) (Vidal 1999), used patient-controlled (PCA) rescue analgesia. A post hoc sensitivity analysis was carried out to determine whether including this study influenced the overall results. Removing the study from the analysis of ketoprofen 50 mg in non-dental surgery gave a lower (better) estimate of NNT (4.3 (3.0 to 7.5) compared with 5.3 (3.7 to 9.9) with the study included), but confidence intervals overlapped. The study did have very much lower response rates in both the active (4%) and placebo (2%) treatment arms, compared with other studies in non-dental surgery (active 44% to 69%, placebo 15% to 38%). It is not clear whether this low response rate in Vidal 1999 is due to chance, or the nature of the surgery (which is known to be very painful over several days) or the easy availability of rescue medication, which may have encouraged participants to use it earlier, and so drop out of the study.

Number of patients achieving at least 50% pain relief with dexketoprofen

Dexketoprofen 5 mg versus placebo: Only one study, with 82 participants in the comparison, provided data (Gay 1996) and no analyses were undertaken.

Dexketoprofen 10 mg/12.5 mg versus placebo: Five studies with 452 participants provided data; one study used dexketoprofen 10 mg (Gay 1996) and four studies used dexketoprofen 12.5 mg (Harrison 1996; McGurk 1998; Schreiber 1996;Vidal 1999) (Analysis 5.1 see total).

- The proportion of participants experiencing at least 50% pain relief over 4 to 6 hours with dexketoprofen 10 mg/12.5 mg was 45% (104/230).
- The proportion of participants experiencing at least 50% pain relief over 4 to 6 hours with placebo was 17% (38/222).
- The relative benefit of treatment compared with placebo was 2.7 (2.0 to 3.7).
- The NNT for at least 50% pain relief over 4 to 6 hours was 3.6 (2.8 to 5.0).

Dexketoprofen 20 mg/25 mg versus placebo: Five studies with 523 participants provided data; one study used dexketoprofen 20 mg (Gay 1996) and four studies used dexketoprofen 25 mg (Harrison 1996; McGurk 1998; Schreiber 1996;Vidal 1999) (Analysis 6.1; Figure 3, see total).

- The proportion of participants experiencing at least 50% pain relief over 4 to 6 hours with dexketoprofen 20 mg/25 mg was 47% (129/225).
- The proportion of patients experiencing at least 50% pain relief over 4 to 6 hours with placebo was 15% (38/248).
- The relative benefit of treatment compared with placebo was 3.3 (2.4 to 4.5).
- The NNT for at least 50% pain relief over 4 to 6 hours was 3.2 (2.6 to 4.1).

Dexketoprofen 50 mg and 100 mg versus placebo: Only one study, with 82 participants in the comparison, provided data for 50 mg (McGurk 1998), and one study with 77 participants in the comparison for 100 mg (Cooper 1998). No analyses were undertaken for these doses.

Summary of results C: Number of participants with ≥ 50% pain relief over 4 to 6 hours with dexketoprofen

Dose	Studies	Participants	Ketoprofen (%)	Placebo (%)	NNT (95%CI)
10/12.5 mg	5	452	45	17	3.6 (2.8 to 5.0)
20/25 mg	5	523	47	15	3.2(2.6 to 4.1)

Sensitivity analysis of primary outcome

Trial size: There were insufficient data for either dose of dexketoprofen to compare results of studies where both treatment arms had fewer than 40 participants with those having 40 or more participants. Individual treatment arms ranged in size from 26 to 55 participants.

Quality score: All studies scored three or more so no analysis was carried out.

Pain model

Dexketoprofen 10 mg/12.5 mg:

- Three studies (251 participants) used dexketoprofen 10 mg/12.5 mg in dental surgery (Gay 1996; Harrison 1996;McGurk 1998). Overall 47% (61/131) of participants achieved 50% pain relief with dexketoprofen and 14% (17/120) with placebo. The relative benefit for treatment compared with placebo was 3.3 (2.0 to 5.3), giving an NNT for at least 50% pain relief over 4 to 6 hours of 3.1 (2.3 to 4.6).
- Two studies (201 participants) used dexketoprofen 10 mg/12.5 mg in other types of surgery (Schreiber 1996; Vidal 1999). Overall 43% (43/99) of participants achieved 50% pain relief with dexketoprofen and 21% (21/102) with placebo. The relative benefit for treatment compared with placebo was 2.1 (1.4 to 3.3), giving an NNT for at least 50% pain relief over 4 to 6 hours of 4.4 (2.8 to 9.7) (Analysis 5.1).

- Four studies (322 participants) used dexketoprofen 20 mg/25 mg in dental surgery (Cooper 1998; Gay 1996; Harrison 1996; McGurk 1998). Overall 47% (82/176) of participants achieved 50% pain relief with dexketoprofen and 12% (17/146) with placebo. The relative benefit for treatment compared with placebo was 4.5 (2.8 to 7.2), giving an NNT for at least 50% pain relief over 4 to 6 hours of 2.9 (2.3 to 3.9).
- Two studies (201 participants) used dexketoprofen 20 mg/25 mg in other types of surgery (Schreiber 1996; Vidal 1999). Overall 47% (47/99) of participants achieved 50% pain relief with dexketoprofen and 21% (21/102) with placebo. The relative benefit for treatment compared with placebo was 2.3 (1.6 to 3.5), giving an NNT for at least 50% pain relief over 4 to 6 hours of 3.7 (2.5 to 7.0) (Analysis 6.1; Figure 3).

Although at both doses the NNT was lower (better) in dental studies than in other types of surgery, the 95% CIs overlap considerably, indicating no significant difference in this group of studies.

Summary of results D: Number of participants with ≥ 50% pain relief over 4 to 6 hours with dexketoprofen in dental and other types of surgery

Dose and type of Surgery	Studies	Participants	Dexketoprofen (%)	Placebo (%)	NNT (95%CI)
10/12.5 mg Dental	3	251	47	14	3.1 (2.3 to 4.6)
10/12.5 mg Other surgery	2	201	43	21	4.4 (2.8 to 9.7)
20/25 mg Dental	4	322	47	12	2.9 (2.3 to 3.9)
20/25 mg Other surgery	2	201	47	21	3.7 (2.5 to 7.0)

Study with PCA rescue analgesia: One study, in hallux valgus surgery (Vidal 1999), used patient-controlled (PCA) rescue analgesia. This study had lower response rates in both the active and placebo treatment arms than the other study in non-dental pain (Schreiber 1996). For Vidal 1999, the response rate was 30% (14/47) with both dexketoprofen 12.5 mg and 25 mg, and 2% (1/47) with placebo, while for Schreiber 1996 the rates were 56% (29/52) with dexketoprofen 12.5 mg, 63% (33/52) with dexketoprofen 25 mg, and 36% (20/55) with placebo. It is not clear whether this low response rate in Vidal 1999 is due to chance, or the nature of the surgery (which is known to be very painful over several days) or the easy availability of rescue medication, which may have encouraged participants to use it earlier, and so drop out of the study.

Comparison of ketoprofen and dexketoprofen—Since the analgesic effect of ketoprofen is due to the S(+)-enantiomer (Barbanoj 2001), the implication is that use of dexketoprofen alone should produce equivalent analgesia to double-dose ketoprofen. In these studies, indirect comparison of ketoprofen 50 mg (NNT for at least 50% pain relief over 4 to 6 hours in dental studies: 1.8 (1.5 to 2.2) and dexketoprofen 20/25 mg (2.9 (2.3 to 3.9)) did not demonstrate equivalent efficacy (z = 2.89; P for difference = 0.0039). The same

result was found for ketoprofen 25 mg and dexketoprofen 10/12.5 mg (z = 2.87; P for difference = 0.0041).

Use of rescue medication with ketoprofen

Proportion of participants using rescue medication

- Two studies (198 participants) using 12.5 mg ketoprofen reported this outcome, both at 6 hours (Seymour 1996; Seymour 2000). The mean proportion using rescue medication with ketoprofen was 80% (79/99) and with placebo was 98% (97/99), giving an NNTp of 5.5 (3.8 to 10) (Analysis 1.2).
- Six studies (402 participants) using 25 mg ketoprofen reported this outcome, all at 6 hours (Arnold 1990; Cooper 1988; Mehlisch 1984; Olson 1999; Olson 2001; Seymour 1996). The mean proportion using rescue medication with ketoprofen was 46% (99/216) and with placebo was 79% (147/186), giving an NNTp of 3.0 (2.4 to 4.1) (Analysis 2.2).
- Seven studies (554 participants) using 50 mg ketoprofen reported this outcome, five at 6 hours (McGurk 1998; Mehlisch 1984; Olson 1999; Turek 1988; Vidal 1999), and two at 8 hours (Schreiber 1996; Sunshine 1993). Overall the mean proportion using rescue medication with ketoprofen was 48% (135/279) and with placebo was 75% (205/275), giving an NNTp of 3.8 (2.9 to 5.3). For 6 hours only, the mean proportion using rescue medication with ketoprofen was 48% (85/177) and with placebo was 81% (140/172), giving an NNTp of 3.0 (2.3 to 4.1) (Analysis 3.2).
- Four studies (259 participants) using 100 mg ketoprofen reported this outcome, three at 6 hours (Arnold 1990; Cooper 1988; Mehlisch 1984), and one at 8 hours (Sunshine 1993). Overall the mean proportion using rescue medication with ketoprofen was 44% (57/130) and with placebo was 81% (104/129), giving an NNTp of 2.7 (2.1 to 2.9). For 6 hours only, the mean proportion using rescue medication with ketoprofen was 43% (35/82) and with placebo was 85% (69/81), giving an NNTp of 2.4 (1.8 to 3.4) (Analysis 4.2).

Many more participants needed rescue medication within 6 hours with the 12.5 mg dose than the higher doses (12.5 mg vs 50 mg z = 2.37, P = 0.018).

Summary of results E: Participants using rescue medication within 6 hours with ketoprofen

Dose	Studies	Participants	Ketoprofen (%)	Placebo (%)	NNTp (95%CI)
12.5 mg	2	198	80	98	5.5 (3.8 to 10)
25 mg	6	402	46	79	3.0 (2.4 to 4.1)
50 mg	5	349	48	81	3.0 (2.3 to 4.1)
100 mg	3	163	43	85	2.4 (1.8 to 3.4)

Time to use of rescue medication: Five studies reported the median time to use of rescue medication (McGurk 1998; Olson 2001; Seymour 1996; Seymour 2000;Sunshine 1993). The

study using ketoprofen 50 mg and 100 mg in participants who had undergone Caesarian section (Sunshine 1993) had notably longer times to use of rescue medication in both active (7 to 9 hours) and placebo (6 hours) treatment arms than the dental studies. Based on very limited data (< 200 participants in each comparison), the median time to use of rescue medication in the dental studies was around 5 hours for ketoprofen 25 mg and 50 mg, and 2 hours for placebo.

Seven studies reported the mean time to use of rescue medication (Arnold 1990; Cooper 1984; Cooper 1988; Mehlisch 1984; Olson 1999; Turek 1988; Vidal 1999). Based on very limited data (< 200 participants in each comparison), the mean time to use of rescue medication in dental studies was 4 to 4.5 hours with 25 mg to 100 mg ketoprofen, and 2.5 hours with placebo. In non-dental studies it was about 6 hours for ketoprofen 25 mg and 50 mg, and 5 hours for placebo in episiotomy pain, and 2 hours for both ketoprofen 50 mg and placebo in bunionectomy and other elective surgery. The study in bunionectomy pain used morphine PCA as rescue analgesia (Vidal 1999).

Details of results for individual studies are in Table 1.

Use of rescue medication with dexketoprofen

Proportion of participants using rescue medication

- Five studies (446 participants) using 10/12.5 mg dexketoprofen reported this outcome, four at 6 hours (Gay 1996;Harrison 1996; McGurk 1998; Vidal 1999), and one at 8 hours (Schreiber 1996). Overall the mean proportion using rescue medication with dexketoprofen was 48% (109/228) and with placebo was 69% (151/218), giving an NNTp of 4.7 (3.3 to 8.0). For 6 hours only, the mean proportion using rescue medication with ketoprofen was 54% (95/176) and with placebo was 74% (121/163), giving an NNTp of 4.9 (3.3 to 9.7) (Analysis 5.2).
- Seven studies (597 participants) using 20/25 mg dexketoprofen reported this outcome, five at 6 hours (Cooper 1998; Gay 1996; Harrison 1996; McGurk 1998; Vidal 1999), one at 8 hours (Schreiber 1996), and one at 24 hours (Jackson 2004). Overall the mean proportion using rescue medication with dexketoprofen was 52% (161/312) and with placebo was 73% (207/285), giving an NNTp of 4.8 (3.5 to 7.4). For 6 hours only, the mean proportion using rescue medication with ketoprofen was 52% (114/218) and with placebo was 75% (141/189), giving an NNTp of 4.5 (3.2 to 7.6) (Analysis 6.2).

There was no obvious difference between these two doses for the number of participants needing rescue medication within 6 hours.

Summary of results F: Participants using rescue medication within 6 hours with dexketoprofen

Dose	Studies	Participants	Ketoprofen (%)	Placebo (%)	NNTp (95%CI)
10/12.5 mg	4	339	54	74	4.9 (3.3 to 9.7)
20/25 mg	6	407	52	75	4.5 (3.2 to 7.6)

Time to use of rescue medication: Two studies reported the median time to use of rescue medication, both in dental pain (Cooper 1998; Jackson 2004). Based on very limited data (< 200 participants in the comparison), the weighted mean of the median time to use of rescue medication was 4.2 hours with dexketoprofen 25 mg, and 2.2 hours for placebo.

