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Single dose oral ibuprofen plus caffeine for acute postoperative pain in adults (Review)

Derry S, Wiffen PJ, Moore RA

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[Intervention Review]

Single dose oral ibuprofen plus caffeine for acute postoperative pain in adults

Sheena Derry[1], Philip J Wiffen[2], R Andrew Moore[3]

[1]Oxford, UK. [2]Thame, UK. [3]Plymouth, UK

Contact: Sheena Derry, Oxford, Oxfordshire, UK. sheena.derry@retired.ox.ac.uk.

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ABSTRACT

Background

There is good evidence that combining two different analgesics in fixed doses in a single tablet can provide better pain relief in acute pain and headache than either drug alone, and that the drug-specific benefits are essentially additive. This appears to be broadly true in postoperative pain and migraine headache across a range of different drug combinations, and when tested in the same and different trials. Adding caffeine to analgesics also increases the number of people obtaining good pain relief. Combinations of ibuprofen and caffeine are available without prescription in some parts of the world.

Objectives

To assess the analgesic efficacy and adverse effects of a single oral dose of ibuprofen plus caffeine for moderate to severe 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), MEDLINE, EMBASE, the Oxford Pain Relief Database, two clinical trial registries, and the reference lists of articles. The date of the most recent search was 1 February 2015.

Selection criteria

Randomised, double-blind, placebo- or active-controlled clinical trials of single dose oral ibuprofen plus caffeine for acute postoperative pain in adults.

Data collection and analysis

Two review authors independently considered trials for inclusion in the review, assessed risk of bias, and extracted data. We used the area under the pain relief versus time curve to derive the proportion of participants with at least 50% pain relief over six hours prescribed either ibuprofen plus caffeine or placebo. We calculated the risk ratio (RR) and number needed to treat to benefit (NNT). We used information on the 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 effects.

Main results

We identified five randomised, double-blind studies with 1501 participants, but only four had been published and had relevant outcome data. These four studies were of high quality, although two of the studies were small.

Both ibuprofen 200 mg + caffeine 100 mg and ibuprofen 100 mg + caffeine 100 mg produced significantly more participants than placebo who achieved at least 50% of maximum pain relief over six hours, and both doses significantly reduced remedication rates (moderate quality evidence). For at least 50% of maximum pain relief, the NNT was 2.1 (95% confidence interval 1.8 to 2.5) for ibuprofen 200 mg + caffeine 100 mg (four studies, 334 participants) and 2.4 (1.9 to 3.1) for ibuprofen 100 mg + caffeine 100 mg (two studies, 200 participants) (moderate quality evidence). These values were close to those predicted by published models for combination analgesics in acute pain, and were supported by low (good) NNT values for prevention of remedication.

Adverse event rates were low, and no sensible analysis was possible.

Authors' conclusions

For ibuprofen 200 mg + caffeine 100 mg particularly, the low NNT value is among the lowest (best) values for analgesics in this pain model. The combination is not commonly available, but can be probably be achieved by taking a single 200 mg ibuprofen tablet with a cup of modestly strong coffee or caffeine tablets. In principle, this can deliver good analgesia at lower doses of ibuprofen.

PLAIN LANGUAGE SUMMARY

Single dose oral ibuprofen plus caffeine for acute postoperative pain in adults

Acute pain is often felt soon after injury. Most people who have surgery have moderate or severe pain afterwards. Painkillers (analgesics) are tested in people with pain, often following the removal of wisdom teeth. This pain is usually treated with painkillers taken by mouth. Results can be applied to other forms of acute pain.

A series of Cochrane reviews looks at how good painkillers are. We know that in some circumstances combining different painkillers in the same tablet or taking separate tablets at the same time gives good pain relief to more people than either painkiller alone. This is particularly true using a combination of two painkillers that work by different mechanisms. This review looked at how good the combination of ibuprofen and caffeine was in relieving moderate or severe pain after surgery.

We searched up to 1 February 2015 and found four studies with a maximum of 334 participants with information for analysis. Ibuprofen 200 mg plus caffeine 100 mg provided effective pain relief for 6 in 10 (59%) participants, compared with 1 in 10 (11%) participants with placebo (moderate quality evidence).

