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Single dose oral ibuprofen plus paracetamol (acetaminophen) for acute postoperative pain (Review)

Derry CJ, Derry S, Moore RA

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[Intervention Review]

Single dose oral ibuprofen plus paracetamol (acetaminophen) for acute postoperative pain

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ABSTRACT

Background

Combining two different analgesics in fixed doses in a single tablet can provide better pain relief than either drug alone in acute pain. This appears to be broadly true across a range of different drug combinations, in postoperative pain and migraine headache. Some combinations of ibuprofen and paracetamol are available for use without prescription in some acute pain situations.

Objectives

To assess the efficacy and adverse effects of single dose oral ibuprofen plus paracetamol for acute postoperative pain using methods that permit comparison with other analgesics evaluated in standardised trials using almost identical methods and outcomes.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) on *The Cochrane Library* (Issue 4 of 12, 2013), MEDLINE (1950 to May 21st 2013), EMBASE (1974 to May 21st 2013), the Oxford Pain Database, ClinicalTrials.gov, and reference lists of articles.

Selection criteria

Randomised, double-blind clinical trials of single dose, oral ibuprofen plus paracetamol compared with placebo or the same dose of ibuprofen alone for acute postoperative pain in adults.

Data collection and analysis

Two review authors independently considered trials for inclusion in the review, assessed quality, and extracted data. We used validated equations to calculate the area under the pain relief versus time curve and derive the proportion of participants with at least 50% of maximum pain relief over six hours. We calculated relative risk (RR) and number needed to treat to benefit (NNT) for ibuprofen plus paracetamol, ibuprofen alone, or placebo. We used information on use of rescue medication to calculate the proportion of participants requiring rescue medication and the weighted mean of the median time to use. We also collected information on adverse events.

Main results

Searches identified three studies involving 1647 participants. Each of them examined several dose combinations. Included studies provided data from 508 participants for the comparison of ibuprofen 200 mg + paracetamol 500 mg with placebo, 543 participants for the comparison of ibuprofen 400 mg + paracetamol 1000 mg with placebo, and 359 participants for the comparison of ibuprofen 400 mg + paracetamol 1000 mg with ibuprofen 400 mg alone.

The proportion of participants achieving at least 50% maximum pain relief over 6 hours was 69% with ibuprofen 200 mg + paracetamol 500 mg, 73% with ibuprofen 400 mg + paracetamol 1000 mg, and 7% with placebo, giving NNTs of 1.6 (1.5 to 1.8) and 1.5 (1.4 to 1.7) for the lower and higher doses respectively compared with placebo. For ibuprofen 400 mg alone the proportion was 52%, giving an NNT for ibuprofen 400 mg + paracetamol 1000 mg compared with ibuprofen alone of 5.4 (3.5 to 12).

Ibuprofen + paracetamol at the 200/500 mg and 400/1000 mg doses resulted in longer times to remedication than placebo. The median time to use of rescue medication was 7.6 hours for ibuprofen 200 mg + paracetamol 500 mg, 8.3 hours with ibuprofen 400 mg + paracetamol 1000 mg, and 1.7 hours with placebo. Fewer participants needed rescue medication with ibuprofen + paracetamol combination than with placebo or ibuprofen alone. The proportion was 34% with ibuprofen 200 mg + paracetamol 500 mg, 25% with ibuprofen 400 mg + paracetamol 1000 mg, and 79% with placebo, giving NNTs to prevent use of rescue medication of 2.2 (1.8 to 2.9) and 1.8 (1.6 to 2.2) respectively compared with placebo. The proportion of participants using rescue medication with ibuprofen 400 mg was 48%, giving an NNT to prevent use for ibuprofen 400 mg + paracetamol 1000 mg compared with ibuprofen alone of 4.3 (3.0 to 7.7).

The proportion of participants experiencing one or more adverse events was 30% with ibuprofen 200 mg + paracetamol 500 mg, 29% with ibuprofen 400 mg + paracetamol 1000 mg, and 48% with placebo, giving NNT values in favour of the combination treatment of 5.4 (3.6 to 10.5) and 5.1 (3.5 to 9.5) for the lower and higher doses respectively. No serious adverse events were reported in any of the included studies. Withdrawals for reasons other than lack of efficacy were fewer than 5% and balanced across treatment arms.

Authors' conclusions

Ibuprofen plus paracetamol combinations provided better analgesia than either drug alone (at the same dose), with a smaller chance of needing additional analgesia over about eight hours, and with a smaller chance of experiencing an adverse event.

PLAIN LANGUAGE SUMMARY

Single dose oral ibuprofen plus paracetamol (acetaminophen) for acute postoperative pain

Acute pain is often felt soon after injury, and most people who have surgery will have pain of moderate or severe intensity without treatment for their pain. In many, though not all, circumstances, the pain can be treated with oral analgesics. Many oral analgesics are available, and this review is one of a series examining how effective each one is, at particular doses.

This review examines a combination of fixed doses of ibuprofen and paracetamol (known as acetaminophen in the USA and some parts of the world). Both are commonly used analgesics, which probably work by different mechanisms. We know that combining different analgesics in the same tablet gives good pain relief to more people than either analgesic alone, at the same dose.

This review found data in three clinical trials, involving 1647 people with moderate or severe pain after having wisdom teeth removed. This is used commonly to test analgesic effectiveness, because results are applicable to other forms of acute pain after trauma.

Ibuprofen 200 mg plus paracetamol 500 mg or ibuprofen 400 mg plus paracetamol 1000 mg provided effective pain relief for about 7 in 10 (70%) of participants, compared with just under 1 in 10 (7%) of participants with placebo. The analgesic effects lasted longer and there were fewer adverse events with the combinations than with placebo.

BACKGROUND

Description of the condition

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 and/or nerve 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 increase awareness of the range of analgesics that are potentially available, and present evidence for relative analgesic efficacy through indirect comparisons with placebo, in very similar trials performed in a standard manner, with very similar outcomes, and over the same duration. Such relative analgesic efficacy does not in itself determine choice of drug for any situation or patient, but guides policy-making at the local level. The series covers all analgesics licensed for acute postoperative pain in the UK, and dipyrone, which is commonly used in Spain, Portugal, and Latin-American countries. The results have been examined in an overview (Moore 2011a), and important individual reviews include ibuprofen (Derry 2009), paracetamol (Toms 2008), codeine (Derry 2010), and etoricoxib (Clarke 2012).

Description of the intervention

Acute pain trials

Single dose trials in acute pain are commonly short in duration, rarely lasting longer than 12 hours. The numbers of participants are 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 four to six hours for shorter-acting drugs, and up to 12 or 24 hours for longer-acting drugs. Pain relief of half the maximum possible pain relief or better (at least 50% pain relief) is typically regarded as a clinically useful outcome. 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 four to six hours (Moore 2005). Patients usually remain in the hospital or clinic for at least the first six hours following the intervention, with measurements supervised, although they may then be allowed home to make their own measurements in trials of longer duration.

Knowing the relative efficacy of different analgesic drugs at various doses can be helpful.

Ibuprofen

Ibuprofen was developed in the 1960s and is used extensively throughout the world for relief of pain and inflammation in both acute and chronic conditions. It is available over the counter in most countries, usually as 200 mg tablets, with 1200 mg as the recommended maximum daily dose for adults. Under medical supervision, up to 3200 mg daily may be taken, divided into three doses. Soluble salts of ibuprofen have lower (better) NNTs (Derry 2009).

A major concern regarding the use of conventional NSAIDs postoperatively is the possibility of bleeding from both the operative site (because of the inhibition of platelet aggregation) (Forrest 2002) and from the upper gastrointestinal tract (especially in patients stressed by surgery, the elderly, frail, or dehydrated). Other potentially serious adverse events include acute liver injury, acute renal injury, heart failure, and adverse reproductive outcomes (Hernandez-Diaz 2001). However, such complications are more likely to occur with chronic use and NSAIDs generally present fewer risks if used in the short term, as in the treatment of postoperative pain (Rapoport 1999).

Paracetamol

Paracetamol (acetaminophen) was first identified as the active metabolite of two older antipyretic drugs, acetanilide and phenacetin, in the late nineteenth century. It became available in the UK on prescription in 1956, and over-the-counter in 1963 (PIC 2008). Since then it has become one of the most popular antipyretic and analgesic drugs worldwide, and is often also used

in combination with other drugs. The usual adult dose is 500 mg to 1000 mg, with a maximum of 4000 mg in 24 hours.

Paracetamol has a recognised potential for hepatotoxicity and is thought to be responsible for approximately half of all cases of liver failure in the UK (Hawton 2001), and about 40% in the USA (Norris 2008). Acute paracetamol hepatotoxicity at therapeutic doses is extremely unlikely despite reports of so-called therapeutic misadventure (Prescott 2000). In recent years legislative changes restricting pack sizes and the maximum number of tablets permitted in over-the-counter sales were introduced in the UK (CSM 1997) on the basis of evidence that poisoning is less frequent in countries that restrict availability (Gunnell 1997; Hawton 2001). The contribution of these changes, which are inconvenient and costly (particularly for chronic pain sufferers), to any observed reduction in incidence of liver failure or death, remains uncertain (Hawkins 2007). In 2011, the FDA announced a restriction to 325 mg paracetamol per tablet in prescription combinations, and increased warning labels in an attempt to reduce the risk of severe liver injury and allergic reactions associated with paracetamol (FDA 2011). Concerns have arisen over the safety of paracetamol in patients with compromised hepatic function (those with severe alcoholism, cirrhosis or hepatitis), but these have not been substantiated (Dart 2000; PIC 2008). Other concerns have been raised about potential cardiovascular safety of paracetamol (Hinz 2012).

How the intervention might work

NSAIDs 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 nociceptive processes. Ibuprofen, like most NSAIDs, causes reversible inhibition of the cyclooxygenases, which interferes with thromboxane and prostaglandin synthesis, and increases production of anti-inflammatory lipoxins.

The lack of significant anti-inflammatory activity of paracetamol implies a mode of action distinct from that of NSAIDs, yet, despite years of use and research, the mechanisms of action of paracetamol are not fully understood. Paracetamol has been shown to have no significant effects on COX-1 or COX-2 (Schwab 2003), but it has come to be considered as a selective COX-2 inhibitor (Hinz 2008). Significant paracetamol-induced inhibition of prostaglandin production has been demonstrated in tissues in the brain, spleen, and lung (Botting 2000; Flower 1972). A 'COX-3 hypothesis', wherein the efficacy of paracetamol is attributed to its specific inhibition of a third cyclooxygenase isoform enzyme, COX-3 (Botting 2000; Chandrasekharan 2002; PIC 2008) now has little credibility, and a central mode action of paracetamol is thought to be likely (Graham 2005).