Three studies reported the mean time to use of rescue medication, two in dental pain (Gay 1996; McGurk 1998), and one following bunionectomy (Vidal 1999). The times in the bunionectomy study were notably shorter than in the dental studies, with remedication times of 2.3 for dexketoprofen, and 1.7 for placebo. This study used morphine PCA as rescue analgesia, and the data were not combined. Based on very limited data (< 200 participants in each comparison), for dental studies the weighted mean of the mean time to use of rescue medication was 4.9 with dexketoprofen 10/12.5 mg, 5.2 with dexketoprofen 20/25 mg, and 3.6 with placebo.

Details of results for individual studies are in Table 1.

Adverse events with ketoprofen

Any adverse event: Ten studies reported the numbers of participants experiencing at least one adverse event over a period of 6 hours post dose (Arnold 1990; Cooper 1984; Cooper 1988; McGurk 1998; Olson 1999;Olson 2001; Seymour 1996; Seymour 2000; Sunshine 1998;Turek 1988). One study (Mehlisch 1984) did not report this outcome, and three multiple dose studies did not report adverse event data for the single dose phase (Schreiber 1996; Sunshine 1993;Vidal 1999). Adverse events were generally described as subjective complaints of mild or moderate intensity, and many could be attributed to the surgical procedure itself, or the anaesthetic.

- Three studies using ketoprofen 12.5 mg reported on the number of participants with at least one adverse event (Seymour 1996; Seymour 2000; Sunshine 1998): 6% (8/138) with ketoprofen and 4% (6/136) with placebo (Analysis 1.3).
- Seven studies using ketoprofen 25 mg reported on the number of participants with at least one adverse event (Arnold 1990; Cooper 1984; Cooper 1988; Olson 1999; Olson 2001;Seymour 1996; Sunshine 1998): 10% (27/259) with ketoprofen and 10% (22/231) with placebo (Analysis 2.3).
- Four studies using ketoprofen 50 mg reported on the number of participants with at least one adverse event (Cooper 1984; McGurk 1998; Olson 1999; Turek 1988): 21% (29/141) with ketoprofen and 14% (18/137) with placebo (Analysis 3.3).
- Three studies using ketoprofen 100 mg reported on the number of participants with at least one adverse event (Arnold 1990; Cooper 1984; Cooper 1988): 22% (19/86) with ketoprofen and 18% (16/89) with placebo (Analysis 4.3).

There was no difference in numbers of participants reporting at least one adverse event between ketoprofen and placebo (Summary of results G).

Summary of results G: Participants with at least one adverse event					
Dose	**Studies**	**Participants**	**Ketoprofen (%)**	**Placebo (%)**	**NNH (95%CI)**
12.5 mg	3	274	6	4	not calculated
25 mg	7	490	10	10	not calculated
50 mg	4	278	21	13	not calculated
100 mg	3	175	22	18	not calculated

Serious adverse events: No study reported any serious adverse events.

Adverse events with dexketoprofen

Any adverse event: Four studies reported the numbers of participants experiencing at least one adverse event over a period of 6 hours post dose (Cooper 1998; Gay 1996; Harrison 1996; McGurk 1998). One study (Jackson 2004) reported over 24 hours, and two multiple dose studies did not report adverse event data for the single dose phase (Schreiber 1996; Vidal 1999). Adverse events were generally described as subjective complaints of mild or moderate intensity, and many could be attributed to the surgical procedure itself, or the anaesthetic.

- Three studies using dexketoprofen 10/12.5 mg reported on the number of participants with at least one adverse event (Gay 1996; Harrison 1996; McGurk 1998): 9% (12/132) with ketoprofen and 14% (18/126) with placebo (Analysis 5.3).
- Five studies using dexketoprofen 20/25 mg reported on the number of participants with at least one adverse event (Cooper 1998; Gay 1996; Harrison 1996; Jackson 2004; McGurk 1998): 20% (43/220) with ketoprofen and 13% (26/193) with placebo (Analysis 6.3).

At neither dose was there a difference in numbers of participants reporting at least one adverse event between ketoprofen and placebo (Summary of results H).

Summary of results H: Participants with at least one adverse event					
Dose	**Studies**	**Participants**	**Dexketoprofen (%)**	**Placebo (%)**	**NNH (95%CI)**
10/12.5 mg	3	258	9	14	not calculated
20/25 mg	5	413	20	13	not calculated

Serious adverse events: No study reported any serious adverse events.

Withdrawals with ketoprofen and dexketoprofen: Participants who took rescue medication were classified as with-drawals due to lack of efficacy, and details are reported under “Use of rescue medication” above.

Most studies reported some exclusions from efficacy analyses, and sometimes safety analyses. Exclusions may not be of any particular consequence in single dose acute pain studies, where most result from patients not having moderate or severe pain (McQuay 1982). Adverse event withdrawals were infrequent. Arnold 1990 reported one adverse event withdrawal due to nausea and dizziness with single dose ketoprofen 25 mg, McGurk 1998 reported one with single dose dexketoprofen 50 mg, and one with placebo (no details), and Harrison 1996 reported one with single dose dexketoprofen 25 mg, and one with placebo (no details). In two multiple dose studies (Schreiber 1996; Vidal 1999) there were two adverse event withdrawals with dexketoprofen 12.5 mg, three with dexketoprofen 25 mg, and two with placebo.

See ‘Additional Table 1’ for details of measures of pain relief and use of rescue medication, and ‘Additional Table 2’ for details of adverse events and withdrawals.

See Analysis 1.1; Analysis 1.2; Analysis 1.3; Analysis 2.1; Analysis 2.2; Analysis 2.3; Analysis 3.1; Analysis 3.2; Analysis 3.3; Analysis 4.1; Analysis 4.2; Analysis 4.3; Analysis 5.1; Analysis 5.2; Analysis 5.3; Analysis 6.1; Analysis 6.2; Analysis 6.3; Figure 2; Figure 3 for further information.

DISCUSSION

This review included a total of 18 studies; 11 studied ketoprofen only, four dexketoprofen only, and three studied both ketoprofen and dexketoprofen. For ketoprofen versus placebo information was available on 1510 participants, and for dexketoprofen versus placebo information on 970 participants. Studies involved acute pain following dental, orthopaedic, obstetric, gynaecological and general surgery. Ketoprofen was given to 968 participants at doses of 6.25 mg to 150 mg (mostly 25 mg and 50 mg) in comparisons with 520 participants given placebo. Dexketoprofen was given to 681 participants at doses of 5 mg to 100 mg (mostly 10 mg to 25 mg) in comparisons with 289 participants given placebo. Methodological quality was good, with all studies scoring above the minimum required to minimise bias.

The results of this review are confounded by relatively small numbers of studies and participants, and by clinical heterogeneity in the non-dental pain models. In particular, a study in bunionectomy (Vidal 1999) was insensitive, in keeping with a similar finding in rofecoxib trials (Bulley 2009). A consequence of this is that data from dental studies only, provided useful information. For ketoprofen, dental studies gave a sensible dose-response trend with an NNT of 2.4 at 12.5 mg improving to 1.6 at 100 mg for at least 50% pain relief compared with placebo. For dexketoprofen there was no pronounced dose response. However, the relatively small numbers of participants and indirect nature of comparisons makes demonstration of dose response difficult in these studies (McQuay 2007).

The same problems with small numbers and indirect comparisons affected comparisons of doses of ketoprofen and dexketoprofen, where similar efficacy would be expected for dexketoprofen at half the dose of ketoprofen. The amount of information available was inadequate to exclude that there is a 2:1 dose ratio between ketoprofen and dexketoprofen

for the same effect in acute pain. This was not found, though in another review a direct comparison on very limited numbers across different pain models did find the expected result (Moore 2008).

Results for different pain models were clearly heterogeneous in this data set, as Figure 2 shows for ketoprofen 50 mg, comparing dental, post surgical, and bunionectomy studies. There are too few studies to make any generalisations about effects of different pain models on analgesic efficacy estimates (Barden 2004; Moore 1998).

Overall, the results for ketoprofen and dexketoprofen are those expected for NSAID drugs in acute postoperative pain in participants with established pain of at least moderate intensity. NNTs for at least 50% pain relief for ketoprofen and dexketoprofen were generally between two and three in dental studies, comparable with other commonly used analgesics at recommended doses (e.g. ibuprofen 400 mg - NNT 2.3, Derry C 2009a; diclofenac 50 mg - NNT 2.7, Derry P 2009). Median time to use of rescue medication was also comparable at 4 to 5 hours. Efficacy appears to be a little better than with paracetamol 1000 mg - NNT 3.2 (Toms 2008), and worse than with etoricoxib 120 mg - NNT 1.6 (Clarke 2009).

In these single dose studies adverse events did not differ from placebo at any dose of ketoprofen and dexketoprofen, and there were no serious adverse events reported. Withdrawals due to adverse events were uncommon and also did not differ from placebo. Long term multiple dose studies should be used for meaningful analysis of adverse events since, even in acute pain settings, analgesics are likely to be used in multiple doses. The difficulty in the postoperative setting is that there are many sequelae of surgery and anaesthesia that manifest as adverse events, such as nausea, vomiting, or abdominal discomfort, while others, like headache, can be caused by events such as acute caffeine withdrawal over the postoperative period. The main issue is that of rare but serious adverse events, and these are more likely to be found in large observational studies.

Loss of information from withdrawals or exclusions was small, and is unlikely to have led to an overestimate of efficacy because it is as likely to be related to poor reporting as poor methods. In single dose studies most exclusions occur for protocol violations such as failing to meet baseline pain requirements, or failing to return for post-treatment visits after the acute pain results are concluded (McQuay 1982). For missing data it has been shown that over the 4 to 6 hour period, there is no difference between baseline observation carried forward and last observation carried forward, but the former gives the more conservative estimate over longer duration observations (Moore 2005).

AUTHORS' CONCLUSIONS

Implications for practice

Ketoprofen is an effective single dose oral analgesic in acute, moderate to severe postoperative pain, equivalent to other commonly used analgesics, such as ibuprofen and diclofenac. In dental surgery doses of 25 mg and above provide at least 50% pain relief to over 60% of participants treated, and the duration of action is around 5 hours. Adverse events did not differ from placebo.

Dexketoprofen was expected to give equivalent efficacy to ketoprofen at half the dose, but did not do so in these studies with limited data. A theoretical reduction in adverse events compared with the same dose of ketoprofen could not be demonstrated, since both drugs did not differ from placebo. Dexketoprofen cannot be recommended as a better tolerated alternative to ketoprofen, based on limited data from these single dose studies.

Implications for research

More studies in clinically homogeneous conditions are needed to determine whether dexketoprofen can provide the theoretical advantage of equivalent efficacy and reduced adverse events for half the dose of ketoprofen. Additional information on time to use of rescue medication is needed to provide more robust estimates of duration of action.

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CHARACTERISTICS OF STUDIES

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

Arnold 1990

Methods	RCT, DB, single oral dose, four parallel groups. Medication administered when baseline pain was of moderate to severe intensity Pain assessed at 0, 30 min, 1, 2, 3, 4, 5, 6 h.
Participants	General surgery (including gynaecological and orthopaedic) N = 59 M = 35, F = 24 Age: 22 - 70 years
Interventions	Ketoprofen 25 mg, n = 14 Ketoprofen 100 mg, n = 16 Ibuprofen 400 mg, n = 15 Placebo, n = 14
Outcomes	PI: std 4 point scale PR: std 5 point scale PGE: std 5 point scale Time to use of rescue medication Number using rescue medication Adverse events: any, serious
Notes	Oxford Quality Score: R1, DB2, W0 4 h analgesic and anti-inflammatory washout before surgery

Cooper 1984

Methods	RCT, DB, single oral dose, five parallel groups. Medication administered when baseline pain was of moderate to severe intensity Pain assessed at 0, 30 min, 1, 2, 3, 4, 5, 6 h.
Participants	Surgical removal of impacted third molars N = 181 (153 analysed) M = 48, F = 105 Mean age 23 years
Interventions	Ketoprofen 25 mg, n = 30 Ketoprofen 50 mg, n = 31 Ketoprofen 100 mg, n = 31 Aspirin 650 mg, n = 31 Placebo, n = 30
Outcomes	PI: std 4 point scale PR: std 5 point scale PGE: std 5 point scale Time to use of rescue medication Adverse events: any, serious Withdrawals
Notes	Oxford Quality Score: R1, DB2, W1 6 h analgesic, anti-inflammatory or sedative washout before surgery

Cooper 1988

Methods	RCT, DB, single oral dose, four parallel groups. Medication administered when baseline pain was of moderate to severe intensity Pain assessed at 0, 1, 2, 3, 4, 5, 6 h.
Participants	Surgical removal of impacted third molars N = 181 (161 analysed) M= 59, F = 102 Mean age 23 years
Interventions	Ketoprofen 25 mg, n = 42 Ketoprofen 100 mg, n = 39 Ibuprofen 400 mg, n = 37 Placebo, n = 43
Outcomes	PI: std 4 point scale PR: std 5 point scale PGE: std 5 point scale Numbers of participants using rescue medication Time to use of rescue medication Numbers with any adverse event Withdrawals
Notes	Oxford Quality Score: R1, DB2, W1