Adverse events occurred at similar rates with the ibuprofen plus caffeine combination and placebo in these single dose studies (low quality evidence). No serious adverse events or withdrawals due to adverse events occurred with the combination.

The combination of ibuprofen 200 mg + caffeine 100 mg is not commonly available, but can probably be achieved by taking a single 200 mg ibuprofen tablet with a cup of modestly strong coffee. Common sources of caffeine include not only caffeine tablets (100 mg is sufficient), but coffee (100 mg to 150 mg per mug or cup with a volume of about 240 mL or 8 fl oz, or a double espresso), but also tea (75 mg per mug), cola drinks (up to 40 mg per drink), energy drinks (approximately 80 mg per drink), plain chocolate (up to 50 mg per bar), and caffeine tablets (100 mg per tablet).

Some people may get good levels of pain relief with a lower dose of ibuprofen when the ibuprofen is combined with caffeine.

Summary of findings for the main comparison.

Ibuprofen plus caffeine compared with placebo for moderate to severe acute postoperative pain in adults

Patient or population: Adults with acute pain

Settings: Hospital or community

Intervention: Oral ibuprofen 200 mg + caffeine 100 mg

Comparison: Oral placebo

Outcomes	Probable outcome with		Relative effect and NNT or NNH (95% CI)	Number of studies, participants, events	Quality of the evidence (GRADE)	Comments
	Comparator	Intervention				
At least 50% of maximum pain relief over 4 to 6 h	100 in 1000	590 in 1000	RR 5.5 (3.5 to 8.7) NNT 2.1 (1.8 to 2.5)	4 studies 334 participants 119 events	Moderate	Number of events below 200
Participants remedicating within 8 hours	600 in 1000	260 in 1000	RR 0.5 (0.4 to 0.6) NNTp 2.9 (2.2 to 4.3)	3 studies 293 participants 128 events	Moderate	Number of events below 200
Participants with at least 1 adverse event	60 in 1000	110 in 1000	RR 1.9 (0.91 to 3.8) NNH not calculated	4 studies 336 participants 28 events	Low	Very small number of events
Participants with a serious adverse event	No serious adverse events			4 studies 336 participants 0 events	Low	Studies underpowered to detect these events

GRADE Working Group grades of evidence

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

NNH: number needed to harm; NNT: number needed to treat; NNTp: number needed to treat to prevent an event; RR: risk ratio

BACKGROUND

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), codeine (Derry 2010), paracetamol (Toms 2008), and etoricoxib (Clarke 2012), and combinations of ibuprofen with paracetamol (Derry 2013a), codeine (Derry 2013b), and oxycodone (Derry 2013c). Knowing the relative efficacy of different analgesic drugs at various doses can be helpful.

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 or nerve injury, or both. The management of postoperative pain and inflammation is a critical component of patient care.

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 (McQuay 2012). 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.

Ibuprofen

Ibuprofen is a nonsteroidal anti-inflammatory drug (NSAID). It 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 better efficacy (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).

Caffeine

Caffeine is a naturally occurring compound found in the seeds, leaves, and fruit of many plants, where it is thought to function as a natural pesticide. It has a long (at least 5000 years) history of human consumption in the form of beverages such as tea and coffee, and foodstuffs such as chocolate. Caffeine intake varies widely among individuals and populations, but can be broadly divided into low (< 100 mg per day), moderate (100 mg to 400 mg per day), and high intake (> 400 mg per day), with the majority of people falling within the moderate intake range. Common sources of caffeine today include coffee (100 mg to 150 mg per mug or cup with a volume of about 240 mL or 8 fl oz, or a double espresso), tea (75 mg per mug), cola drinks (up to 40 mg per drink), energy drinks (approximately 80 mg per drink), plain chocolate (up to 50 mg per bar), and caffeine tablets (100 mg per tablet). Some 'high-energy' drinks have the caffeine content of five or six mugs of coffee. Caffeine tablets are also available, usually as 100 mg or 200 mg tablets.

Caffeine is a methylxanthine that is known to act as a central nervous system stimulant. It has a wide range of physiological effects in humans (Sawynok 1993) including increased wakefulness, alertness, endurance, heart rate, and blood pressure, and is regarded as a psychostimulant (enhances mood; Donovan 2001).