Combination analgesics

We now have convincing evidence that combining two analgesics can provide additional levels of analgesia in acute pain and headache (Moore 2011b; Moore 2012), and that the drug-specific effects are essentially additive. Results confirm that the assumption that the efficacy of combination analgesics is the sum of the efficacies of the individual analgesic components is broadly true across a range of different drug combinations, in postoperative pain and migraine headache, and when tested in the same and different trials (Moore 2012). There is no convincing evidence for combination analgesics in chronic pain, however (Chaparro 2012).

Why it is important to do this review

Ibuprofen and paracetamol are both widely available and inexpensive, with proven efficacy for relief of acute postoperative pain (Derry 2009; Toms 2008). In combination paracetamol has been shown to significantly enhance the efficacy of codeine (Toms 2009) and oxycodone (Gaskell 2009). Ibuprofen and paracetamol are frequently used in combination in clinical practice and are available as a fixed dose combination tablet over-the-counter in some countries. It is important to know how this combination compares with other analgesics assessed in the same way (Moore 2011a).

OBJECTIVES

To assess the efficacy and adverse effects of single dose oral ibuprofen plus paracetamol for acute postoperative pain using methods that permit comparison with other analgesics evaluated in standardised trials using almost identical methods and outcomes.

METHODS

Criteria for considering studies for this review

Types of studies

We included studies of double-blind trials of single dose oral ibuprofen plus paracetamol compared with placebo or the same dose of ibuprofen alone, for the treatment of moderate to severe postoperative pain in adults, with at least 10 participants randomly allocated to each treatment group. We included multiple

dose studies if appropriate data from the first dose were available, and cross-over studies provided that data from the first arm were presented separately.

We excluded the following:

- review articles, case reports, and clinical observations;
- studies of experimental pain;
- studies where pain relief is assessed only by clinicians, nurses, or carers (i.e. not patient-reported);
- studies of less than four hours duration or studies that fail to present data over four to six hours post dose.

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

Types of participants

We included studies of adult participants (> 15 years) with established postoperative pain of moderate to severe intensity following day surgery or in-patient surgery. For studies using a visual analogue scale (VAS), we considered that pain intensity of greater than 30/100 mm equates to pain of at least moderate intensity (Collins 1997).

Types of interventions

Ibuprofen plus paracetamol, administered as a single oral dose, compared with matched placebo or the same dose of ibuprofen alone for postoperative pain. The ibuprofen and paracetamol had to be administered as separate tablets taken together, or in a combined tablet. We included all dose combinations.

Types of outcome measures

We collected the following data where available:

- participant characteristics;
- patient reported pain at baseline (physician, nurse, or carer reported pain was not included in the analysis);
- patient reported pain relief expressed at least hourly over four to six hours using validated pain scales (pain intensity and pain relief in the form of VAS or categorical scales, or both);
- patient global assessment of efficacy (PGE), using a standard categorical scale;
- time to use of rescue medication;
- number of participants using rescue medication;
- number of participants with one or more adverse events;
- number of participants with serious adverse events;
- number of withdrawals (all-cause, adverse events).

Primary outcomes

Participants achieving at least 50% of maximum pain relief over four to six hours.

Secondary outcomes

- Median (or mean) time to use of rescue medication;
- Number of participants using rescue medication;
- Number of participants with: any adverse event; any serious adverse event (as reported in the study); withdrawal due to an adverse event;
- Other withdrawals: withdrawals for reasons other than lack of efficacy (participants using rescue medication.

Search methods for identification of studies

Electronic searches

We searched the following databases:

- The Cochrane Central Register of Controlled Trials (CENTRAL) on *The Cochrane Library*, (Issue 4 of 12, 2013);
- MEDLINE (via OVID) (1950 to 21 May 2013);
- EMBASE (via OVID) (1974 to 21 May 2013);
- Oxford Pain Relief Database (Jadad 1996a).

See Appendix 1 for the MEDLINE search strategy, Appendix 2 for the EMBASE search strategy, and Appendix 3 for the CENTRAL search strategy. We did not limit the searches by language.

Searching other resources

We searched for additional studies in reference lists of retrieved articles and reviews, and in clinicaltrials.gov. The manufacturers of the combination formulation (Reckitt Benckiser) had already supplied information on published and unpublished studies.

Data collection and analysis

Selection of studies

Two review authors independently assessed and agreed the search results for studies to be included in the review. Disagreements would be resolved by consensus or referral to a third review author.

Data extraction and management

Two review authors extracted data and recorded them on a standard data extraction form. One review author entered data suitable for pooling into RevMan 5.1 (RevMan 2011).

Assessment of risk of bias in included studies

Two review authors independently assessed each study for methodological quality using a three-item, five-point scale (Jadad 1996b), and agreed a consensus score.
The scale used is as follows.

- Is the study randomised? If yes - 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 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.

We also completed a 'Risk of bias' table, using methods adapted from those described by the Cochrane Pregnancy and Childbirth Group. Two authors independently assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) with any disagreements resolved by discussion. The following were assessed for each study.

- Random sequence generation (checking for possible selection bias). The method used to generate the allocation sequence was assessed as: low risk of bias (any truly random process, e.g. random number table; computer random number generator); high risk of bias (any non-random process, e.g. odd or even date of birth; hospital or clinic record number) - these studies would be excluded; unclear risk of bias.
- Allocation concealment (checking for possible selection bias). The method used to conceal allocation to interventions prior to assignment assessed whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment. The methods were assessed as: low risk of bias (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes); high risk of bias (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth) - theses studies would be excluded; unclear risk of bias.
- Blinding of outcome assessment (checking for possible detection bias). The methods used to blind study participants and outcome assessors from knowledge of which intervention a participant received were assessed. Studies were considered to be at low risk of bias if they stated that they were blinded and described the method used to achieve blinding (e.g. identical tablets; matched in appearance and smell), or at unknown risk if they stated that they were blinded, but did not provide an adequate description of how it was achieved. Single blind and open studies would be excluded.
- Size (checking for possible biases confounded by small size). Small studies have been shown to overestimate treatment effects, probably due to methodological weaknesses (Nuesch 2010). Studies were considered to be at low risk of bias if they had ≥ 200 participants, at unknown risk of they had 50 to 200 participants, and at high risk if they had < 50 participants.

Measures of treatment effect

We used relative risk (or 'risk ratio', RR) to establish statistical difference. We used numbers needed to treat (NNT) and pooled percentages as absolute measures of benefit or harm.
We used the following terms to describe adverse outcomes in terms of harm or prevention of harm.

- When significantly fewer adverse outcomes occur with treatment than with control (placebo or active) we use the term the *number needed to treat to prevent one event* (NNTp).
- When significantly more adverse outcomes occur with treatment compared with control (placebo or active) we use the term the *number needed to harm or cause one event* (NNH).

Unit of analysis issues

We accepted only randomisation to the individual patient.

Dealing with missing data

The only likely issue with missing data in these studies is from imputation using last observation carried forward when a patient requests rescue medication. We have previously shown that this does not affect results for up to six hours after taking study medication (Barden 2004).

Assessment of heterogeneity

We examined heterogeneity visually using L'Abbé plots (L'Abbé 1987), a visual method for assessing differences in results of individual studies.

Data synthesis

We followed QUOROM guidelines (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 randomised to each treatment group who took the study medication. We planed to analyse for different doses separately.
For each study we converted the mean TOTPAR, SPID, VAS TOTPAR, or VAS SPID (Appendix 4) values for active and placebo to %maxTOTPAR or %maxSPID by division into the calculated maximum value (Cooper 1991), and calculated the proportion of participants in each treatment group who achieved at least 50%maxTOTPAR using verified equations (Moore 1996; Moore 1997a; Moore 1997b). We then converted these proportions into the number of participants achieving at least 50%maxTOTPAR by multiplying by the total number of participants in the treatment group. We used this information on the number of

participants with at least 50%maxTOTPAR for active and placebo to calculate relative benefit or relative risk, and number needed to treat to benefit (NNT) or harm (NNH). Because adverse events with ibuprofen/paracetamol combinations were less frequent than with placebo, this is described as an NNTp, the number needed to treat to *prevent* an adverse event. NNTp was also used to describe differences in remedication rates, where remedication rates were lower with active treatment than control.

We accepted the following pain measures for the calculation of TOTPAR or SPID:

- 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';
- VAS for pain relief;
- VAS for pain intensity.

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

For each treatment group we extracted the number of participants reporting treatment-emergent adverse effects, and calculated relative benefit and risk estimates with 95% confidence intervals (CI) using a fixed-effect model (Morris 1995). We calculated NNT and NNH with 95% CIs using the pooled number of events using the method devised by Cook and Sackett (Cook 1995). We assumed a statistically significant difference from control when the 95% CI of the relative risk or relative benefit did not include the number one.

Subgroup analysis and investigation of heterogeneity

We planned subgroup analyses to determine the effect of dose and presenting condition (pain model: dental versus other postoperative pain). A minimum of two studies and 200 participants had to be available in any subgroup or sensitivity analysis (Moore 1998), which was restricted to the primary outcome (50% of maximum pain relief over four to six hours) and the dose with the greatest amount of data. We determined significant differences between NNT, NNTp, or NNH for different groups in subgroup and sensitivity analyses using the z test (Tramèr 1997).

Sensitivity analysis

We planned sensitivity analyses for quality score (two versus three or more) and trial size (39 or fewer versus 40 or more per treatment arm).

RESULTS

Description of studies

Included studies

Searches identified three studies that fulfilled the inclusion criteria for this review (Daniels 2011; Mehlisch 2010a; Mehlisch 2010b). All three were published in full peer-reviewed journals, but additional information from unpublished clinical trial reports was available for two studies (Mehlisch 2010a; Mehlisch 2010b). No PRISMA flowchart was required.