Cooper 1998

Methods	RCT, DB, single oral dose, four parallel groups. Medication administered when baseline pain was of moderate to severe intensity Pain assessed at 0, 15, 30, 45 min, 1, 2, 3, 4, 5, 6 h.
Participants	Surgical removal of impacted third molars N= 177 M = 75, F = 102 Mean age 23 years
Interventions	Dexketoprofen 25 mg, n = 50 Dexketoprofen 100 mg, n = 51

	Paracetamol 1000 mg, n =50 Placebo, n = 26
Outcomes	PI: 100 mm VAS and std 4 point scale PR: std 5 point scale Time to use of rescue medication Number using rescue medication Adverse events: any, serious Withdrawals
Notes	Oxford Quality Score: R1, DB2, W1 Minimum 4 h analgesic, caffeine and sedative washout before surgery

Gay 1996

Methods	RCT, DB, single oral dose, five parallel groups. Medication administered when baseline pain was of moderate to severe intensity Pain assessed at 0, 15, 30, 45, 60, 90 min, 2, 3, 4, 5 and 6 h
Participants	Surgical removal of impacted third molars N = 206 (204 analysed) M = 85, F = 119 Mean age 24 years
Interventions	Dexketoprofen tromethamine 5 mg, n = 41 Dexketoprofen tromethamine 10 mg, n = 42 Dexketoprofen tromethamine 20 mg, n = 41 Ibuprofen 400 mg, n = 41 Placebo, n = 41
Outcomes	PI: 100 mm VAS and std 4 point scale PR: std 5 point scale PGE: non std 4 point scale Time to use of rescue medication Number using rescue medication Adverse events: any, serious Withdrawals
Notes	Oxford Quality Score: R1, DB2, W1 12 h analgesic and anti-inflammatory wash out before surgery Rescue medication permitted after 1 h

Harrison 1996

Methods	RCT, DB, single oral dose, three parallel groups. Medication administered when baseline pain was of moderate to severe intensity Pain assessed at 0, 10, 20, 30, 45, 60, 90 min, 2, 3, 4, 5, 6 h
Participants	Surgical removal of impacted third molars N = 141 (137 in efficacy analysis) M = 63, F = 78 Mean age 26 years
Interventions	Dexketoprofen tromethamine 12.5 mg, n = 49 Dexketoprofen tromethamine 25 mg, n = 46 Placebo, n = 46
Outcomes	PI: 100 mm VAS and std 4 point scale PR: std 5 point scale PGE: non std 4 point scale Number using rescue medication Adverse events: any, serious Withdrawals
Notes	Oxford Quality Score: R2, DB2, W1 12 h analgesic and anti-inflammatory wash out before surgery

	Rescue medication permitted after 1 h

Jackson 2004

Methods	RCT, DB, single oral dose, five parallel groups. Medication administered when baseline pain was of moderate to severe intensity Pain assessed at 0, 15, 30, 45 min, 1, 2, 3, 4, 5, 6, 7, 8 and 24 h
Participants	Surgical removal of impacted third molars N = 123 (120 analysed) M = 39, F = 81 Mean age 29 years
Interventions	Dexketoprofen trometamol 25 mg, n = 42 Rofecoxib 50 mg, n = 37 Placebo, n = 41
Outcomes	PI: standard 4 point scale and 100 mm visual analogue scale PR: standard 5 point scale and 100 mm visual analogue scale PGE: standard 5 point scale Time use of rescue medication Number using rescue medication Adverse events: any, serious Withdrawals
Notes	Oxford Quality Score: R1, DB2, W1

McGurk 1998

Methods	RCT, DB, single oral dose, five parallel groups. Medication administered when baseline pain was of moderate to severe intensity Pain assessed at 0, 10, 20, 30, 45, 60, 90 min, 2, 3, 4, 5, 6 h
Participants	Surgical removal of impacted third molars N = 210 (200 in efficacy analysis) M = 88, F = 122 Mean age 28 years
Interventions	Dexketoprofen trometamol 12.5 mg, n = 44 Dexketoprofen trometamol 25 mg, n = 41 Dexketoprofen trometamol 50 mg, n = 43 Ketoprofen 50 mg (racemic), n = 43 Placebo, n = 39
Outcomes	PI: 100 mm VAS and std 4 point scale PR: std 5 point scale PGE: non std 4 point scale Number using rescue medication Adverse events: any, serious Withdrawals
Notes	Oxford Quality Score: R2, DB2, W1 12 h analgesic and anti-inflammatory wash out before surgery Rescue medication permitted after 1 h

Mehlisch 1984

Methods	RCT, DB, single oral dose, five parallel groups. Medication administered when baseline pain was of moderate to severe intensity Pain assessed at 0, 30 min, 1, 2, 3, 4, 5, 6 h.

Participants	Surgical removal of impacted third molars N = 138 (129 analysed) M/F not given Mean age = 26 years
Interventions	**1** Ketoprofen 25 mg, n = 24 **2** Ketoprofen 50 mg, n = 27 **3** Ketoprofen 100 mg, n = 27 **4** Codeine 90 mg, n = 27 **5** Placebo, n = 24
Outcomes	PI: std 4 point scale PR: std 5 point scale PGE: 5 point scale (1 to 5 and reverse order) Number using rescue medication Adverse events: any
Notes	Oxford Quality Score: R1, DB2, W0 Minimum 3 h analgesic, anti-inflammatory and psychotropic washout before surgery

Olson 1999

Methods	RCT, DB, single dose oral liquid formulation of ketoprofen, four parallel groups Medication administered when baseline pain was of severe intensity Pain assessed at 0, 15, 30, 60, 90 min, 2, 3, 4, 5, 6 h.
Participants	Episiotomy N = 108 (terminated early, recruitment target n=276) All female patients Mean age 24 years
Interventions	Ketoprofen 25 mg liquid formulation, n = 28 Ketoprofen 50 mg liquid formulation, n = 26 Dipyrone 500 mg liquid formulation, n = 27 Placebo, n = 27
Outcomes	PI: std 4 point scale PR: std 5 point scale PGE: non-std 4 point scale Time to use of rescue medication Number using rescue medication Adverse events; any, severe Withdrawals
Notes	Oxford Quality Score: R1, DB1, W1 2 patients entered with 2nd degree vaginal tears Minimum 6 h washout before surgery for any medication that could confound results

Olson 2001

Methods	RCT, DB, triple dummy, single oral dose, 4 parallel groups. Medication administered when baseline pain was of moderate to severe intensity Pain assessed at 0, 10, 20, 30, 45, 60, 90 min, 2, 3, 4, 5, 6 h
Participants	Surgical removal of impacted third molars N = 239 M = 76, F = 163 Mean age = 23 years
Interventions	Ketoprofen 25 mg, n = 67 Ibuprofen liquigel 400 mg, n = 67 Paracetamol 1000 mg, n = 66

	Placebo, n = 39
Outcomes	PI: 100 mm VAS and std 4 point scale PR: std 5 point scale PGE: non std 4 point scale Time to use of rescue medication Number using rescue medication Adverse events: any, serious Withdrawals
Notes	Oxford Quality Score: R2, DB2, W1 Analgesic and anti-inflammatory wash out before surgery (5 × half-life)

Schreiber 1996

Methods	RCT, DB, single and multiple oral dose phases, four parallel groups Medication administered when baseline pain was of moderate to severe intensity Pain assessed at 0, 30 min, 1, 2, 4 h after the 1st dose.
Participants	Knee (meniscus or ligament reconstruction) or ankle surgery N = 230 M = 110, F = 103 Mean age 40 years
Interventions	Dexketoprofen tromethamine 12.5 mg, n = 52 Dexketoprofen tromethamine 25 mg, n = 52 Ketoprofen 50 mg, n = 54 Placebo, n = 55
Outcomes	PI: 100 mm VAS and std 4 point scale PR: std 5 point scale PGE: non std 4 point scale Number using rescue medication Withdrawals
Notes	Oxford Quality Score: R2, DB2, W1 12 h analgesic and anti-inflammatory wash out before surgery

Seymour 1996

Methods	R, DB, double dummy, single oral dose, five parallel groups. Medication administered when baseline pain was of moderate to severe intensity Pain assessed at 0, 15, 30, 45, 60, 90 min, 2, 3, 4, 5, 6 h.
Participants	Surgical removal of impacted third molars N = 206 M = 66, F = 140 Mean age = 25 years
Interventions	Ketoprofen 12.5 mg, n = 42 Ketoprofen 25 mg, n = 41 Paracetamol 500 mg, n = 41 Paracetamol 1000 mg, n = 41 Placebo, n = 41
Outcomes	PGE: non std 4 point scale Time to use of rescue medication Number using rescue medication Adverse events: any, serious Withdrawals
Notes	Oxford Quality Score: R1, DB2, W1 12 h analgesic washout before surgery

Seymour 2000

Methods	RCT, DB, single oral dose, three parallel groups. Medication administered when baseline pain was of moderate to severe intensity Pain assessed at 0, 15, 30, 45, 60, 90 min, 2, 3, 4, 5, 6 h.
Participants	Surgical removal of impacted third molars N = 180 M= 58, F = 122 Mean age = 27 years
Interventions	Buffered ketoprofen 12.5 mg, n = 61 Ibuprofen 200 mg, n = 59 Placebo, n = 60
Outcomes	PI: std 4 point scale PR: 100 mm VAS and std 5 point scale PGE: non std 4 point scale Time to use of rescue medication Number using rescue medication Adverse events: any, serious Withdrawals
Notes	Oxford Quality Score: R1, DB2, W1 12 h analgesic washout before surgery

Sunshine 1993

Methods	RCT, DB, single and multiple oral dose, parallel groups. Medication administered when baseline pain was of severe intensity Pain assessed at 0, 30, 60 min then hourly to 8 h.
Participants	Caesarian section N = 250 All F Mean age 26 years
Interventions	Ketoprofen 50 mg, n = 48 Ketoprofen 100 mg, n = 48 Paracetamol 650 mg, n = 48 Paracetamol/oxycodone 650/10 mg, n = 48 Placebo, n = 48
Outcomes	PI: std 4 point scale PR: 100 mm VAS and std 5 point scale PGE: non std 4 point scale Time to use of rescue medication Number using rescue medication Withdrawals
Notes	Oxford Quality Score: R1, DB2, W1

Sunshine 1998

Methods	RCT, DB, single oral dose, five parallel groups. Medication administered when baseline pain was of severe intensity Pain assessed at 0, 15, 30 min, 1, 1.5, 2, 3, 3.5, 4, 5 and 6 h
Participants	Surgical removal of one or more impacted third molars N = 179 (175 analysed for efficacy) M= 58, F = 117 Mean age 22 years
Interventions	Ketoprofen 6.25 mg, n = 35 Ketoprofen 12.5 mg, n = 35 Ketoprofen 25 mg, n = 35

	Ibuprofen 200 mg, n = 35 Placebo, n = 35
Outcomes	PI: std 4 point scale PR: 100 mm VAS and std 5 point scale Adverse events: any, serious Withdrawals
Notes	Oxford Quality Score: R1, DB2, W1 24 h analgesic washout before surgery

Turek 1988

Methods	RCT, DB, single oral dose, three parallel groups. Medication administered when baseline pain was of severe intensity Pain assessed at 0, 30 min, 1, 2, 3, 4, 5 and 6 h.
Participants	Elective surgery (113 orthopedic, 23 abdominal, 11 gynaecology, 8 urology, and 6 miscellaneous procedures) N = 161 (160 analysed) M = 81, F = 81 Mean age 47 years
Interventions	Ketoprofen 150 mg, n = 39 Ketoprofen 50 mg, n = 41 Placebo, n = 42
Outcomes	PI: std 4 point scale PR: std 5 point scale PGE: non std 4 point scale Time to use of rescue medication Number using rescue medication Adverse events: any, serious Withdrawals
Notes	Oxford Quality Score: R1, DB2, W1 3 h analgesic and anti-inflammatory wash out before surgery.

Vidal 1999

Methods	RCT, DB, single and multiple oral dose phases, four parallel groups Medication administered when baseline pain was of severe intensity Pain assessed at 0, 15, 30, 45 min, 1, 2, 3, 4, 5, 6 h for single dose phase
Participants	Hallux vagus (bunion) surgery N = 188 (172 analysed) M = 25, F = 163 Mean age 54 years
Interventions	Dexketoprofen trometamol 12.5 mg, n = 47 Dexketoprofen trometamol 25 mg, n = 47 Ketoprofen 50 mg, n = 47 Placebo, n = 47
Outcomes	PI: 100 mm VAS and std 4 point scale PR: std 5 point scale PGE: non std 4 point scale Time to use of rescue medication Number using rescue medication Withdrawals
Notes	Oxford Quality Score: R2, DB2, W1 Rescue medication via PCA morphine

DB - double blind; M - male; N - total number of participants; n - number of participants in treatment arm; F - female; PGE - patient global evaluation of efficacy; PI - pain intensity; PR - pain relief; R - randomised; RCT - randomised controlled trial; std - standard; W - withdrawals

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

Study	Reason for exclusion
Avila 1991	No placebo, no baseline pain
Bagan 1998	No placebo
Berti 2000	No placebo, preoperative administration
Gallardo 1982	3 h study period, no 4 h data
Giudice 1987	No placebo
Jimenez-Martinez 2004	No placebo
Kantor 1984	Includes participants with uterine cramps
Letarget 1998	No placebo
Lobo 1983	3 h study period, no 4 h data
Olmedo 2001	No 4 to 6 hour data reported
Perez 2002	No placebo
Schreiber 1998	No placebo
Sunshine 1986	Includes participants with uterine cramps
Tufano 1981	Study not randomised or double blind. Intravenous route
Zapata 2000	No placebo

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

Akural 2009

Methods	RCT, DB, single oral dose, three parallel groups. Medication administered when baseline pain was of severe intensity Pain assessed at baseline and every 15 mins to 2 h, then hourly to 8 h
Participants	Surgical removal of one or two impacted third molars N = 82 Mean age 23 years
Interventions	Ketoprofen 100 mg Paracetamol 1000 mg Ketoprofen100 mg + paracetamol 1000 mg Placebo
Outcomes	PI: std 4 point scale Use of rescue medication
Notes	Awaiting data extraction

Balzanelli 1996

Methods

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Participants	
Interventions	
Outcomes	
Notes	Awaiting inter-library loan

Yatomi 1979

Methods	
Participants	
Interventions	
Outcomes	
Notes	Japanese - unable to obtain copy

DATA AND ANALYSES

Comparison 1
Ketoprofen 12.5 mg versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants with at least 50% pain relief over 4 to 6 hours	3	274	Risk Ratio (M-H, Fixed, 95% CI)	4.21 [2.68, 6.63]
2 Participants using rescue medication over 6 hours	2	198	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.74, 0.90]
3 Participants with any adverse event	3	274	Risk Ratio (M-H, Fixed, 95% CI)	1.33 [0.48, 3.64]

Comparison 2
Ketoprofen 25 mg versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants with at least 50% pain relief over 4 to 6 hours	8	333	Risk Ratio (M-H, Fixed, 95% CI)	4.88 [3.48, 6.85]
1. 1 Dental surgery	6	432	Risk Ratio (M-H, Fixed, 95% CI)	5.07 [3.50, 7.36]
1.2 Other surgery	2	83	Risk Ratio (M-H, Fixed, 95% CI)	3.96 [1.77, 8.86]
2 Participants using rescue medication over 6 hours	6	402	Risk Ratio (M-H, Fixed, 95% CI)	0.60 [0.52, 0.69]
3 Participants with any adverse event	7	490	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [0.68, 1.96]

Comparison 3
Ketoprofen 50 mg versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants with at least 50% pain relief over 4 to 6 hours	8	624	Risk Ratio (M-H, Fixed, 95% CI)	2.67 [2.06, 3.46]
1. 1 Dental surgery	3	190	Risk Ratio (M-H, Fixed, 95% CI)	9.04 [4.23, 19.30]
1.2 Other surgery	5	434	Risk Ratio (M-H, Fixed, 95% CI)	1.82 [1.38, 2.41]
2 Participants using rescue medication over 6 to 8 hours	7	554	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.57, 0.73]
2.1 6 hours	5	349	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.51, 0.68]
2.2 8 hours	2	205	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.61, 0.98]
3 Participants with any adverse event	4	278	Risk Ratio (M-H, Fixed, 95% CI)	1.55 [0.91, 2.62]

Comparison 4
Ketoprofen 100 mg versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Patients with at least 50% pain relief	5	321	Risk Ratio (M-H, Fixed, 95% CI)	3.72 [2.62, 5.28]
1. 1 Dental surgery	3	195	Risk Ratio (M-H, Fixed, 95% CI)	6.93 [3.85, 12.48]
1.2 Other surgery	2	126	Risk Ratio (M-H, Fixed, 95% CI)	1.94 [1.26, 3.00]
2 Participants using rescue medication over 6 to 8 hours	4	259	Risk Ratio (M-H, Fixed, 95% CI)	0.54 [0.44, 0.67]
2.1 6 hours	3	163	Risk Ratio (M-H, Fixed, 95% CI)	0.49 [0.38, 0.65]
2.2 8 hours	1	96	Risk Ratio (M-H, Fixed, 95% CI)	0.63 [0.44, 0.89]
3 Participants with any adverse event	3	175	Risk Ratio (M-H, Fixed, 95% CI)	1.19 [0.65, 2.16]

Comparison 5
Dexketoprofen 10/12.5 mg versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Patients with at least 50% pain relief	5	452	Risk Ratio (M-H, Fixed, 95% CI)	2.68 [1.95, 3.68]
1.1 Dental surgery	3	251	Risk Ratio (M-H, Fixed, 95% CI)	3.29 [2.05, 5.31]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.2 Other surgery	2	201	Risk Ratio (M-H, Fixed, 95% CI)	2.14 [1.40, 3.27]
2 Participants using rescue medication over 6 to 8 hours	5	446	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.59, 0.80]
2.1 6 hours	4	339	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.63, 0.85]
2.2 8 hours	1	107	Risk Ratio (M-H, Fixed, 95% CI)	0.49 [0.30, 0.82]
3 Participants with any adverse event	3	258	Risk Ratio (M-H, Fixed, 95% CI)	0.63 [0.32, 1.26]

Comparison 6
Dexketoprofen 20/25 mg versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants with at least 50% pain relief over 4 to 6 hours	6	523	Risk Ratio (M-H, Fixed, 95% CI)	3.27 [2.40, 4.46]
1.1 Dental surgery	4	322	Risk Ratio (M-H, Fixed, 95% CI)	4.32 [2.72, 6.88]
1.2 Other surgery	2	201	Risk Ratio (M-H, Fixed, 95% CI)	2.34 [1.56, 3.53]
2 Participants using rescue medication over 6 to 8 hours	7	597	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.62, 0.78]
2.1 6 hours	5	407	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.59, 0.79]
2.2 8 hours	2	190	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.57, 0.89]
3 Participants with any adverse event	5	413	Risk Ratio (M-H, Fixed, 95% CI)	1.30 [0.82, 2.08]

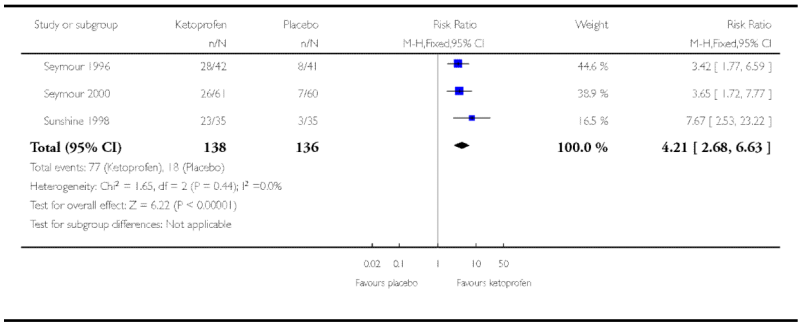
Analysis 1.1

Comparison 1 Ketoprofen 12.5 mg versus placebo, Outcome 1 Participants with at least 50% pain relief over 4 to 6 hours

Review: Single dose oral ketoprofen and dexketoprofen for acute postoperative pain in adults

Comparison: 1 Ketoprofen 12.5 mg versus placebo

Outcome: 1 Participants with at least 50% pain relief over 4 to 6 hours



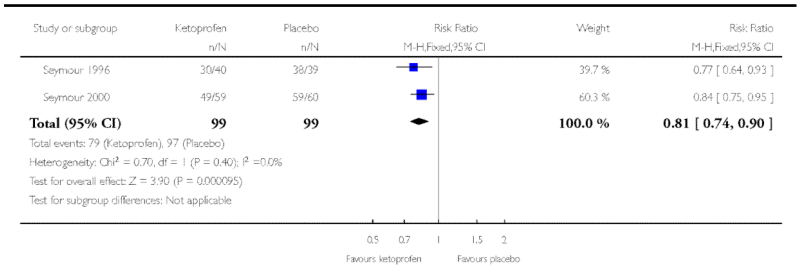
Analysis 1.2

Comparison 1 Ketoprofen 12.5 mg versus placebo, Outcome 2 Participants using rescue medication over 6 hours

Review: Single dose oral ketoprofen and dexketoprofen for acute postoperative pain in adults

Comparison: 1 Ketoprofen 12.5 mg versus placebo

Outcome: 2 Participants using rescue medication over 6 hours



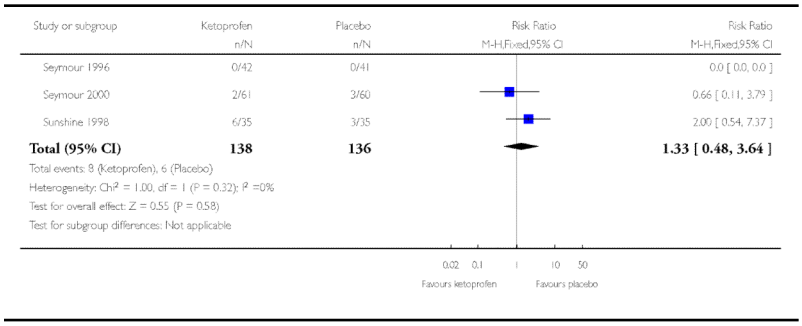
Analysis 1.3

Comparison 1 Ketoprofen 12.5 mg versus placebo, Outcome 3 Participants with any adverse event

Review: Single dose oral ketoprofen and dexketoprofen for acute postoperative pain in adults

Comparison: 1 Ketoprofen 12.5 mg versus placebo

Outcome: 3 Participants with any adverse event



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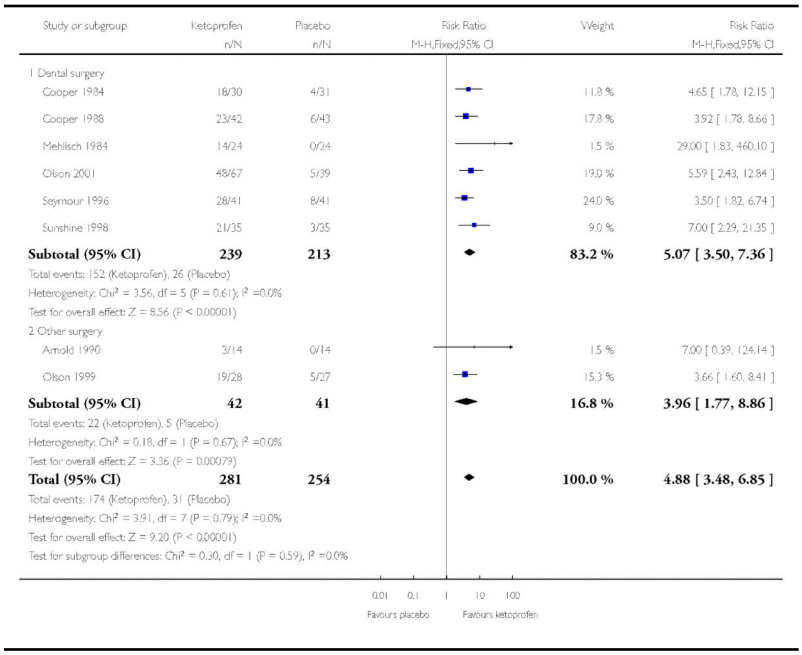
Analysis 2.1

Comparison 2 Ketoprofen 25 mg versus placebo, Outcome 1 Participants with at least 50% pain relief over 4 to 6 hours

Review: Single dose oral ketoprofen and dexketoprofen for acute postoperative pain in adults

Comparison: 2 Ketoprofen 25 mg versus placebo

Outcome: 1 Participants with at least 50% pain relief over 4 to 6 hours



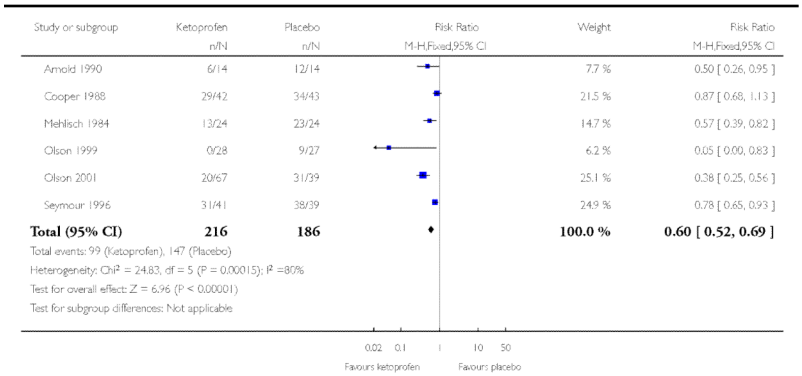
Analysis 2.2

Comparison 2 Ketoprofen 25 mg versus placebo, Outcome 2 Participants using rescue medication over 6 hours

Review: Single dose oral ketoprofen and dexketoprofen for acute postoperative pain in adults

Comparison: 2 Ketoprofen 25 mg versus placebo

Outcome: 2 Participants using rescue medication over 6 hours



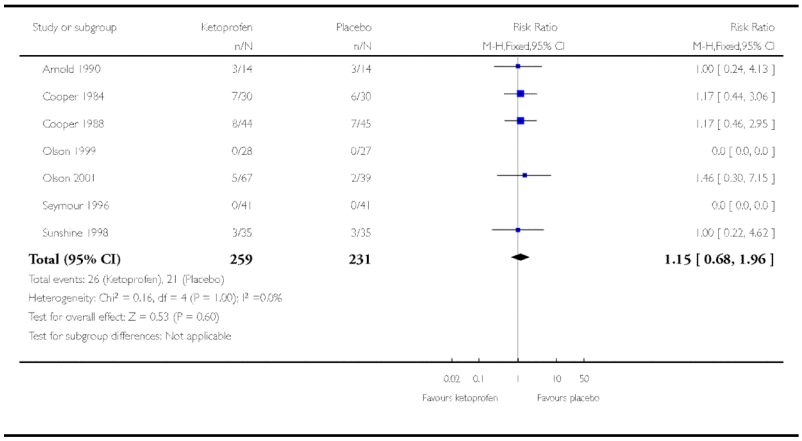
Analysis 2.3

Comparison 2 Ketoprofen 25 mg versus placebo, Outcome 3 Participants with any adverse event