All of the included studies recruited participants aged 16 years or older (mean ages ranged from 20 to 21 years). The majority of participants were female (60% to 74%) and all had undergone surgical extraction of at least three impacted third molars, two of which had to be mandibular. Exclusion criteria included history of migraine, gastrointestinal disorder, or other history of significant disease or psychotic illness. A washout period from concomitant medications was stipulated by two of the reviews. In each of the studies, medication was administered when baseline pain reached a moderate or severe intensity. Pain intensity and pain relief were measured on standard 4- and 5-point scales, respectively, at set time intervals after dosing.

The three studies involved 1647 participants and used both placebo and active comparators. Each of the studies looked at a number of different dose combinations and comparators. The following treatments were administered.

- Ibuprofen 100 mg + paracetamol 250 mg (Mehlisch 2010b), n = 71
- Ibuprofen 200 mg + paracetamol 500 mg (Daniels 2011; Mehlisch 2010a; Mehlisch 2010b), n = 349
- Ibuprofen 400 mg + paracetamol 1000 mg (Daniels 2011; Mehlisch 2010a; Mehlisch 2010b), n = 384
- Ibuprofen 400 mg + codeine 25.6 mg (Daniels 2011), n = 169
- Ibuprofen 200 mg (Mehlisch 2010b), n = 75
- Ibuprofen 400 mg (Mehlisch 2010a; Mehlisch 2010b), n = 143
- Paracetamol 1000 mg + codeine 30 mg (Daniels 2011), n = 113
- Paracetamol 500 mg (Mehlisch 2010b), n = 76
- Paracetamol 1000 mg (Mehlisch 2010a; Mehlisch 2010b), n = 108
- Placebo (Daniels 2011; Mehlisch 2010a; Mehlisch 2010b), n = 159

Full details are in the Characteristics of included studies table.

Two further studies were identified that were ongoing but likely to satisfy inclusion criteria (NCT00921700; NCT01559259). If appropriate this review will be updated to include these studies once results become available. Full details are in the Characteristics of ongoing studies table.

Excluded studies

Four studies were excluded after reading the full paper (Menhinick 2004; Merry 2010; Mitchell 2008; Naidu 1994). Full details are in the Characteristics of excluded studies table.

Risk of bias in included studies

Included studies were all randomised and double-blind and provided information about withdrawals and dropouts. The methodological quality of the trials was determined using the Oxford Quality Scale. All three studies provided adequate description of the methods of randomisation and double-blinding and information about withdrawals and dropouts, and thus scored 5/5 on the scale. Details for individual studies are provided in the Characteristics of included studies table.

In addition a Risk of bias table was created which considered random sequence generation, allocation concealment, blinding, and study size (Figure 1; Figure 2).

Figure 1. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

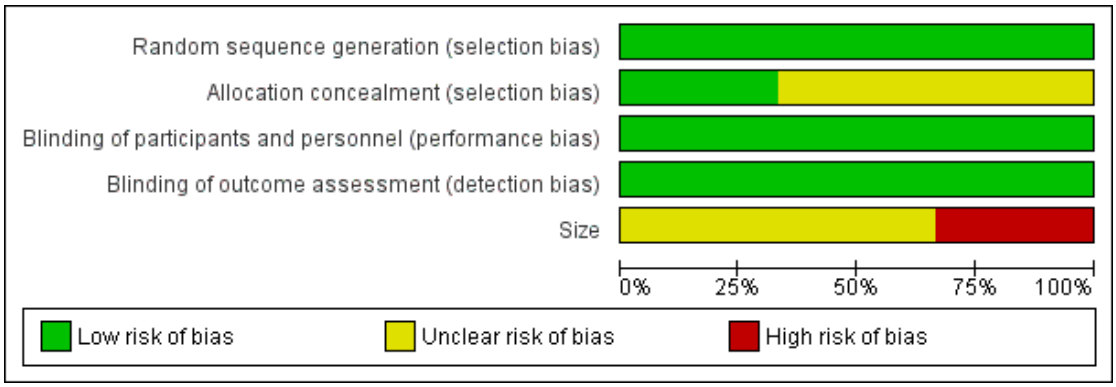
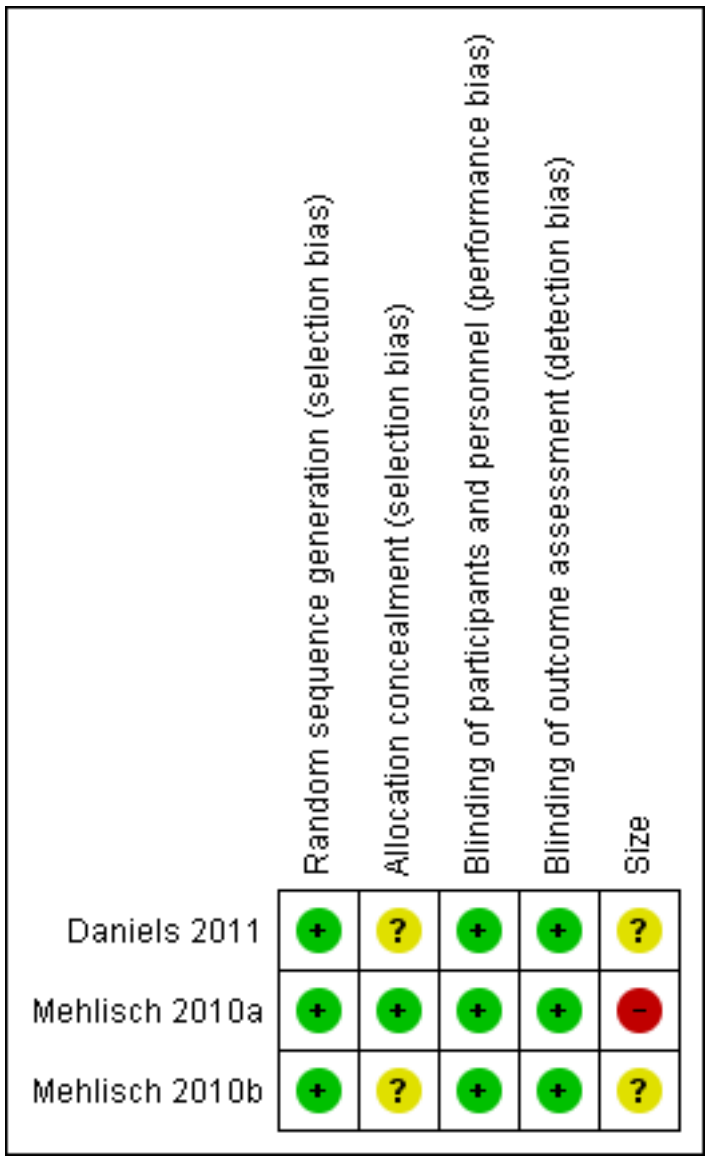


Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

All studies reported that they were randomised and adequately described the method used to generate the schedule. One study (Mehlisch 2010a) described the methods used to conceal the random allocation, but the other two did not.

Blinding

All studies were double blind and adequately described how this was achieved.

Other potential sources of bias

Treatment group size was an issue. Small studies are thought to be at increased risk of bias, probably because the conduct of small studies is more likely to be less rigorous, allowing critical criteria such as blinding to be compromised. None of the treatment groups in this review was large enough to be confident that bias would be avoided; one (Mehlisch 2010a) had treatment group sizes that put it at high risk of bias.

Effects of interventions

Details of outcomes in individual studies are in Appendix 5 (efficacy) and Appendix 6 (adverse events and withdrawals).

Number of participants achieving at least 50% pain relief

All studies reported data from which this outcome could be calculated, and results are tabulated in Summary of results A.

Ibuprofen 100 mg + paracetamol 250 mg versus placebo

One study (Mehlisch 2010b) compared ibuprofen 100 mg + paracetamol 250 mg with placebo; 46/71 participants experienced at least 50% pain relief over 6 hours with the active treatment, and 8/73 with placebo. There were insufficient data for analysis.

Ibuprofen 200 mg + paracetamol 500 mg versus placebo

Three studies (Daniels 2011; Mehlisch 2010a; Mehlisch 2010b) provided data comparing ibuprofen 200 mg + paracetamol 500 mg with placebo.

- The proportion of participants experiencing at least 50% pain relief over 6 hours with ibuprofen 200 mg + paracetamol 500 mg was 69% (240/349; range 55% to 74%).
- The proportion of participants experiencing at least 50% pain relief over 6 hours with placebo was 7% (10/159; range 0% to 11%).
- The relative benefit of treatment compared with placebo was 10.3 (5.7 to 19); the NNT for at least 50% pain relief over 6 hours was 1.6 (1.5 to 1.8) (Analysis 1.1; Figure 3).

Figure 3. Forest plot of comparison: ibuprofen 200 mg + paracetamol 500 mg versus placebo, outcome: 1.1 Participants with ≥50% pain relief.

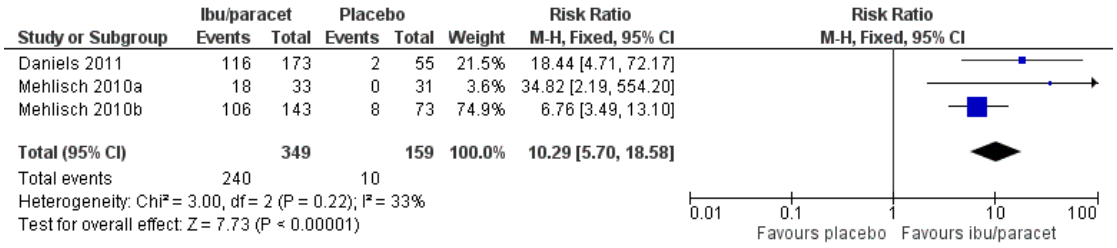
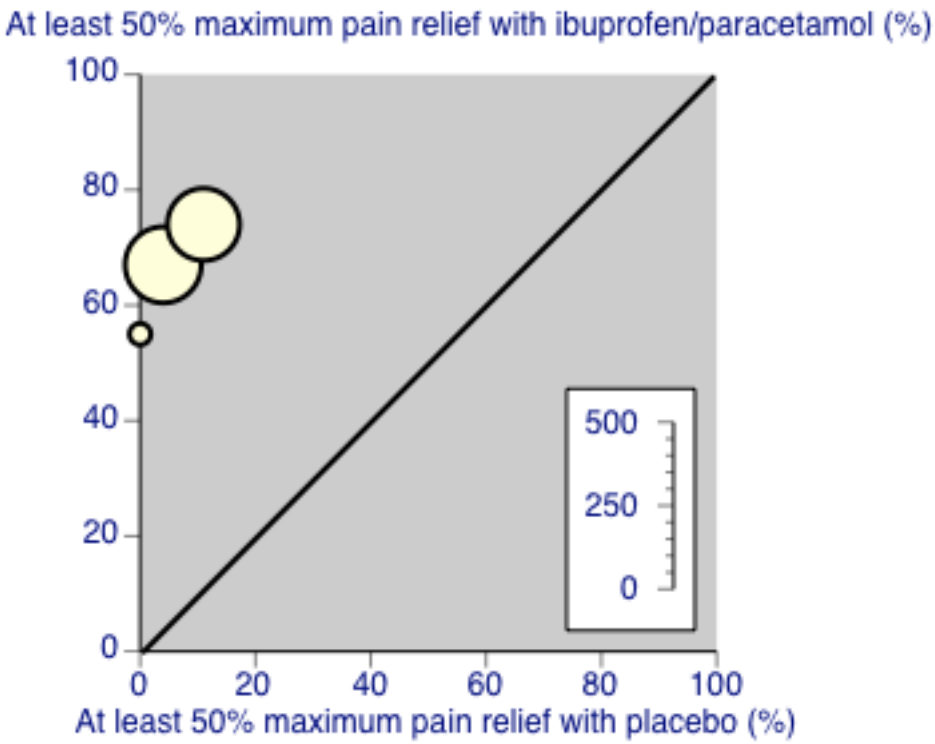


Figure 4 shows the distribution of results for ibuprofen 200 mg plus paracetamol 500 mg compared with placebo. Results were consistent between studies.