Review: Single dose oral ketoprofen and dexketoprofen for acute postoperative pain in adults

Comparison: 2 Ketoprofen 25 mg versus placebo

Outcome: 3 Participants with any adverse event



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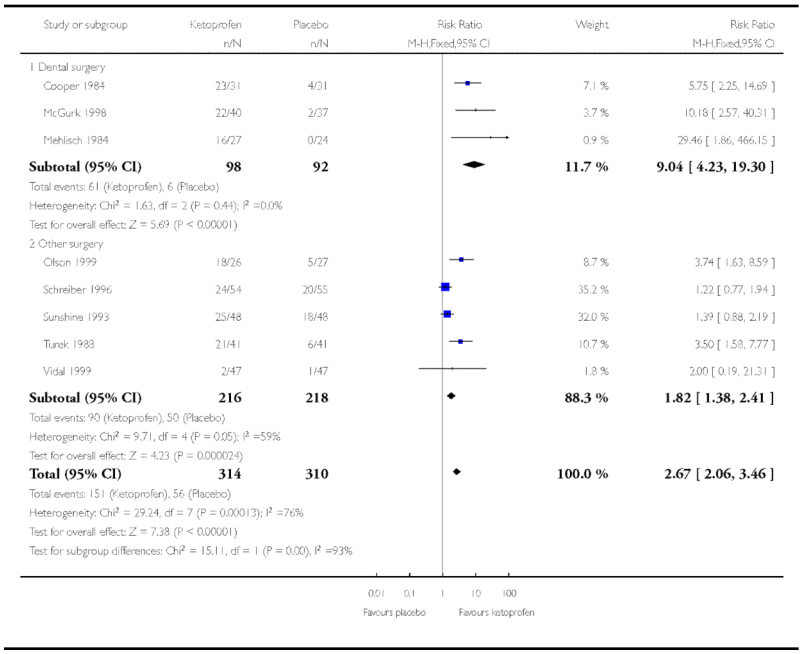
Analysis 3.1

Comparison 3 Ketoprofen 50 mg versus placebo, Outcome 1 Participants with at least 50% pain relief over 4 to 6 hours

Review: Single dose oral ketoprofen and dexketoprofen for acute postoperative pain in adults

Comparison: 3 Ketoprofen 50 mg versus placebo

Outcome: 1 Participants with at least 50% pain relief over 4 to 6 hours



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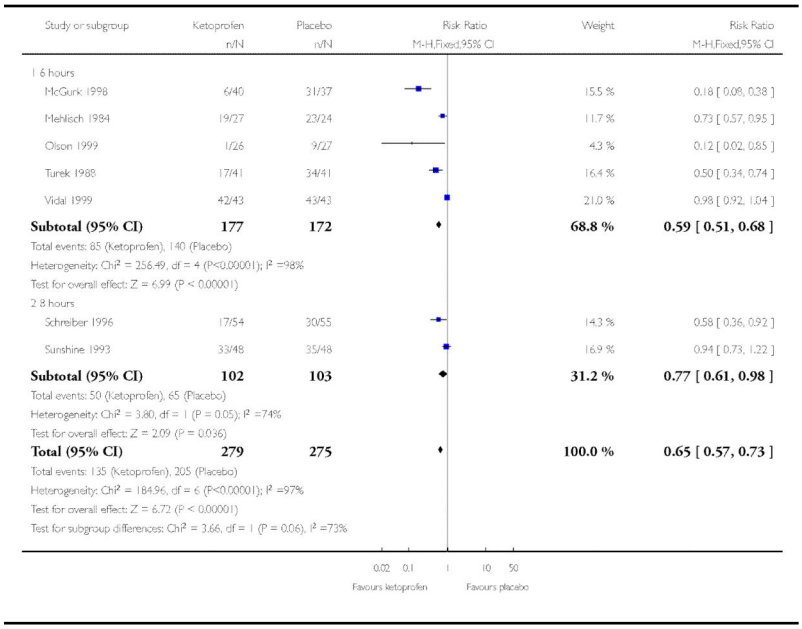
Analysis 3.2

Comparison 3 Ketoprofen 50 mg versus placebo, Outcome 2 Participants using rescue medication over 6 to 8 hours

Review: Single dose oral ketoprofen and dexketoprofen for acute postoperative pain in adults

Comparison: 3 Ketoprofen 50 mg versus placebo

Outcome: 2 Participants using rescue medication over 6 to 8 hours



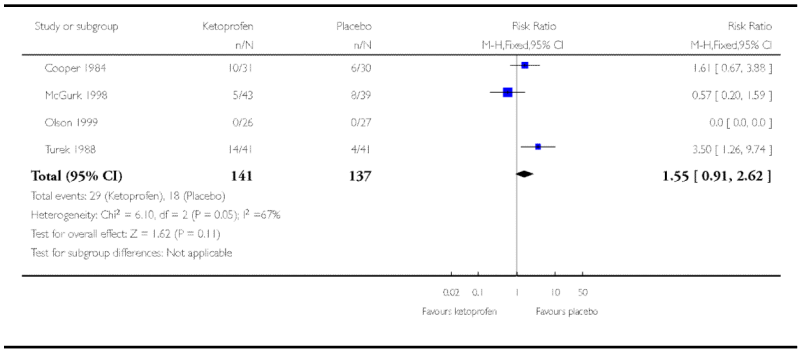
Analysis 3.3

Comparison 3 Ketoprofen 50 mg versus placebo, Outcome 3 Participants with any adverse event

Review: Single dose oral ketoprofen and dexketoprofen for acute postoperative pain in adults

Comparison: 3 Ketoprofen 50 mg versus placebo

Outcome: 3 Participants with any adverse event



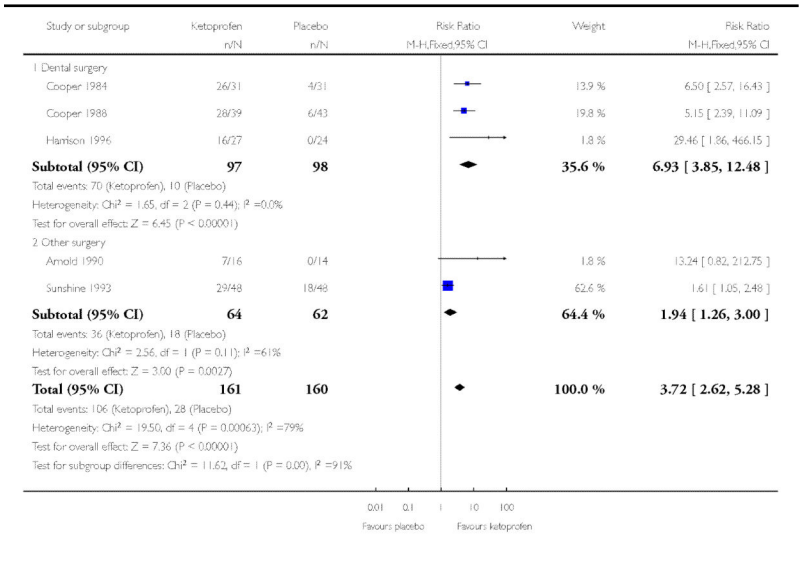
Analysis 4.1

Comparison 4 Ketoprofen 100 mg versus placebo, Outcome 1 Patients with at least 50% pain relief

Review: Single dose oral ketoprofen and dexketoprofen for acute postoperative pain in adults

Comparison: 4 Ketoprofen 100 mg versus placebo

Outcome: 1 Patients with at least 50% pain relief



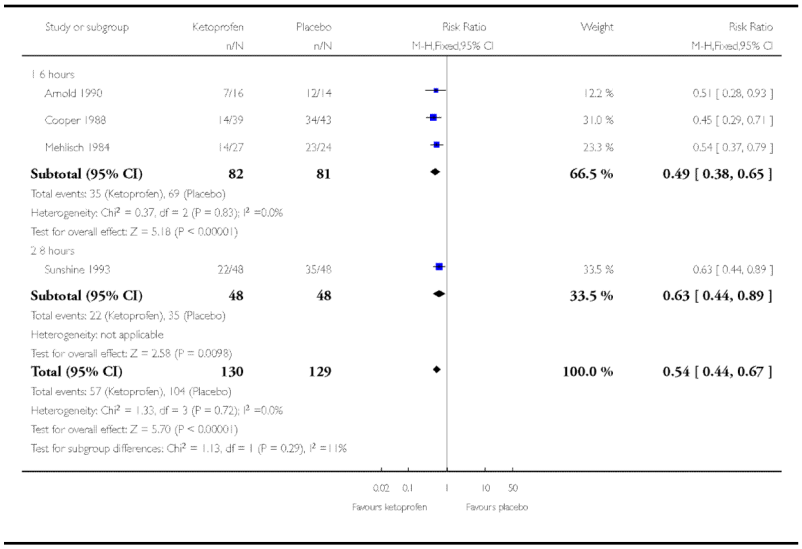
Analysis 4.2

Comparison 4 Ketoprofen 100 mg versus placebo, Outcome 2 Participants using rescue medication over 6 to 8 hours

Review: Single dose oral ketoprofen and dexketoprofen for acute postoperative pain in adults

Comparison: 4 Ketoprofen 100 mg versus placebo

Outcome: 2 Participants using rescue medication over 6 to 8 hours



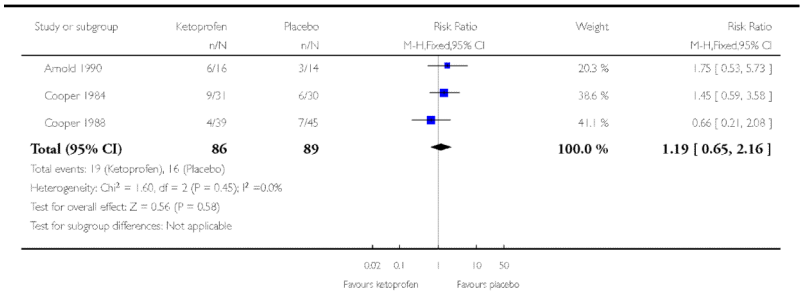
Analysis 4.3

Comparison 4 Ketoprofen 100 mg versus placebo, Outcome 3 Participants with any adverse event

Review: Single dose oral ketoprofen and dexketoprofen for acute postoperative pain in adults

Comparison: 4 Ketoprofen 100 mg versus placebo

Outcome: 3 Participants with any adverse event



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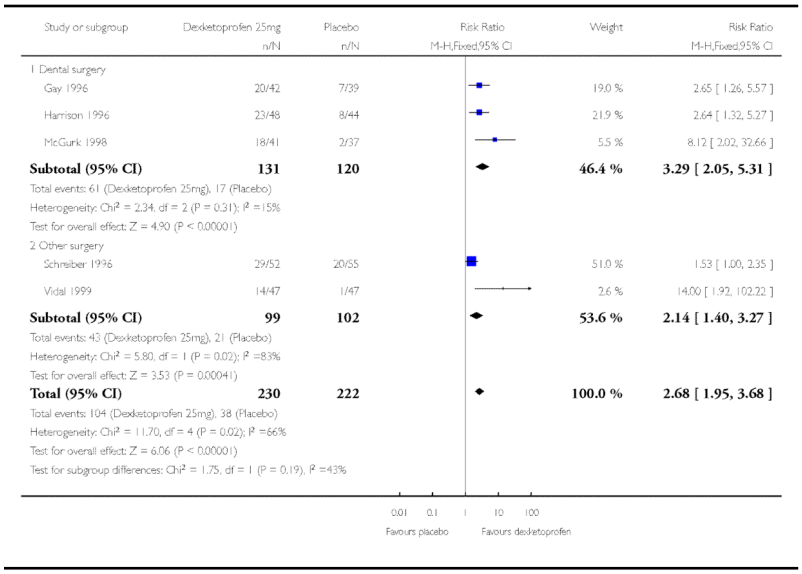
Analysis 5.1

Comparison 5 Dexketoprofen 10/12.5 mg versus placebo, Outcome 1 Patients with at least 50% pain relief

Review: Single dose oral ketoprofen and dexketoprofen for acute postoperative pain in adults

Comparison: 5 Dexketoprofen 10/12.5 mg versus placebo

Outcome: 1 Patients with at least 50% pain relief



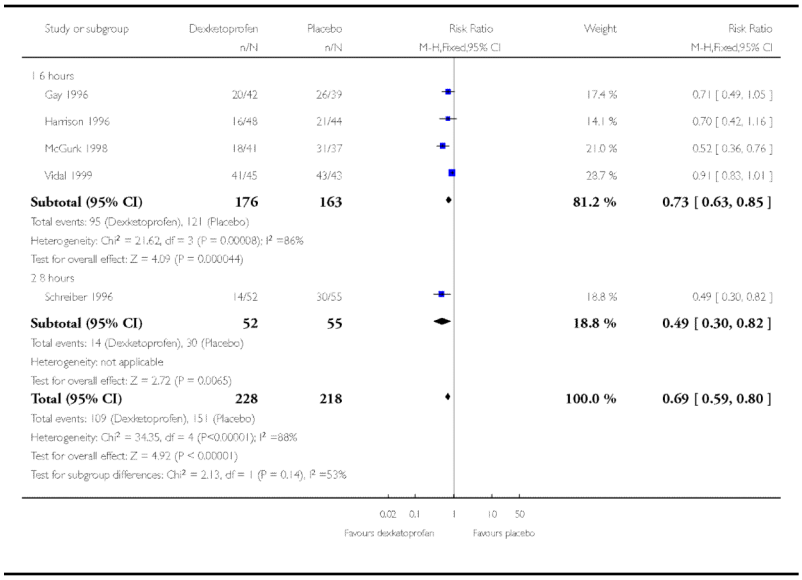
Analysis 5.2

Comparison 5 Dexketoprofen 10/12.5 mg versus placebo, Outcome 2 Participants using rescue medication over 6 to 8 hours

Review: Single dose oral ketoprofen and dexketoprofen for acute postoperative pain in adults

Comparison: 5 Dexketoprofen 10/12.5 mg versus placebo

Outcome: 2 Participants using rescue medication over 6 to 8 hours



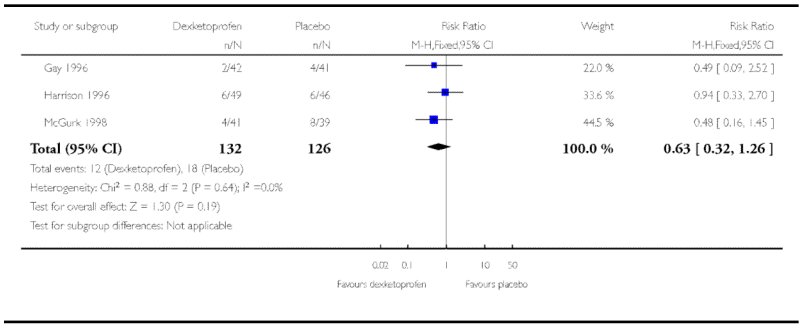
Analysis 5.3

Comparison 5 Dexketoprofen 10/12.5 mg versus placebo, Outcome 3 Participants with any adverse event

Review: Single dose oral ketoprofen and dexketoprofen for acute postoperative pain in adults

Comparison: 5 Dexketoprofen 10/12.5 mg versus placebo

Outcome: 3 Participants with any adverse event



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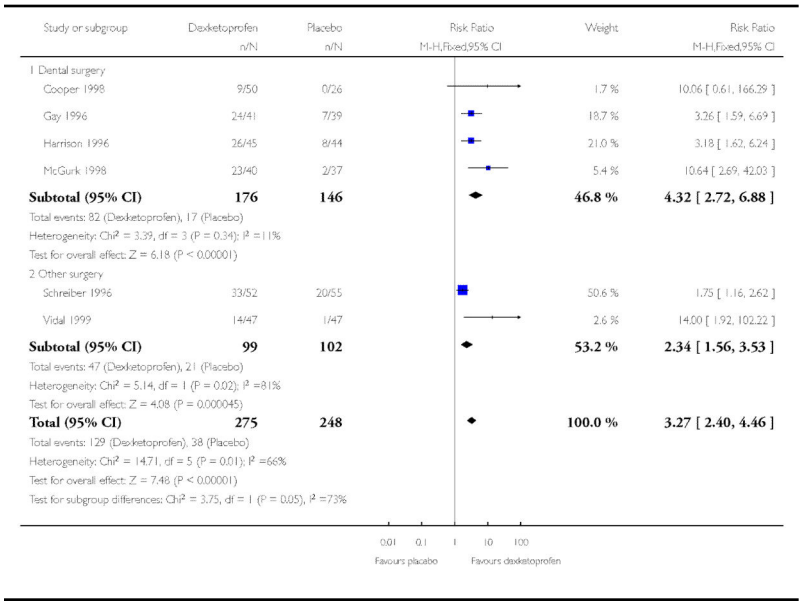
Analysis 6.1

Comparison 6 Dexketoprofen 20/25 mg versus placebo, Outcome 1 Participants with at least 50% pain relief over 4 to 6 hours

Review: Single dose oral ketoprofen and dexketoprofen for acute postoperative pain in adults

Comparison: 6 Dexketoprofen 20/25 mg versus placebo

Outcome: 1 Participants with at least 50% pain relief over 4 to 6 hours



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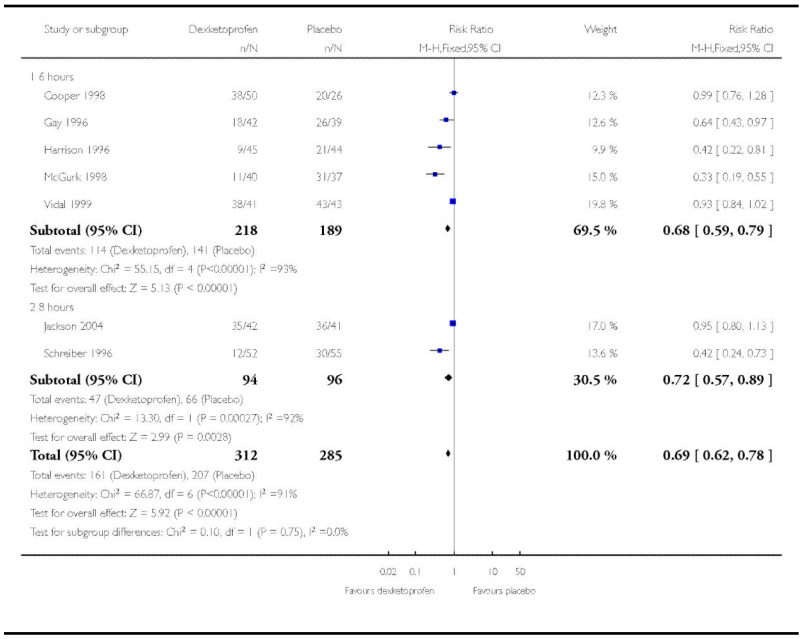
Analysis 6.2

Comparison 6 Dexketoprofen 20/25 mg versus placebo, Outcome 2 Participants using rescue medication over 6 to 8 hours

Review: Single dose oral ketoprofen and dexketoprofen for acute postoperative pain in adults

Comparison: 6 Dexketoprofen 20/25 mg versus placebo

Outcome: 2 Participants using rescue medication over 6 to 8 hours



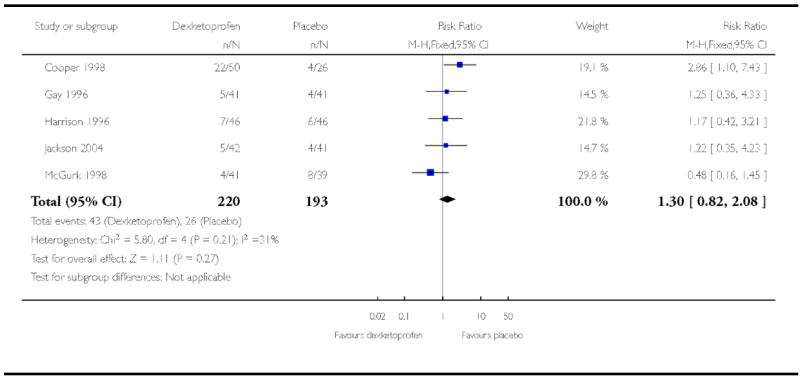
Analysis 6.3

Comparison 6 Dexketoprofen 20/25 mg versus placebo, Outcome 3 Participants with any adverse event

Review: Single dose oral ketoprofen and dexketoprofen for acute postoperative pain in adults

Comparison: 6 Dexketoprofen 20/25 mg versus placebo

Outcome: 3 Participants with any adverse event



Appendix 1. MEDLINE search strategy (via OVID)

1. ketoprofen/
2. (ketoprofen OR Orudis OR Oruvail).mp.
3. (dexketoprofen).mp.
4. OR/1-3
5. Pain, postoperative/.
6. ((postoperative adj4 pain$) or (post-operative adj4 pain$) or post-operative-pain$ or (post$ adj4 pain$) or (postoperative adj4 analgesi$) or (post-operative adj4 analgesi$) or (“post-operative analgesi$”)).mp.
7. ((post-surgical adj4 pain$) or (“post surgical” adj4 pain$) or (post-surgery adj4 pain$)).mp.
8. ((“pain-relief after surg$”) or (“pain following surg$”) or (“pain control after”)).mp.
9. ((“post surg$” or post-surg$) AND (pain$ or discomfort)).mp.
10. ((pain$ adj4 “after surg$”) or (pain$ adj4 “after operat$”) or (pain$ adj4 “follow$ operat$”) or (pain$ adj4 “follow$ surg$”)).mp.
11. ((analgesi$ adj4 “after surg$”) or (analgesi$ adj4 “after operat$”) or (analgesi$ adj4 “follow$ operat$”) or (analgesi$ adj4 “follow$ surg$”)).mp.
12. OR/5-11

13. randomized controlled trial.pt.
14. controlled clinical trial.pt.
15. randomized.ab.
16. placebo.ab.
17. drug therapy.fs.
18. randomly.ab.
19. trial.ab.
20. groups.ab.
21. OR/13-20
22. humans.sh.
23. 21 AND 22
24. 4 AND 12 AND 23

Appendix 2. EMBASE search strategy (via OVID)

1. ketoprofen/
2. (ketoprofen OR Orudis OR Oruvail).mp.
3. dexketoprofen/
4. (dexketoprofen).mp.
5. OR/1-4
6. Pain, postoperative/
7. ((postoperative adj4 pain$) or (post-operative adj4 pain$) or post-operative-pain$ or (post$ adj4 pain$) or (postoperative adj4 analgesi$) or (post-operative adj4 analgesi$) or (“post-operative analgesi$”)).mp.
8. ((post-surgical adj4 pain$) or (“post surgical” adj4 pain$) or (post-surgery adj4 pain$)).mp.
9. ((“pain-relief after surg$”) or (“pain following surg$”) or (“pain control after”)).mp.
10. ((“post surg$” or post-surg$) AND (pain$ or discomfort)).mp.
11. ((pain$ adj4 “after surg$”) or (pain$ adj4 “after operat$”) or (pain$ adj4 “follow$ operat$”) or (pain$ adj4 “follow$ surg$”)).mp.
12. ((analgesi$ adj4 “after surg$”) or (analgesi$ adj4 “after operat$”) or (analgesi$ adj4 “follow$ operat$”) or (analgesi$ adj4 “follow$ surg$”)).mp.
13. OR/6-12
14. clinical trials.sh.

15. controlled clinical trials.sh.
16. randomized controlled trial.sh.
17. double-blind procedure.sh.
18. (clin$ adj25 trial$)
19. ((doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$))
20. placebo$
21. random$
22. OR/14-21
23. 5 AND 13 AND 22

Appendix 3. CENTRAL search strategy

1. MESH descriptor Ketoprofen.
2. (ketoprofen OR Orudis OR Oruvail):ti,ab,kw.
3. MESH descriptor Dexketoprofen.
4. (dexketoprofen):ti,ab,kw.
5. OR/1-4
6. MESH descriptor Pain, postoperative
7. ((postoperative near/4 pain$) or (post-operative near/4 pain$) or post-operative-pain$ or (post$ near/4 pain$) or (postoperative near/4 analgesi$) or (post-operative near/4 analgesi$) or (“post-operative analgesi$”)):ti,ab,kw.
8. ((post-surgical near/4 pain$) or (“post surgical” near/4 pain$) or (post-surgery near/4 pain$)):ti,ab,kw.
9. ((“pain-relief after surg$”) or (“pain following surg$”) or (“pain control after”)):ti,ab,kw.
10. (“post surg$” or post-surg$) AND (pain$ or discomfort)):ti,ab,kw.
11. ((pain$ near/4 “after surg$”) or (pain$ near/4 “after operat$”) or (pain$ near/4 “follow$ operat$”) or (pain$ near/4 “follow$ surg$”)):ti,ab,kw.
12. ((analgesi$ near/4 “after surg$”) or (analgesi$ near/4 “after operat$”) or (analgesi$ near/4 “follow$ operat$”) or (analgesi$ near/4 “follow$ surg$”)):ti,ab,kw.
13. or/6-12
14. Randomized controlled trial.pt
15. MeSH descriptor Double-blind Method
16. 14 or 15
17. 5 and 13 and 16

18. Limit 17 to Clinical Trials (CENTRAL)

Appendix 4. Glossary

Categorical rating scale

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

VAS

Visual analogue scale: lines with left end labelled “no relief of pain” and right end labelled “complete relief of pain”, seem to overcome this limitation. Patients mark the line at the point which corresponds to their pain. The scores are obtained by measuring the distance between the no relief end and the patient’s mark, usually in millimetres. The main advantages of VAS are that they are simple and quick to score, avoid imprecise descriptive terms and provide many points from which to choose. More concentration and coordination are needed, which can be difficult post-operatively or with neurological disorders.

TOTPAR

Total pain relief (TOTPAR) is calculated as the sum of pain relief scores over a period of time. If a patient had complete pain relief immediately after taking an analgesic, and maintained that level of pain relief for six hours, they would have a six-hour TOTPAR of the maximum of 24. Differences between pain relief values at the start and end of a measurement period are dealt with by the trapezoidal rule.