Figure 4. Studies comparing ibuprofen 200 mg + paracetamol 500 mg with placebo, with the outcome of at least 50% maximum pain relief over 4 to 6 hours.



Ibuprofen 400 mg + paracetamol 1000 mg versus placebo

Three studies (Daniels 2011; Mehlisch 2010a; Mehlisch 2010b) provided data comparing ibuprofen 400 mg + paracetamol 1000 mg with placebo.

- The proportion of participants experiencing at least 50% pain relief over 6 hours with ibuprofen 400 mg + paracetamol 1000 mg was 72% (278/384; range 67% to 74%).
- The proportion of participants experiencing at least 50% pain relief over 6 hours with placebo was 6% (10/159; range 0% to 11%).
- The relative benefit of treatment compared with placebo was 11.2 (6.2 to 20); the NNT for at least 50% pain relief over 6 hours was 1.5 (1.4 to 1.7) (Analysis 2.1; Figure 5).

Figure 5. Forest plot of comparison: Ibuprofen 400 mg + paracetamol 1000 mg versus placebo, outcome: 2.1 Participants with ≥ 50% pain relief.

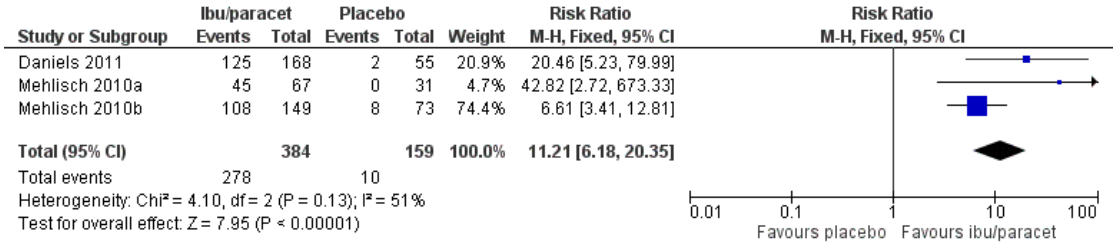
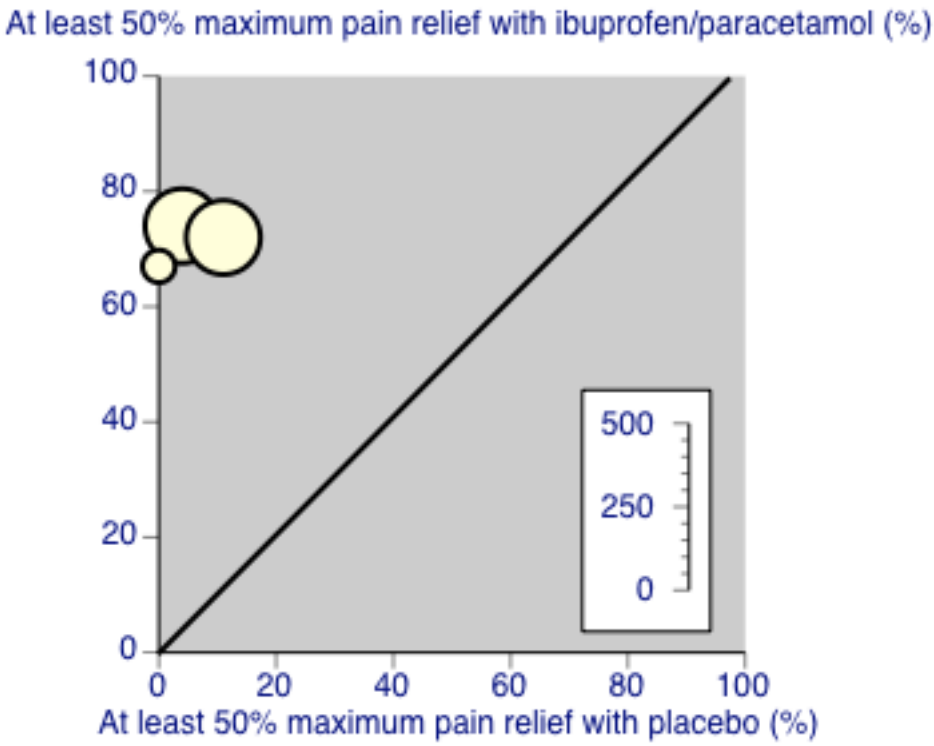


Figure 6 shows the distribution of results for ibuprofen 400 mg plus paracetamol 1000 mg compared with placebo. Results were consistent between studies.

Figure 6. Studies comparing ibuprofen 400 mg plus paracetamol 1000 mg with placebo, with the outcome of at least 50% maximum pain relief over 4-6 hours



Ibuprofen 200 mg + paracetamol 500 mg versus ibuprofen 200 mg

One study (Mehlisch 2010b) compared ibuprofen 200 mg + parac-

etamol 500 mg with ibuprofen 200 mg alone; 106/143 participants experienced at least 50% pain relief over 6 hours with the combination, and 42/75 with ibuprofen alone. There were insufficient data for analysis.

Ibuprofen 400 mg + paracetamol 1000 mg versus ibuprofen 400 mg

Two studies (Mehlisch 2010a; Mehlisch 2010b) provided data comparing ibuprofen 400 mg + paracetamol 1000 mg with ibuprofen 400 mg alone.

- The proportion of participants experiencing at least 50% pain relief over 6 hours with ibuprofen 400 mg + paracetamol 1000 mg was 71% (153/216; range 67% to 72%).
- The proportion of participants experiencing at least 50% pain relief over 6 hours with ibuprofen 400 mg was 52% (75/143; range 42% to 62%).
- The relative benefit of combination treatment compared with ibuprofen alone was 1.3 (1.1 to 1.6); the NNT for at least 50% pain relief over 6 hours was 5.4 (3.5 to 12.2) (Analysis 3.1).

Summary of results A: Number of participants with ≥ 50% pain relief over 6 hours

Dose: ibu/para (mg)	Studies	Participants	Ibu + para (%)	Placebo (%)	NNT (95%CI)
100/250	1	144	65	11	not calculated
200/500	3	508	69	7	1.6 (1.5 to 1.8)
400/1000	3	543	73	7	1.5 (1.4 to 1.7)
				Ibu 200 mg (%)	
200/500	1	218	74	56	not calculated
				Ibu 400 mg (%)	
400/1000	2	359	71	52	5.4 (3.5 to 12)

ibu = ibuprofen; para = paracetamol.

Subgroup analyses

Subgroup analyses for dose have been carried out as part of the main analysis. All studies included participants who had undergone third molar extraction, so no analysis was possible for presenting condition.

Sensitivity analyses

All studies scored 5/5 on the Oxford Quality Scale, so no analysis was possible for methodological quality. Only one comparison had fewer than 40 participants in both treatment arms (Mehlisch 2010a, ibuprofen 200 mg + paracetamol 500 mg, 64 participants). Removing this study from the analysis did not change the result.

Rescue medication

Median time to use of rescue medication

Only two studies reported the median time to use of rescue medication (Daniels 2011; Mehlisch 2010a). The weighted mean of median times to remedication ranged from 7.6 hours with ibuprofen 200 mg + paracetamol 500 mg (data from 206 participants) to 8.3 hours with ibuprofen 400 mg + paracetamol 1000 mg (data from 235 participants), compared with just 1.7 hours with placebo (data from 86 participants).

Number of participants using rescue medication

Two studies (Mehlisch 2010a; Mehlisch 2010b) reported this outcome after 8 hours and provided sufficient data for analysis of ibuprofen 200 mg + paracetamol 500 mg and ibuprofen 400 mg + paracetamol 1000 mg versus placebo, as well as ibuprofen 400 mg + paracetamol 1000 mg versus ibuprofen 400 mg alone.

Ibuprofen 200 mg + paracetamol 500 mg versus placebo

Two studies (Mehlisch 2010a; Mehlisch 2010b) provided data comparing ibuprofen 200 mg + paracetamol 500 mg with placebo.

- The proportion of participants using rescue medication within 8 hours with ibuprofen 200 mg + paracetamol 500 mg was 34% (60/176; range 28% to 61%).
- The proportion of participants using rescue medication within 8 hours with placebo was 79% (82/104; range 73% to 94%).
- The relative benefit of treatment compared with placebo was 0.46 (0.37 to 0.58); the NNTp was 2.2 (1.8 to 2.9) (Analysis 1.2).

Ibuprofen 400 mg + paracetamol 1000 mg versus placebo

Two studies (Mehlisch 2010a; Mehlisch 2010b) provided data comparing ibuprofen 400 mg + paracetamol 1000 mg with placebo.

- The proportion of participants using rescue medication within 8 hours with ibuprofen 400 mg + paracetamol 1000 mg was 25% (53/216; range 21% to 31%).
- The proportion of participants using rescue medication within 8 hours with placebo was 79% (82/104; range 73% to 94%).
- The relative benefit of treatment compared with placebo was 0.31 (0.24 to 0.40); the NNTp was 1.8 (1.6 to 2.2) (Analysis 2.2).

Ibuprofen 400 mg + paracetamol 1000 mg versus ibuprofen 400 mg

Two studies (Mehlisch 2010a; Mehlisch 2010b) provided data comparing ibuprofen 400 mg + paracetamol 1000 mg with ibuprofen 400 mg alone.

- The proportion of participants using rescue medication within 8 hours with ibuprofen 400 mg + paracetamol 1000 mg was 25% (53/216; range 21% to 31%).
- The proportion of participants using rescue medication within 8 hours with ibuprofen 400 mg was 48% (68/143; range 28% to 68%).
- The relative benefit of combination treatment compared with ibuprofen alone was 0.57 (0.42 to 0.77); the NNTp was 4.3 (3.0 to 7.7) (Analysis 3.2).

Adverse events

The most commonly reported adverse events were those expected following third molar surgery: swelling of the face, nausea, vomiting, headache, dizziness. These events are commonly associated with surgery and anaesthesia.

Any adverse event

All studies reported the number of participants with one or more adverse events for each treatment arm, although in two studies (Mehlisch 2010a; Mehlisch 2010b) this was reported after 8 hours, and in one study (Daniels 2011) after 12 hours. In the authors' judgement these time points were comparable and all data were analysed together.

Ibuprofen 200 mg + paracetamol 500 mg versus placebo

Three studies (Daniels 2011; Mehlisch 2010a; Mehlisch 2010b) provided data comparing ibuprofen 200 mg + paracetamol 500 mg with placebo.

- The proportion of participants experiencing any adverse event with ibuprofen 200 mg + paracetamol 500 mg was 30% (104/349; range 25% to 67%);
- The proportion of participants experiencing any adverse event with placebo was 48% (77/159; range 38% to 68%);
- The relative benefit of treatment compared with placebo was 0.69 (0.55 to 0.85); the NNTp was 5.4 (3.6 to 11) (Analysis 1.3).

Ibuprofen 400 mg + paracetamol 1000 mg versus placebo

Three studies (Daniels 2011; Mehlisch 2010a; Mehlisch 2010b) provided data comparing ibuprofen 400 mg + paracetamol 1000 mg with placebo.

- The proportion of participants experiencing any adverse event with ibuprofen 400 mg + paracetamol 1000 mg was 29% (111/384; range 18% to 69%);
- The proportion of participants experiencing any adverse event with placebo was 48% (77/159; range 38% to 68%);
- The relative benefit of treatment compared with placebo was 0.62 (0.50 to 0.77); the NNTp was 5.1 (3.5 to 9.5) (Analysis 2.3).

Ibuprofen 400 mg + paracetamol 1000 mg versus ibuprofen 400 mg

Two studies (Mehlisch 2010a; Mehlisch 2010b) provided data comparing ibuprofen 400 mg + paracetamol 1000 mg with ibuprofen 400 mg.

- The proportion of participants experiencing any adverse event with ibuprofen 400 mg + paracetamol 1000 mg was 37% (80/216; range 23% to 69%);
- The proportion of participants experiencing any adverse event with ibuprofen 400 mg was 55% (78/143; range 35% to 75%);
- The relative benefit of treatment compared with placebo was 0.81 (0.66 to 0.99); the NNTp was 5.7 (3.6 to 14) (Analysis 3.3).

Serious adverse events

There were no serious adverse events reported in any of the included studies.

Withdrawals

Withdrawal due to lack of efficacy is considered under use of rescue medication. Withdrawals for other reasons were no more than 5% and balanced across treatment arms. All reported adverse event withdrawals were due to early vomiting. There were too few events for analysis (Appendix 6).

DISCUSSION

The background to this review is a knowledge that combinations of different analgesics provide additive effects in acute pain and migraine (Moore 2011b; Moore 2012). The main thrust of this review is to assess the analgesic efficacy of ibuprofen and paracetamol combination analgesics because they are becoming available to the public without prescription, and combinations may be used to some extent in treating acute pain in hospital or in primary care.

Summary of main results

Three studies were identified for inclusion. These studies provided data from 508 participants for the comparison of ibuprofen 200 mg + paracetamol 500 mg with placebo, 543 participants for the comparison of ibuprofen 400 mg + paracetamol 1000 mg with placebo, and 359 participants for the comparison of ibuprofen 400 mg + paracetamol 1000 mg with ibuprofen 400 mg alone. There were insufficient data for analysis of any other comparisons.
In summary, ibuprofen plus paracetamol combinations provided better analgesia than either drug alone (at the same dose), with a smaller chance of needing additional analgesia over about eight hours, and with a smaller chance of experiencing an adverse event.
The proportion of participants achieving at least 50% pain relief over 6 hours with ibuprofen 200 mg + paracetamol 500 mg was 69%, compared to 73% with ibuprofen 400 mg + paracetamol 1000 mg, and 7% with placebo, giving NNTs of 1.6 (1.5 to 1.8) and 1.5 (1.4 to 1.7) for the lower and higher doses respectively.
The proportion of participants achieving at least 50% pain relief over 6 hours with ibuprofen 400 mg alone was 52%, giving an NNT for ibuprofen 400 mg + paracetamol 1000 mg compared with ibuprofen alone of 5.4 (3.5 to 12.2).
In studies reporting median time to use of rescue medication, treatment with ibuprofen + paracetamol combination at both the 200/500 mg and 400/1000 mg doses resulted in longer times to remedication when compared with placebo. The median time to use of rescue medication for ibuprofen 200 mg + paracetamol 500 mg was 7.6 hours, compared to 8.3 hours with ibuprofen 400 mg + paracetamol 1000 mg, and 1.7 hours with placebo. Fewer participants required rescue medication with the ibuprofen + paracetamol combination than with placebo or ibuprofen alone. The proportion of participants using rescue medication with ibuprofen 200 mg + paracetamol 500 mg was 34%, compared with 25% with ibuprofen 400 mg + paracetamol 1000 mg, and 79% with placebo, giving NNTps of 2.2 (1.8 to 2.9) and 1.8 (1.6 to 2.2) respectively. The proportion of participants using rescue medication with ibuprofen 400 mg was 48%, giving an NNTp for ibuprofen 400 mg + paracetamol 1000 mg compared with ibuprofen alone of 4.3 (3.0 to 7.7).
The proportion of participants experiencing one or more adverse events with ibuprofen 200 mg + paracetamol 500 mg was 30%, compared to 29% with ibuprofen 400 mg + paracetamol 1000 mg, and 48% with placebo, giving NNTp of 5.4 (3.6 to 10.5) and 5.1 (3.5 to 9.5) for the lower and higher doses respectively (i.e. in favour of the combination treatment). The proportion of participants experiencing one or more adverse events with ibuprofen 400 mg alone was 37%. No serious adverse events were reported in any of the included studies. Withdrawals for reasons other than lack of efficacy were fewer than 5% and balanced across treatment arms, but there were too few events for analysis.

Overall completeness and applicability of evidence

The main limitation of the review is the relatively small number of studies and participants for some combinations. However, the general results are in accord with those known for ibuprofen and paracetamol alone (Derry 2009; Toms 2008) and for combination drugs in acute pain (Moore 2011b; Moore 2012). Since all three studies used the dental pain model, applicability to other types of acute pain may be questioned, but other analgesics are known to perform similarly in dental and other types of postoperative pain of comparable severity, and clinical practice demonstrates applicability to other types of acute nociceptive pain.

Quality of the evidence

All studies were randomised and double-blind and provided information about withdrawals and dropouts, scoring 5/5 on the Oxford Quality Scale, and indicating that they are likely to be methodologically robust. Studies were valid in that they recruited participants with adequate baseline pain and used clinically useful outcome measures. The studies themselves were of high quality, but sample sizes were somewhat limited.

Potential biases in the review process

We carried out extensive searches to identify relevant studies, but there always remains the possibility of unidentified studies. We

calculated that for ibuprofen 400 mg plus paracetamol 1000 mg, an additional 2353 participants would have to have been involved in unpublished trials with zero treatment effects for the NNT for at least 50% pain relief to increase above 8, a level we consider to be the limit of clinical utility for this outcome (Moore 2008). It is very unlikely that this amount of unidentified information exists. We know of two ongoing studies (NCT00921700; NCT01559259) with an estimated enrolment of 600 participants.

There are no other known potential biases in the review process.

Agreements and disagreements with other studies or reviews

We are unaware of any previous systematic reviews of ibuprofen plus paracetamol in acute pain in adults.

AUTHORS' CONCLUSIONS

Implications for practice

Combinations of ibuprofen plus paracetamol are better analgesics than either drug alone. There were sufficient studies and participants, together with consistent large effects for pain, remedication, and adverse event benefits, to consider that this is an important finding, as good analgesia was provided by relatively low doses of ibuprofen and paracetamol. Given that neither is without risk of potential toxicity, which is likely to be dose-dependent, this is a useful finding. While the results here were obtained from dental pain, considerable evidence has shown results from this pain model to be similar for other acute pain situations.

Implications for research

It is not clear what are the implications for research. Studies offer no new methodological insights, and while additional data are always welcome, there are potential balancing ethical issues from including participants in studies that do not add to existing knowledge in a meaningful way. However, as these studies were confined to dental extraction in young participants, there is a need for additional studies in other postoperative situations, and especially in older, sicker patients. Further studies in other acute painful conditions, such as headache, are also needed.

ACKNOWLEDGEMENTS

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Daniels 2011

Methods	Randomised, double-blind, single-dose, 5 parallel groups. Medication administered when baseline pain reached a moderate to severe intensity Pain assessed at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 and 12 hours
Participants	Surgical removal of impacted third molar. Mean age 20 years. N = 678 (598 analysed). M = 271, F = 407.
Interventions	Ibuprofen 200 mg + paracetamol 500 mg, n = 173. Ibuprofen 400 mg + paracetamol 1000 mg, n = 168. Ibuprofen 400 mg + codeine 25.6 mg, n = 169. Paracetamol 1000 mg + codeine 30 mg, n = 113. Placebo, n = 55.
Outcomes	PI: std 4-point scale. PR: std 5-point scale. Median time to use of rescue medication. Number of participants reporting any adverse event and serious adverse events Number of participants withdrawing because of an adverse event
Notes	Oxford Quality Score: R2, DB2, W1. Total = 5/5.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Patients were randomised, according to a computer-generated system"
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Each treatment consisted of 2 white tablets of a similar size and was administered as a single oral dose taken with approximately 300 mL of water
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Each treatment consisted of 2 white tablets of a similar size and was administered as a single oral dose taken with approximately 300 mL of water
Size	Unclear risk	Treatment groups sizes 55 to 173.