SPID

Summed pain intensity difference (SPID) is calculated as the sum of the differences between the pain scores over a period of time. Differences between pain intensity values at the start and end of a measurement period are dealt with by the composite trapezoidal rule. This is a simple method that approximately calculates the definite integral of the area under the pain relief curve by calculating the sum of the areas of several trapezoids that together closely approximate to the area under the curve.

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

See “Measuring pain” in Bandolier’s Little Book of Pain, Oxford University Press, Oxford. 2003; pp 7-13 (Moore 2003).

WHAT’S NEW

Last assessed as up-to-date: 14 September 2011.

Date	Event	Description
15 September 2011	Review declared as stable	The authors scanned the literature in August 2011 and are confident that there will be no need to update this search until at least 2015

HISTORY

Protocol first published: Issue 4, 2008

Review first published: Issue 4, 2009

Date	Event	Description
8 February 2011	Amended	Contact details updated.
24 September 2010	Amended	Contact details updated.
28 September 2009	Amended	Incorrect date of protocol first published has now been corrected

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Indicates the major publication for the study

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PLAIN LANGUAGE SUMMARY

Single dose oral ketoprofen and dexketoprofen for acute postoperative pain in adults

A single dose of ketoprofen 25 mg to 100 mg provides a high level of pain relief to 60% to 70% of those with moderate or severe postoperative pain. It has similar efficacy to other commonly used analgesics at standard doses, including ibuprofen and naproxen, with a duration of action around 5 hours. Single dose dexketoprofen at 10 mg to 25 mg provides a high level of pain relief to 45% to 50% of patients for about 4 hours. Adverse events were generally mild to moderate in severity, and no more common with either drug than with placebo in these singe dose studies.

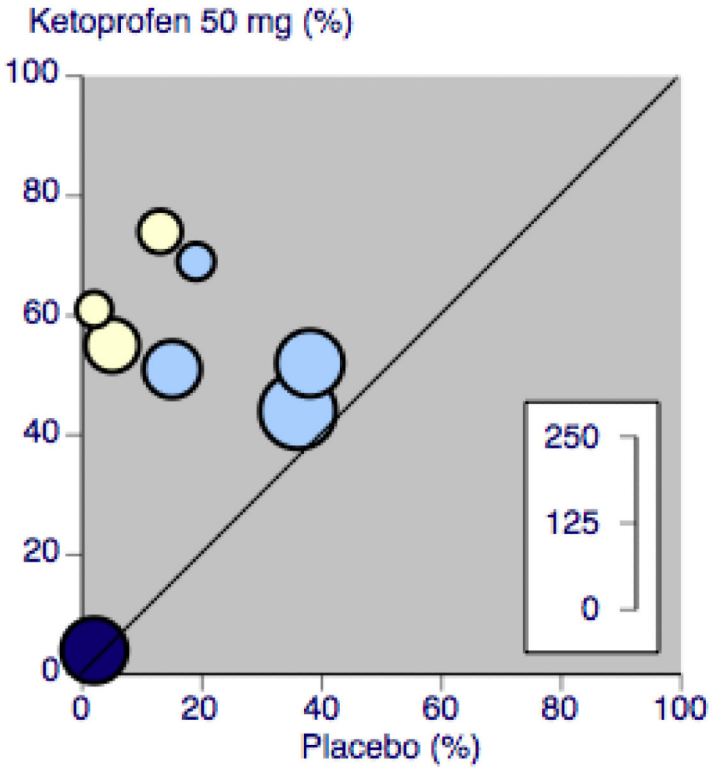

Figure 1.

Percent of participants with at least 50% pain relief over 4 to 6 hours. Size of circle is proportional to size of study (inset scale). Dental studies: yellow. Bunionectomy study: dark blue. Other non-dental studies: light blue.

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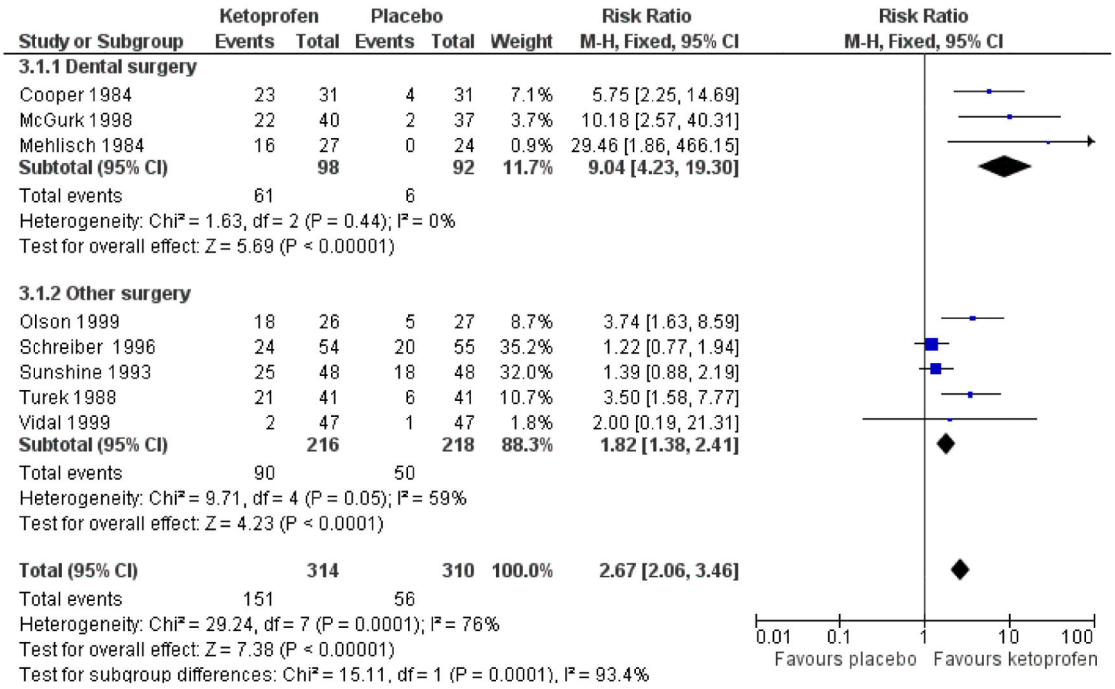

Figure 2.

Forest plot of comparison: 3 Ketoprofen 50 mg versus placebo, outcome: 3.1 Participants with at least 50% pain relief over 4 to 6 hours.

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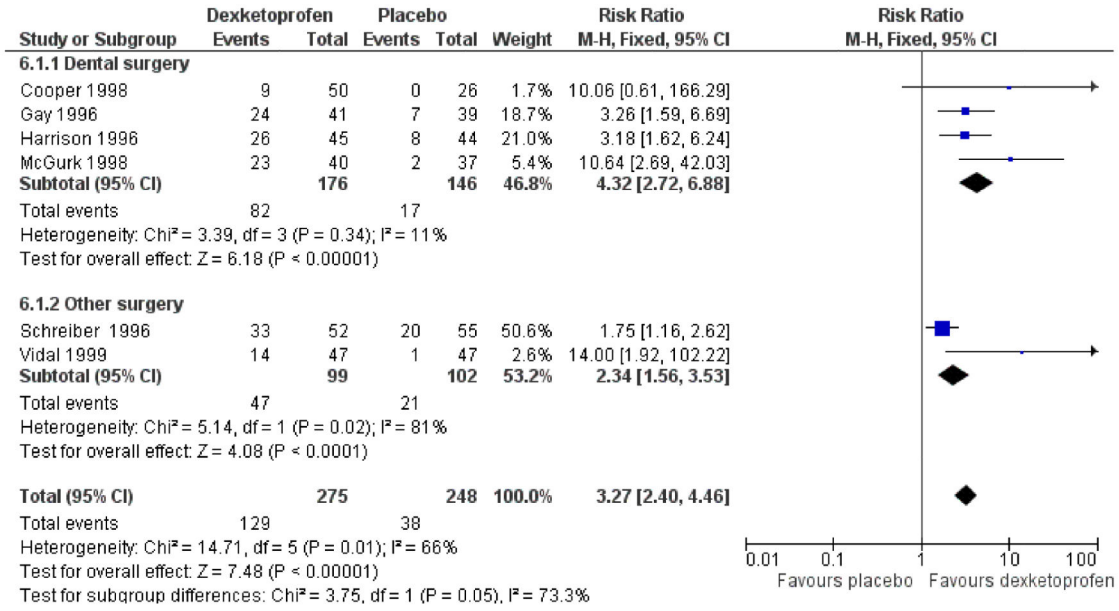

Figure 3.

Forest plot of comparison: 6 Dexketoprofen 20/25 mg versus placebo, outcome: 6.1 Participants with at least 50% pain relief over 4 to 6 hours.

Table 1
Summary of outcomes: analgesia and use of rescue medication

			Analgesia						Rescue medication			
Study ID	Treatment		PI or PR		Number with 50% PR		PGE: v good or excellent		Median time to use (hr)		% using	
Arnold 1990	**1**	ketoprofen 25 mg, n = 14	TOTPAR 6:		**(1)**	3/14	at 6 h:		Mean:		at 6 h:	
	2	Ketoprofen 100 mg, n = 16	**(1)**	6.0	**(2)**	7/16	**(1)**	2/14	**(1)**	4.8	**(1)**	46
	3	Ibuprofen 400 mg, n = 15	**(2)**	9.8	**(4)**	0/14	**(2)**	7/16	**(2)**	4.4	**(2)**	45
	4	Placebo, n = 14	**(4)**	1.5			**(4)**	1/14	**(4)**	2.4	**(4)**	83
Cooper 1984	**1**	Ketoprofen 25 mg, n = 30	TOTPAR 6:		**(1)**	18/30	No usable data		Mean:		No data	
	2	Ketoprofen 50 mg, n = 31	**(1)**	13.6	**(2)**	23/31			**(1)**	4.8		
	3	Ketoprofen 100 mg, n = 31	**(2)**	15.5	**(3)**	26/31			**(2)**	4.8		
	4	Aspirin 650 mg, n = 31	**(3)**	17.1	**(5)**	4/31			**(3)**	4.9		
	5	Placebo, n = 31	**(5)**	4.63					**(5)**	2.6		
Cooper 1988	**1**	Ketoprofen 25 mg, n = 42	TOTPAR 6:		**(1)**	23/42	at 6 h:		Mean:		at 6 h:	
	2	Ketoprofen 100 mg, n = 39	**(1)**	12.0	**(2)**	28/39	**(1)**	17/42	**(1)**	5.0	**(1)**	69
	3	Ibuprofen 400 mg, n = 37	**(2)**	15.2	**(4)**	6/43	**(2)**	21/39	**(2)**	4.3	**(2)**	36
	4	Placebo, n = 43	**(4)**	4.7			**(4)**	2/43	**(4)**	3.0	**(4)**	79
Cooper 1998	**1**	Dexketoprofen 25 mg, n = 50	TOTPAR 6:		**(1)**	9/50	No data		**(1)**	2.1	at 6 h:	
	2	Dexketoprofen 100 mg, n = 51	**(1)**	5.3	**(2)**	17/51			**(2)**	3.3	**(1)**	76
	3	Paracetamol 1000 mg, n =50	**(2)**	8.2	**(4)**	0/26			**(4)**	1.7	**(2)**	57
	4	Placebo, n = 26	**(4)**	4.5							**(4)**	78
Gay 1996	**1**	Dexketoprofen 5 mg, n = 41	TOTPAR 6:		**(1)**	18/41	No usable data		Mean:		at 6 h:	
	2	Dexketoprofen 10 mg, n = 42	**(1)**	9.8	**(2)**	20/42			**(1)**	5.0	**(1)**	34
	3	Dexketoprofen 20 mg, n = 41	**(2)**	10.5	**(3)**	24/41			**(2)**	4.82	**(2)**	48
			(3)	11.3	**(5)**	7/39			**(3)**	5.0	**(3)**	43
			(5)	5.2					**(5)**	3.65	**(5)**	67

		Analgesia				Rescue medication			
	4 Ibuprofen 400 mg, n = 41 **5** Placebo, n = 41								
Harrison 1996	Dexketoprofen 12.5 mg, n = 49 Dexketoprofen 25 mg, n = 46 Placebo, n = 46	TOTPAR 6: **1** 10.6 **2** 12.4 **3** 5.2	**1** 23/48 **2** 26/45 **3** 8/44	No usable data	No data		at 6 h: **1** 33 **2** 20 **3** 48	
Jackson 2004	**1** Dexketoprofen 25 mg, n = 42 **2** Rofecoxib 50mg, n = 38 **3** Placebo, n = 43	No usable data		No usable data	**(1)** 6.6 **(3)** 2.5		at 24 h: **(1)** 83 **(3)** 88	
McGurk 1998	**1** Ketoprofen 50 mg, n = 43 **2** Dexketopfofen 12.5 mg, n = 44 **3** Dexketopfofen 25 mg, n = 41 **4** Dexketop-fofen 50 mg, n = 43Placebo, n = 39	TOTPAR 6: **1** 10.2 **2** 12.6 **3** 12.3 **4** 12.2 **5** 3.2	**1** 22/40 **2** 18/41 **3** 23/40 **4** 24/42 **5** 2/37	No usable data	Mean: **1** 5.5 **2** 4.9 **3** 5.3 **4** 5.4 **5** 3.6		at 6 h: **1** 15 **2** 41 **3** 27 **4** 24 **5** 71	
Mehlisch 1984	**1** Ketoprofen 25 mg, n = 24 **2** Ketoprofen 50 mg, n = 27 **3** Ketoprofen 100 mg, n = 27 **4** Codeine 90 mg, n = 27 **5** Placebo, n = 24	TOTPAR 6: **1** 12.4 **2** 12.7 **3** 12.8 **4** 1.8	**1** 14/24 **2** 16/27 **3** 16/27 **4** 0/24	No usable data	No data		at 6 h: **1** 54 **2** 72 **3** 51 **4** 96	
Olson 1999	**(1)** Ketoprofen (liquid) 25 mg, n = 28 **(2)** Ketoprofen (liquid) 50 mg, n = 26 **(3)** Dipyrone (liquid) 500 mg, n= 27 **(3)** Placebo, n = 27	TOTPAR 6: **(1)** 14.3 **(2)** 14.3	**(1)** 19/28 **(2)** 18/26 **(4)** 5/27	No data	Mean: **1** >6 **2** 5.9 **3** 5.3		at 6 h: **(1)** 0 **(2)** 4 **(4)** 33	