Mehlisch 2010a

Methods	Randomised, double-blind, single-dose, 5 parallel groups. Medication administered when baseline pain reached a moderate to severe intensity Pain assessed at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 7 and 8 hours
Participants	Surgical removal of impacted third molar. Mean age 21 years. N = 234. M = 60, F = 174.
Interventions	Ibuprofen 200 mg + paracetamol 500 mg, n = 33. Ibuprofen 400 mg + paracetamol 1000 mg, n = 67. Ibuprofen 400 mg, n = 69. Paracetamol 1000 mg, n = 34. Placebo, n = 31.
Outcomes	PI: std 4-point scale. PR: std 5-point scale. Median time to use of rescue medication. Number of participants using rescue medication. Number of participants reporting any adverse event and serious adverse events Number of participants withdrawing because of an adverse event
Notes	Oxford Quality Score: R2, DB2, W1. Total = 5/5.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Randomisation was done according to a computer-generated schedule"
Allocation concealment (selection bias)	Low risk	Subjects allocated a unique number in numerical sequence in a predefined order to allow stratification for sex and baseline pain
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Each subject received a single oral dose containing 2 tablets (Advil and/or matching placebo) and 2 caplets (Tylenol ES and/or matching placebo) in a blinded fashion
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Each subject received a single oral dose containing 2 tablets (Advil and/or matching placebo) and 2 caplets (Tylenol ES and/or matching placebo) in a blinded fashion
Size	High risk	Treatment group sizes 31 to 69.

Mehlisch 2010b

Methods	Randomised, double-blind, single dose and multi-dose stages (only single dose stage of trial used), 8 parallel groups Medication administered when baseline pain reached a moderate to severe intensity Pain assessed at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 7 and 8 hours
Participants	Surgical removal of impacted third molar. Mean age 20 years. N = 735. M = 275, F = 460.
Interventions	Ibuprofen 100 mg + paracetamol 250 mg, n = 71. Ibuprofen 200 mg + paracetamol 500 mg, n = 143. Ibuprofen 400 mg + paracetamol 1000 mg, n = 149. Ibuprofen 200 mg, n = 75. Ibuprofen 400 mg, n = 74. Paracetamol 500 mg, n = 76. Paracetamol 1000 mg, n = 74. Placebo, n = 73.
Outcomes	PI: std 4-point scale. PR: std 5-point scale. Median time to use of rescue medication. Number of participants using rescue medication. Number of participants reporting any adverse event and serious adverse events Number of participants withdrawing because of an adverse event
Notes	Oxford Quality Score: R2, DB2, W1. Total = 5/5.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Subjects were randomly assigned to a treatment according to a computer-produced randomisation schedule"
Allocation concealment (selection bias)	Unclear risk	Subjects were allocated a unique number in numerical sequence in a predefined order to allow stratification for sex and baseline pain
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Placebo tablets for oral administration were identical to ibuprofen 200 mg, acetaminophen 500 mg and ibuprofen/acetaminophen combination doses"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Placebo tablets for oral administration were identical to ibuprofen 200 mg, acetaminophen 500 mg and ibuprofen/ac-

Mehlisch 2010b (*Continued*)

		etaminophen combination doses"
Size	Unclear risk	Treatment group sizes 71 to 149.

DB = double blind, N = number of participants in study, n = number of participants in treatment arm, PGE = patient global evaluation, PI = pain intensity, PR = pain relief, R = randomised, W = withdrawals.

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

Study	Reason for exclusion
Menhinick 2004	Nonsurgical intervention.
Merry 2010	One dose given preoperatively. No single dose data.
Mitchell 2008	No suitable comparator (placebo or same dose ibuprofen). No single dose data
Naidu 1994	No suitable comparator (placebo or same dose ibuprofen).

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

NCT00921700

Trial name or title	Analgesic effect of ibuprofen 400 mg/paracetamol 1000 mg, ibuprofen 400 mg/paracetamol 1000 mg/60 mg codeine and paracetamol 1000 mg/codeine 60 mg: a single dose, randomised, placebo-controlled and double-blind study
Methods	Randomised, double-blind, single-dose, 4 parallel groups. Medication administered when baseline pain reached a moderate to severe intensity Pain assessed at baseline and at intervals over 6 hours.
Participants	Surgical removal of impacted third molars. M and F. Age 18 to 30 years.
Interventions	Ibuprofen 400 mg/paracetamol 1000 mg. Ibuprofen 400 mg/ paracetamol 1000 mg/codeine 60 mg. Paracetamol 1000 mg/codeine 60 mg. Placebo. All drugs administered in gelatin capsules.
Outcomes	PI: std 4-point scale. Adverse events.

NCT00921700 (*Continued*)

Starting date	June 2009.
Contact information	Lasse A. Skoglund, DDS, DSci (lasses@odont.uio.no). Per Skjelbred, DDS, MD, PhD (p.skjelbred@ulleval.no).
Notes	Estimated enrolment 200, estimated completion date June 2011, estimated completion of analysis late 2012

NCT01559259

Trial name or title	Evaluation of the efficacy of novel ibuprofen/acetaminophen combination formulations in the treatment of postsurgical dental pain
Methods	Randomised, double-blind, single-dose, 5 parallel groups. Medication administered when baseline pain reached a moderate to severe intensity Pain assessed at baseline and at intervals over 12 hours.
Participants	Surgical extraction of three or more third molar teeth. M and F. Age 16 to 40 years.
Interventions	Ibuprofen 200 mg + acetaminophen 500 mg. Ibuprofen 250 mg + acetaminophen 500 mg. Ibuprofen 300 mg + acetaminophen 500 mg. Ibuprofen 400 mg. Placebo.
Outcomes	PI: std 4-point scale. PR: std 5-point scale. Use of rescue medication. Adverse events.
Starting date	April 2012.
Contact information	Pfizer CT.gov Call Center.
Notes	Estimated enrolment 410, estimated completion date September 2012

F = female; M = male; PI = pain intensity; PR = pain relief; std = standard.

DATA AND ANALYSES

Comparison 1. ibuprofen 200 mg + paracetamol 500 mg versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants with ≥50% pain relief	3	508	Risk Ratio (M-H, Fixed, 95% CI)	10.29 [5.70, 18.58]
2 Participants using rescue medication within 8 h	2	280	Risk Ratio (M-H, Fixed, 95% CI)	0.46 [0.37, 0.58]
3 Participants with any adverse event	3	508	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.55, 0.85]

Comparison 2. Ibuprofen 400 mg + paracetamol 1000 mg versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants with ≥50% pain relief	3	543	Risk Ratio (M-H, Fixed, 95% CI)	11.21 [6.18, 20.35]
2 Participants using rescue medication within 8 h	2	320	Risk Ratio (M-H, Fixed, 95% CI)	0.31 [0.24, 0.40]
3 Participants with any adverse event	3	543	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.50, 0.77]

Comparison 3. Ibuprofen 400 mg + paracetamol 1000 mg versus ibuprofen 400 mg

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Participants with ≥50% pain relief	2	359	Risk Ratio (M-H, Fixed, 95% CI)	1.30 [1.10, 1.55]
2 Participants using rescue medication within 8 h	2	359	Risk Ratio (M-H, Fixed, 95% CI)	0.57 [0.42, 0.77]
3 Participants with any adverse event	2	359	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.66, 0.99]

Analysis 1.1. Comparison 1 ibuprofen 200 mg + paracetamol 500 mg versus placebo, Outcome 1 Participants with ≥50% pain relief.

Review: Single dose oral ibuprofen plus paracetamol (acetaminophen) for acute postoperative pain

Comparison: 1 ibuprofen 200 mg + paracetamol 500 mg versus placebo

Outcome: 1 Participants with ≥50% pain relief

Study or subgroup	Ibu/paracet n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Daniels 2011	116/173	2/55		21.5 %	18.44 [4.71, 72.17]
Mehlisch 2010a	18/33	0/31		3.6 %	34.82 [2.19, 554.20]
Mehlisch 2010b	106/143	8/73		74.9 %	6.76 [3.49, 13.10]
Total (95% CI)	**349**	**159**		**100.0 %**	**10.29 [5.70, 18.58]**
Total events: 240 (Ibu/paracet), 10 (Placebo)					
Heterogeneity: Chi^2 = 3.00, df = 2 (P = 0.22); I^2 =33%					
Test for overall effect: Z = 7.73 (P < 0.00001)					
Test for subgroup differences: Not applicable					

Analysis 1.2. Comparison 1 ibuprofen 200 mg + paracetamol 500 mg versus placebo, Outcome 2 Participants using rescue medication within 8 h.

Review: Single dose oral ibuprofen plus paracetamol (acetaminophen) for acute postoperative pain

Comparison: 1 ibuprofen 200 mg + paracetamol 500 mg versus placebo

Outcome: 2 Participants using rescue medication within 8 h

Study or subgroup	Ibu/paracet n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Mehlisch 2010a	20/33	29/31		29.9 %	0.65 [0.48, 0.87]
Mehlisch 2010b	40/143	53/73		70.1 %	0.39 [0.29, 0.52]
Total (95% CI)	**176**	**104**		**100.0 %**	**0.46 [0.37, 0.58]**
Total events: 60 (Ibu/paracet), 82 (Placebo)					
Heterogeneity: Chi^2 = 6.58, df = 1 (P = 0.01); I^2 =85%					
Test for overall effect: Z = 6.96 (P < 0.00001)					
Test for subgroup differences: Not applicable					

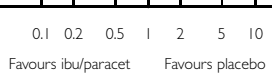
Analysis 1.3. Comparison 1 ibuprofen 200 mg + paracetamol 500 mg versus placebo, Outcome 3 Participants with any adverse event.

Review: Single dose oral ibuprofen plus paracetamol (acetaminophen) for acute postoperative pain

Comparison: 1 ibuprofen 200 mg + paracetamol 500 mg versus placebo

Outcome: 3 Participants with any adverse event

Study or subgroup	Ibu/paracet n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Daniels 2011	43/173	21/55		31.9 %	0.65 [0.43, 1.00]
Mehlisch 2010a	22/33	21/31		21.7 %	0.98 [0.70, 1.39]
Mehlisch 2010b	39/143	35/73		46.4 %	0.57 [0.40, 0.81]
Total (95% CI)	**349**	**159**		**100.0 %**	**0.69 [0.55, 0.85]**
Total events: 104 (Ibu/paracet), 77 (Placebo)					
Heterogeneity: Chi^2 = 5.39, df = 2 (P = 0.07); I^2 =63%					
Test for overall effect: Z = 3.37 (P = 0.00075)					
Test for subgroup differences: Not applicable					

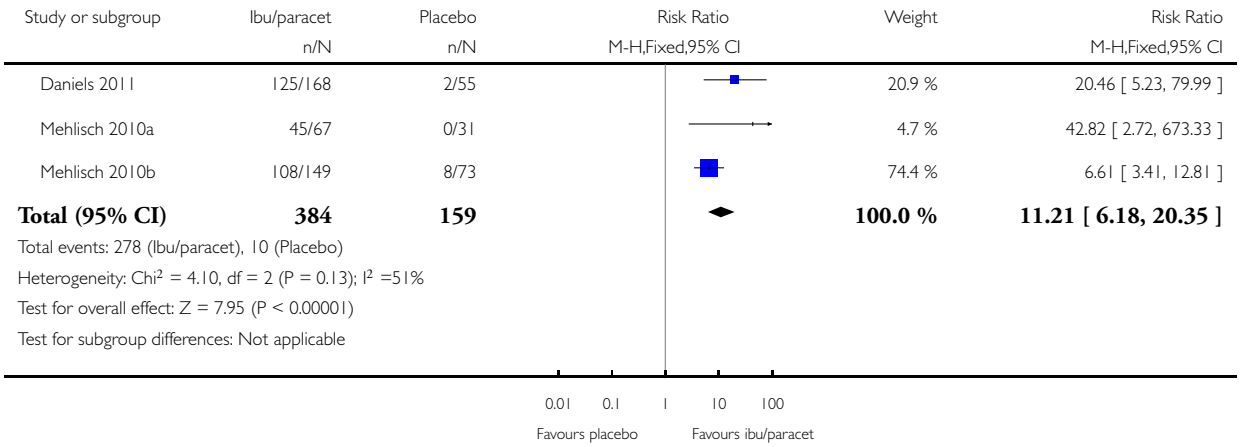


Analysis 2.1. Comparison 2 Ibuprofen 400 mg + paracetamol 1000 mg versus placebo, Outcome 1 Participants with ≥50% pain relief.

Review: Single dose oral ibuprofen plus paracetamol (acetaminophen) for acute postoperative pain

Comparison: 2 Ibuprofen 400 mg + paracetamol 1000 mg versus placebo

Outcome: 1 Participants with ≥50% pain relief



Analysis 2.2. Comparison 2 Ibuprofen 400 mg + paracetamol 1000 mg versus placebo, Outcome 2 Participants using rescue medication within 8 h.

Review: Single dose oral ibuprofen plus paracetamol (acetaminophen) for acute postoperative pain

Comparison: 2 Ibuprofen 400 mg + paracetamol 1000 mg versus placebo

Outcome: 2 Participants using rescue medication within 8 h

Study or subgroup	Ibu/paracet n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Mehlisch 2010a	21/67	29/31		35.8 %	0.34 [0.23, 0.48]
Mehlisch 2010b	32/149	53/73		64.2 %	0.30 [0.21, 0.41]
Total (95% CI)	**216**	**104**		**100.0 %**	**0.31 [0.24, 0.40]**
Total events: 53 (Ibu/paracet), 82 (Placebo)					
Heterogeneity: Chi^2 = 0.25, df = 1 (P = 0.62); I^2 =0.0%					
Test for overall effect: Z = 9.11 (P < 0.00001)					
Test for subgroup differences: Not applicable					

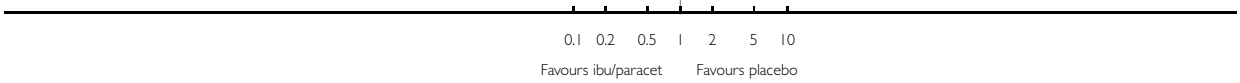
Analysis 2.3. Comparison 2 Ibuprofen 400 mg + paracetamol 1000 mg versus placebo, Outcome 3 Participants with any adverse event.

Review: Single dose oral ibuprofen plus paracetamol (acetaminophen) for acute postoperative pain

Comparison: 2 Ibuprofen 400 mg + paracetamol 1000 mg versus placebo

Outcome: 3 Participants with any adverse event

Study or subgroup	Ibu/paracet n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Daniels 2011	31/168	21/55		29.5 %	0.48 [0.30, 0.77]
Mehlisch 2010a	46/67	21/31		26.8 %	1.01 [0.76, 1.36]
Mehlisch 2010b	34/149	35/73		43.8 %	0.48 [0.33, 0.70]
Total (95% CI)	**384**	**159**		**100.0 %**	**0.62 [0.50, 0.77]**
Total events: 111 (Ibu/paracet), 77 (Placebo)					
Heterogeneity: Chi^2 = 13.80, df = 2 (P = 0.001); I^2 =86%					
Test for overall effect: Z = 4.36 (P = 0.000013)					
Test for subgroup differences: Not applicable					



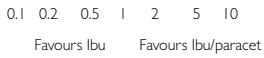
Analysis 3.1. Comparison 3 Ibuprofen 400 mg + paracetamol 1000 mg versus ibuprofen 400 mg, Outcome 1 Participants with ≥50% pain relief.

Review: Single dose oral ibuprofen plus paracetamol (acetaminophen) for acute postoperative pain

Comparison: 3 Ibuprofen 400 mg + paracetamol 1000 mg versus ibuprofen 400 mg

Outcome: 1 Participants with ≥50% pain relief

Study or subgroup	Ibu/paracet n/N	Ibu n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Mehlisch 2010a	45/67	29/69		31.7 %	1.60 [1.16, 2.21]
Mehlisch 2010b	108/149	46/74		68.3 %	1.17 [0.95, 1.43]
Total (95% CI)	**216**	**143**		**100.0 %**	**1.30 [1.10, 1.55]**
Total events: 153 (Ibu/paracet), 75 (Ibu)					
Heterogeneity: Chi^2 = 2.67, df = 1 (P = 0.10); I^2 =63%					
Test for overall effect: Z = 2.99 (P = 0.0028)					
Test for subgroup differences: Not applicable					



Analysis 3.2. Comparison 3 Ibuprofen 400 mg + paracetamol 1000 mg versus ibuprofen 400 mg, Outcome 2 Participants using rescue medication within 8 h.

Review: Single dose oral ibuprofen plus paracetamol (acetaminophen) for acute postoperative pain

Comparison: 3 Ibuprofen 400 mg + paracetamol 1000 mg versus ibuprofen 400 mg

Outcome: 2 Participants using rescue medication within 8 h

Study or subgroup	Ibu/paracet n/N	Ibu n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Mehlisch 2010a	21/67	47/69		62.3 %	0.46 [0.31, 0.68]
Mehlisch 2010b	32/149	21/74		37.7 %	0.76 [0.47, 1.22]
Total (95% CI)	**216**	**143**		**100.0 %**	**0.57 [0.42, 0.77]**
Total events: 53 (Ibu/paracet), 68 (Ibu)					
Heterogeneity: Chi^2 = 2.54, df = 1 (P = 0.11); I^2 =61%					
Test for overall effect: Z = 3.65 (P = 0.00026)					
Test for subgroup differences: Not applicable					

Analysis 3.3. Comparison 3 Ibuprofen 400 mg + paracetamol 1000 mg versus ibuprofen 400 mg, Outcome 3 Participants with any adverse event.

Review: Single dose oral ibuprofen plus paracetamol (acetaminophen) for acute postoperative pain

Comparison: 3 Ibuprofen 400 mg + paracetamol 1000 mg versus ibuprofen 400 mg

Outcome: 3 Participants with any adverse event

Study or subgroup	Ibu/paracet n/N	Ibu n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Mehlisch 2010a	46/67	52/69		59.6 %	0.91 [0.74, 1.12]
Mehlisch 2010b	34/149	26/74		40.4 %	0.65 [0.42, 1.00]
Total (95% CI)	**216**	**143**		**100.0 %**	**0.81 [0.66, 0.99]**
Total events: 80 (Ibu/paracet), 78 (Ibu)					
Heterogeneity: Chi^2 = 2.29, df = 1 (P = 0.13); I^2 =56%					
Test for overall effect: Z = 2.07 (P = 0.038)					
Test for subgroup differences: Not applicable					

APPENDICES

Appendix 1. Search strategy for MEDLINE (via OVID)

1. Ibuprofen/ or (ibuprofen or brufen or propionic acid or isobutylphenyl propionic acid).mp.
2. Acetaminophen/ or (acetaminophen or paracetamol).mp.
3. 1 and 2
4. Pain, Postoperative/
5. ((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.
6. ((post-surgical adj4 pain*) or ("post surgical" adj4 pain*) or (post-surgery adj4 pain*)).mp.
7. ("pain-relief after surg*" or "pain following surg*" or "pain control after").mp.
8. (("post surg*" or post-surg*) and (pain* or discomfort)).mp.
9. ((pain* adj4 "after surg*") or (pain* adj4 "after operat*") or (pain* adj4 "follow* operat*") or (pain* adj4 "follow* surg*")).mp.