			Analgesia					Rescue medication				
Olson 2001	**1**	Ketoprofen 25 mg, n = 67	TOTPAR 6:		**(1)**	48/67		**(1)**	47/67	**(1)**	>6	at 6 h:	
	2	Ibuprofen liquigel 400 mg, n= 67	**(1)**	15.0	**(4)**	5/39		**(4)**	4/39	**(4)**	1.3	**(1)**	20/67
	3	Paracetamol 1000 mg, n = 66	**(4)**	4.3								**(4)**	31/39
	4	Placebo, n = 39											
Schreiber 1996	**1**	Ketoprofen 50 mg, n = 54	TOTPAR 4:		**1**	24/54		No usable data		No data		at 8 h:	
	2	Dexketoprofen 12.5 mg, n = 52	6.8		**2**	29/52						**1**	31
	3	Dexketoprofen 25 mg, n = 52	8.0		**3**	33/52						**2**	27
	4	Placebo, n = 55	9.0		**4**	20/55						**3**	23
			5.8									**4**	55
Seymour 1996	**1**	Ketoprofen 12.5mg, n = 42	No usable data					at 6 h:		**(1)**	4.0	at 6 h:	
	2	Ketoprofen 25 mg, n = 41						**(1)**	28/42	**(2)**	4.1	**(1)**	75
	3	Paracetamol 500 mg, n = 41						**(2)**	28/41	**(5)**	1.8	**(2)**	76
	4	Paracetamol 1000 mg, n = 41						**(5)**	8/41			**(5)**	97
	5	Placebo, n = 41											
Seymour 2000	**1**	Buffered ketoprofen 12.5 mg, n = 61	TOTPAR 6:		**(1)**	26/61		No usable data		**(1)**	2.7	at 6 h:	
	2	Ibuprofen 200 mg, n = 59	**(1)**	9.8	**(3)**	7/60				**(3)**	1.9	**(1)**	87
	3	Placebo, n = 60	**(3)**	4.1								**(3)**	98
Sunshine 1993	**1**	Ketoprofen 50 mg, n = 48	TOTPAR 6:		**(1)**	25/48		No usable data		**(1)**	7.0	at 8 h:	
	2	Ketoprofen 100 mg, n = 48	**(1)**	11.3	**(2)**	29/48				**(2)**	8.8	**(1)**	69
	3	Paracetamol 650 mg, n = 48	**(2)**	12.9	**(5)**	18/48				**(5)**	6.0	**(2)**	46
	4	Paracetamol + oxycodone 650/10 mg, n = 48	**(5)**	8.8								**(5)**	73
	5	Placebo, n = 48											

			Analgesia				Rescue medication		
Sunshine 1998	**1**	Ketoprofen 6.25 mg, n = 35	TOTPAR 6:		**(1)** 10/35	No usable data	No usable data	No usable data	
	2	Ketoprofen 12.5 mg, n = 35	**(1)** 7.2		**(2)** 23/35				
	3	Ketoprofen 25 mg, n = 35	**(2)** 13.7		**(3)** 21/35				
	4	Ibuprofen 200 mg, n = 35	**(3)** 13.0		**(5)** 3/35				
	5	Placebo, n = 35	**(5)** 3.6						
Turek 1988	**1**	Ketoprofen 50 mg, n = 41	TOTPAR 6:		**(1)** 21/41	No usable data	Mean:		at 6 h:	
	2	Ketoprofen 150 mg, n = 39	**(1)** 11.4		**(2)** 22/39		**(1)** 2.3		**(1)** 41	
	3	Paracetamol + codeine 650/60 mg, n = 39	**(2)** 12.2		**(4)** 6/41		**(2)** 3.2		**(2)** 46	
	4	Placebo, n = 42	**(4)** 4.6				**(4)** 2.2		**(4)** 83	
Vidal 1999	**1**	Ketoprofen 50 mg, n = 47	TOTPAR 6:		**1** 2/47	No usable data	Mean:		at 6 h:	
	2	Dexketoprofen 12.5 mg, n = 47	**1** 2.7		**2** 14/47		**1** 1.76		**1** 98	
	3	Dexketoprofen 25 mg, n = 47	**2** 7.4		**3** 14/47		**2** 2.31		**2** 91	
	4	Placebo, n = 47	**3** 7.4		**4** 1/47		**3** 2.2		**3** 93	
			4 2.5				**4** 1.68		**4** 100	

Table 2
Summary of outcomes: adverse events and withdrawals

			Adverse events		Withdrawals	
Study ID	**Treatment**		**Any**	**Serious**	**Adverse event**	**Other**
Arnold 1990	**1**	ketoprofen 25 mg, n = 14	at 6 h: **(1)** 3/14 **(2)** 6/16 **(4)** 3/14	None	(1) 1/14 (nausea and dizziness after 1 h)	None reported
	2	Ketoprofen 100 mg, n = 16				
	3	Ibuprofen 400 mg, n = 15				
	4	Placebo, n = 14				
Cooper 1984	**1**	Ketoprofen 25 mg, n = 30	at 6 h: **(1)** 7/30 **(2)** 10/31 **(3)** 9/31 **(5)** 6/30	None	None	Exclusions due to not taking medication, protocol violations and loss to follow up: **1** 6, **2** 5, **3** 5, **4** 6, **5** 6
	2	Ketoprofen 50 mg, n = 31				
	3	Ketoprofen 100 mg, n = 31				
	4	Aspirin 650 mg, n= 31				
	5	Placebo, n = 31				
Cooper 1988	**1**	Ketoprofen 25 mg, n = 42	at 6 h: **(1)** 8/44 **(2)** 4/39 **(4)** 7/45	None reported	None reported	20 exclusions: 13 lost to follow up and 7 protocol violations
	2	Ketoprofen 100 mg, n = 39				
	3	Ibuprofen 400 mg, n = 37				
	4	Placebo, n = 43				
Cooper 1998	**1**	Dexketoprofen 25 mg, n = 50	at 6 h: **(1)** 22/50 **(2)** 16/51 **(4)** 4/26	None	None	None
	2	Dexketoprofen 100 mg, n = 51				
	3	Paracetamol 1000 mg, n = 50				
	4	Placebo, n = 26				
Gay 1996	**1**	Dexketoprofen 5 mg, n = 41	at 6 h: **(1)** 3/41 **(2)** 2/42 **(3)** 5/41 **(5)** 4/39	None	None	2 exclusions in placebo group due to early remedication
	2	Dexketoprofen 10 mg, n = 42				
	3	Dexketoprofen 20 mg, n = 41				
	4	Ibuprofen 400 mg, n = 41				
	5	Placebo, n = 41				

			Adverse events		Withdrawals	
Study ID	**Treatment**		**Any**	**Serious**	**Adverse event**	**Other**
Harrison 1996	**1**	Dexketoprofen 12.5 mg, n = 49	at 6 h:	None	**1** 0/49	6 exclusions due to protocol violations.
	2	Dexketoprofen 25 mg, n = 46	**1** 6/49		**2** 1/46	
	3	Placebo, n = 46	**2** 7/46		**3** 1/46	
			3 6/46			
Jackson 2004	**1**	Dexketoprofen 25 mg, n = 42	at 24 h:	None	None	3 participants excluded from analyses: 2 in placebo group lost to follow up, 1 in rofecoxib group did not take medication
	2	Rofecoxib 50 mg, n= 38	**(1)** 5/42			
	3	Placebo, n = 43	**(3)** 4/41			
McGurk 1998	**1**	Ketoprofen 50 mg, n = 43	at 6 h:	None	**1** 0/42	10 participants excluded from efficacy analyses due to early remedication or loss to follow up:
	2	Dexketopfofen 12.5 mg, n = 44	**1** 5/43		**2** 0/44	**1** 3,
	3	Dexketopfofen 25 mg, n = 41	**2** 4/41		**3** 0/41	**2** 3,
	4	Dexketopfofen 50 mg, n = 43	**3** 4/41		**4** 1/43	**3** 1,
	5	Placebo, n = 39	**4** 7/43		**5** 1/39	**4** 1,
			5 8/39			**5** 2
Mehlisch 1984	**1**	Ketoprofen 25 mg, n = 24	at 6 h: 54 participants in total	None reported	None reported	9 participants received medication but were not included in analysis. Reasons and groups not given
	2	Ketoprofen 50 mg, n = 27				
	3	Ketoprofen 100 mg, n = 27				
	4	Codeine 90 mg, n= 27				
	5	Placebo, n = 24				
Olson 1999	**(1)**	Ketoprofen liquid 25 mg, n = 28	No adverse events reported	None None	None None	None None
	(2)	Ketoprofen liquid 50 mg, n = 26				
	(3)	Dipyrone liquid 500 mg, n = 27				
	(3)	Placebo, n = 27				
Olson 2001	**1**	Ketoprofen 25 mg, n = 67	at 6 h:	None None	None None	None None
	2	Ibuprofen liquigel 400 mg, n = 67	**(1)** 5/67			
	3	Paracetamol 1000 mg, n = 66	**(4)** 2/39			
	4	Placebo, n = 39				

			Adverse events		Withdrawals	
Study ID	**Treatment**		**Any**	**Serious**	**Adverse event**	**Other**
Schreiber 1996	**1**	Ketoprofen 50 mg, n = 54	No single dose data	None	Multiple dose : **1** 0/54 **2** 1/52 **3** 2/52 **4** 1/55	Multiple dose (includes successful therapy) : **1** 35/54 **2** 36/52 **3** 35/52 **4** 39/55
	2	Dexketoprofen 12.5 mg, n = 52				
	3	Dexketoprofen 25 mg, n = 52				
	4	Placebo, n = 55				
Seymour 1996	**1**	Ketoprofen 12. 5mg, n = 42	at 6 h: **(1)** 0/42 **(2)** 0/41 **(5)** 0/41	None	None	Excusions due to early remedication: **(1)** 2, **(3)** 1, **(4)** 1, **(5)** 2
	2	Ketoprofen 25 mg, n = 41				
	3	Paracetamol 500 mg, n = 41				
	4	Paracetamol 1000 mg, n = 41				
	5	Placebo, n = 41				
Seymour 2000	**1**	Buffered ketoprofen 12.5 mg, n = 61	at 6 h: **(1)** 2/61 **(3)** 3/6059	None	None	Exclusions due to protocol violations: **(2)** 1, **(3)** 1
	2	Ibu 200 mg, n =59				
	3	Placebo, n = 60				
Sunshine 1993	**1**	Ketoprofen 50 mg, n = 48	No single dose data	“No cases of possible clinical concern” (multiple dose included)	None	None
	2	Ketoprofen 100 mg, n = 48				
	3	Paracetamol 650 mg, n = 48P				
	4	aracetamol + oxycodone 650/10 mg, n = 48				
	5	Placebo, n = 48				
Sunshine 1998	**1**	Ketoprofen 6.25 mg, n = 35	at 6 h: **(1)** 3/35 **(2)** 6/35 **(3)** 3/35 **(5)** 3/35	None	None	Exclusions due to early remedication, protocol violation: **(2)** 1, **(3)** 1, **(5)** 2
	2	Ketoprofen 12.5 mg, n = 35				
	3	Ketoprofen 25 mg, n = 35				
	4	Ibuprofen 200 mg, n = 35				
	5	Placebo, n = 35				
Turek 1988	**(1)**	Ketoprofen 50 mg, n = 41	at 6 h: **1** 14/41 **2** 8/39 **3** 4/41	None	None	1 exclusion in placebo group due to protocol violation.
	(2)	Ketoprofen 150 mg, n = 39				
	(3)	Paracetamol + codeine 650/60 mg, n= 39				
	(5)	Placebo, n = 42				

			Adverse events		Withdrawals	
Study ID	**Treatment**		**Any**	**Serious**	**Adverse event**	**Other**
Vidal 1999	**(1)**	Ketoprofen 50 mg, n = 47	No single dose data	None	Multiple dose:	Multiple dose :
					1 0/43	**1** 0/43
	(2)	Dexketoprofen 12.5 mg, n = 47			**2** 1/45	**2** 2/45
	(3)	Dexketoprofen 25 mg, n = 47			**3** 1/41	**3** 2/41
					4 2/43	**4** 3/43
	(3)	Placebo, n = 47				