10. ((analgesi* adj4 “after surg*”) or (analgesi* adj4 “after operat*”) or (analgesi* adj4 “follow* operat*”) or (analgesi* adj4 “follow* surg*”)).mp.
11. exp Surgical Procedures, Operative/
12. or/4-11
13. 3 and 12
14. randomized controlled trial.pt.
15. controlled clinical trial.pt.
16. randomized.ab.
17. placebo.ab.
18. drug therapy.fs.
19. randomly.ab.
20. trial.ab.
21. groups.ab.
22. 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21
23. exp animals/ not humans.sh.
24. 22 not 23
25. 13 and 24

Appendix 2. Search strategy for EMBASE (via OVID)

1. Ibuprofen/ or (ibuprofen or brufen or propionic acid or isobutylphenyl propionic acid).mp.
2. Acetaminophen/ or (acetaminophen or paracetamol).mp.
3. 1 and 2
4. Pain, Postoperative/
5. ((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.
6. ((post-surgical adj4 pain*) or (“post surgical” adj4 pain*) or (post-surgery adj4 pain*)).mp.
7. (“pain-relief after surg*” or “pain following surg*” or “pain control after”).mp.
8. ((“post surg*” or post-surg*) and (pain* or discomfort)).mp.
9. ((pain* adj4 “after surg*”) or (pain* adj4 “after operat*”) or (pain* adj4 “follow* operat*”) or (pain* adj4 “follow* surg*”)).mp.
10. ((analgesi* adj4 “after surg*”) or (analgesi* adj4 “after operat*”) or (analgesi* adj4 “follow* operat*”) or (analgesi* adj4 “follow* surg*”)).mp.
11. exp Surgical Procedures, Operative/
12. or/4-11
13. 3 and 12
14. random*.tw.
15. factorial*.tw.
16. crossover*.tw.
17. cross over*.tw.
18. cross-over*.tw.
19. placebo*.tw.
20. (doubl* adj blind*).tw.
21. (singl* adj blind*).tw.
22. assign*.tw.
23. allocat*.tw.
24. volunteer*.tw.
25. Crossover Procedure/
26. double-blind procedure.tw.
27. Randomized Controlled Trial/
28. Single Blind Procedure/
29. or/14-28
30. 13 and 29

Appendix 3. Search strategy for CENTRAL (The Cochrane Library)

1. MeSH descriptor: [Ibuprofen] this term only
2. (ibuprofen or brufen or propionic acid or "isobutylphenyl propionic acid")
3. MeSH descriptor: [Acetaminophen] this term only
4. (acetaminophen or paracetamol)
5. 1 or 2
6. 3 or 4
7. 5 and 6
8. MeSH descriptor: [Pain, Postoperative] this term only
9. ((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*"))
10. ((post-surgical near/4 pain*) or ("post surgical" near/4 pain*) or (post-surgery near/4 pain*))
11. ("pain-relief after surg*" or "pain following surg*" or "pain control after")
12. (("post surg*" or post-surg*) and (pain* or discomfort))
13. ((pain* near/4 "after surg*") or (pain* near/4 "after operat*") or (pain* near/4 "follow* operat*") or (pain* near/4 "follow* surg*"))
14. ((analgesi* near/4 "after surg*") or (analgesi* near/4 "after operat*") or (analgesi* near/4 "follow* operat*") or (analgesi* near/4 "follow* surg*"))
15. MeSH descriptor: [Surgical Procedures, Operative] explode all trees
16. 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15
17. 7 and 16

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: For pain intensity, lines with left end labelled "no pain" and right end labelled "worst pain imaginable", and for pain relief lines with left end labelled "no relief of pain" and right end labelled "complete relief of pain", seem to overcome the limitation of forcing patient descriptors into particular categories. Patients mark the line at the point which corresponds to their pain or pain relief. 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. 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.

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

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).

Appendix 5. Summary of outcomes in individual studies: efficacy

		Analgesia			Rescue medication	
Study ID	**Treatment**	**PI or PR**	**Number with 50% PR**	**PGE: very good or excellent**	**Median time to use (h)**	**Number using**
Daniels 2011	(1) Ibuprofen 200 mg + paracetamol 500 mg, n = 173 (2) Ibuprofen 400 mg + paracetamol 1000 mg, n = 168 (3) Ibuprofen 400 mg + codeine 25.6 mg, n = 169 (4) Paracetamol 1000 mg + codeine 30 mg, n = 113 (5) Placebo, n = 55	TOTPAR 6: (1) 14.16 (2) 15.48 (3) 13.38 (4) 11.22 (5) 2.64	(1) 116/173 (2) 125/168 (3) 106/169 (4) 57/113 (5) 2/55	"v good and excellent" at 12 h: (1) 97/173 (2) 109/168 (3) 90/169 (4) 41/113 (5) 4/55	(1) 8.18 (2) 9.95 (3) 8.05 (4) 5.78 (5) 1.68	No usable data
NL0408	(1) Ibuprofen 200 mg + paracetamol 500 mg, n = 33 (2) Ibuprofen 400 mg + paracetamol 1000 mg, n = 67 (3) Ibuprofen 400 mg, n = 69 (4) Paracetamol 1000 mg, n = 34 (5) Placebo, n = 31	TOTPAR 6: (1) 11.9 (2) 14.3 (3) 9.6 (4) 8.2 (5) 1.8	(1) 18/33 (2) 45/67 (3) 29/69 (4) 12/34 (5) 0/31	No data	Median (1) 4.5 (2) 4.1 (3) 4.0 (4) 2.9 (5) 1.6 Mean (1) 5.5 (2) 6.3 (3) 4.9 (4) 4.4 (5) 2.4	At 8 h (1) 20/33 (2) 21/67 (3) 47/69 (4) 24/34 (5) 29/31
NL0604	Single dose stage: (1) Ibuprofen (100 mg) + paracetamol (250 mg), n = 71	TOTPAR 6: (1) 13.7 (2) 15.5 (3) 15.1 (4) 12.3	(1) 46/71 (2) 106/143 (3) 108/149 (4) 42/75 (5) 46/74	No usable data	Mean (1) 7.0 (2) 7.3 (3) 7.4 (4) 6.6	At 8 h (1) 27/71 (2) 40/143 (3) 32/149 (4) 29/75

(*Continued*)

	(2) Ibuprofen (200 mg) + paracetamol (500 mg), n = 143 (3) Ibuprofen (400 mg) + paracetamol (1000 mg), n = 149 (4) Ibuprofen (200 mg), n = 75 (5) Ibuprofen (400 mg), n = 74 (6) Paracetamol (500 mg), n = 76 (7) Paracetamol (1000 mg), n = 74 (8) Placebo, n = 73	(5) 13.3 (8) 4.1	(8) 8/73		(5) 7.0 (6) 4.7 (7) 5.3 (8) 3.7	(5) 21/74 (6) 56/76 (7) 51/74 (8) 53/73

Appendix 6. Summary of outcomes in individual studies: adverse events and withdrawals

		Adverse events		Withdrawals	
Study ID	**Treatment**	**Any**	**Serious**	**Adverse event**	**Other**
Daniels 2011	(1) Ibuprofen 200 mg + paracetamol 500 mg, n = 173 (2) Ibuprofen 400 mg + paracetamol 1000 mg, n = 168 (3) Ibuprofen 400 mg + codeine 25.6 mg, n = 169 (4) Paracetamol 1000 mg + codeine 30 mg, n = 113 (5) Placebo, n = 55	At 12 h (1) 43/173 (2) 31/168 (3) 59/169 (4) 45/113 (5) 21/55	None	None	All lost to follow-up: (1) 1/173 (2) 4/168 (3) 2/169 (4) 1/113 (5) 1/55
NL0408	(1) Ibuprofen 200 mg + paracetamol 500 mg, n = 33 (2) Ibuprofen 400 mg + paracetamol	At 8 h (1) 22/33 (2) 46/67 (3) 52/69 (4) 27/34	None	None	(1) 2/33 (lost to follow up, protocol violation) (2) 2/67 (lost to follow up) (3) 4/69 (lost to follow up x2, protocol violation, with-

(*Continued*)

	1000 mg, n = 67 (3) Ibuprofen 400 mg, n = 69 (4) Paracetamol 1000 mg, n = 34 (5) Placebo, n = 31	(5) 21/31			drew consent) (4) 0/34 (5) 4/31 (lack of efficacy x2, lost to follow up x2)
NL0604	Single dose stage: (1) Ibuprofen 100 mg + paracetamol 250 mg, n = 71 (2) Ibuprofen 200 mg + paracetamol 500 mg, n = 143 (3) Ibuprofen 400 mg + paracetamol 1000 mg, n = 149 (4) Ibuprofen 200 mg, n = 75 (5) Ibuprofen 400 mg, n = 74 (6) Paracetamol 500 mg, n = 76 (7) Paracetamol 1000 mg, n = 74 (8) Placebo, n = 73	After single dose only (up to 8 h): (1) 20/71 (2) 39/143 (3) 34/149 (4) 23/75 (5) 26/74 (6) 34/76 (7) 21/74 (8) 35/73	None	Single dose stage: (1) 1/71 (2) 2/143 (3) 3/149 (4) 1/75 (5) 2/74 (6) 2/76 (7) 0/74 (8) 0/73 In each case the AE leading to withdrawal was early vomiting	Single dose stage: (1) 2/71 (investigator decision) (2) 1/143 (protocol violation, other) (3) 0/149 (4) 1/75 (lack of efficacy) (5) 2/74 (AE/intercurrent event x2, investigator decision, other) (6) 4/76 (AE/intercurrent event x2, withdrew consent x2, other x2) (7) 1/74 (lack of efficacy) (8) 3/73 (withdrew consent x3)

WHAT'S NEW

Last assessed as up-to-date: 21 May 2013.

Date	Event	Description
11 October 2017	Review declared as stable	No new studies likely to change the conclusions are expected

HISTORY

Protocol first published: Issue 11, 2012

Review first published: Issue 6, 2013

Date	Event	Description
17 May 2016	Review declared as stable	See Published notes.

CONTRIBUTIONS OF AUTHORS

All authors contributed to writing the protocol. CJD and SD searched for studies, selected studies for inclusion, and carried out data extraction. RAM acted as arbitrator. All authors were involved in analysis and writing the final review. RAM will be responsible for updating the review.

DECLARATIONS OF INTEREST

RAM and SD have received research support from charities, government and industry sources at various times. RAM has consulted for various pharmaceutical companies and has received lecture fees from pharmaceutical companies related to analgesics and other healthcare interventions. CD has no interests to declare.

SOURCES OF SUPPORT

Internal sources

- Oxford Pain Relief Trust, UK.

External sources

- No sources of support supplied

NOTES

A restricted search in November 2015 did not identify any potentially relevant studies. Therefore, this review has now been stabilised following discussion with the authors and editors. The review will be re-assessed for updating in five years.

INDEX TERMS

Medical Subject Headings (MeSH)

Acetaminophen [*administration & dosage; adverse effects]; Acute Pain [*drug therapy]; Administration, Oral; Analgesics, Non-Narcotic [*administration & dosage; adverse effects]; Drug Combinations; Ibuprofen [*administration & dosage; adverse effects]; Pain, Postoperative [*drug therapy]; Randomized Controlled Trials as Topic

MeSH check words

Adult; Humans