How the intervention might work

Clinicians prescribe NSAIDs on a routine basis for a range of mild, moderate, and severe 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 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.

Using combinations of analgesics works well in acute pain, as results are additive (Moore 2012). Combinations of ibuprofen and other analgesics have been shown to be particularly effective in acute pain, with low (good) number needed to treat for an additional beneficial outcome (NNT) values compared with placebo (Derry 2013a; Derry 2013b; Derry 2013c) for levels of benefit patients think useful (Moore 2013).

Caffeine is not thought to be an analgesic when used alone, but it has been added to various analgesics for many years in the belief that it enhances analgesic effect (Sawynok 2011a; Sawynok 2011b). A Cochrane review demonstrated a 10% increase in participants experiencing good levels of pain relief when 100 mg caffeine was added to a standard dose of common analgesics such as paracetamol and ibuprofen (Derry 2014). Caffeine has been shown to potentiate the effects of ibuprofen in animal models (Lopez 2006). The mechanisms by which caffeine may contribute to, or enhance the efficacy of other analgesics are not well understood. It is known to be a competitive antagonist of adenosine A_1 and A_2 receptors at plasma concentrations observed through normal dietary caffeine intake (in the 10 µM to 100 µM range). Many of the putative mechanisms of action are thought of in terms of this disruption of normal adenosine signalling. Proposed mechanisms of action include (Renner 2007; Sawynok 1993; Zhang 2001):

- improved drug absorption through lower gastric pH and increased gastric blood flow;
- reduced metabolic clearance of drugs through reduced hepatic blood flow;
- blockade of peripheral pro-nociceptive adenosine signalling, and activation of the central noradenosine pathway (pain-suppressing systems);
- transcriptional down-regulation of cyclooxygenase-2 (COX-2), via blockade of the adenosine A_{2a} receptor;
- relief of inhibitor adenosine actions on central cholinergic nerve terminals;
- changes in mood and emotional state contributing to changes in the perception of pain.

Why it is important to do this review

There are increasing concerns over the potential for people to ingest too much paracetamol without knowing it, resulting in repeated supratherapeutic ingestions of paracetamol, also described as 'staggered overdose'. The problem is greater with concomitant alcohol abuse (Craig 2012).

There are also increasing concerns about opioid use generally, and codeine in particular, with interest in reducing opioid exposure to the general public, especially in over the counter (OTC) medicines such as paracetamol plus codeine. The presence of widely different proportions of ultra-fast metabolisers of codeine in different communities complicates dose recommendations (Iedema 2011).

Combinations of ibuprofen plus caffeine have been examined in acute pain conditions such as tension headache (Diamond 2000), and combinations of ibuprofen and caffeine are available in some parts of the world, particularly Central and South America.

Since the publication of the Cochrane review on caffeine as an analgesic adjuvant (Derry 2014), and another paper on analgesic combinations (Moore 2012) (both based on the single dose oral analgesic series from the Cochrane Library), caffeine has come to the fore as a possible alternative to opioids for analgesic combination.

OBJECTIVES

To assess the analgesic efficacy and adverse effects of a single oral dose of ibuprofen plus caffeine for moderate to severe 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 double-blind studies of single dose oral ibuprofen plus caffeine compared with placebo 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:

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

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.

We did not consider studies without a placebo group that compared only ibuprofen plus caffeine with the same dose of ibuprofen alone. The reason is that this comparison is considered across a number of different pain conditions in a separate review examining the analgesic adjuvant effect of caffeine in acute pain (Derry 2014).

Types of participants

We included studies of adult participants (15 years or older) 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 mm equated to pain of at least moderate intensity (Collins 1997).

Types of interventions

Ibuprofen plus caffeine or matched placebo administered as a single oral dose for postoperative pain. The ibuprofen and caffeine may have been 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.

- Patient-reported pain at baseline (physician, nurse, or carer-reported pain was not be included in the analysis).
- Patient-reported pain relief expressed at least hourly over four to six hours using validated pain scales (pain intensity or 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 event(s).
- Number of participants with serious adverse events.
- Number of withdrawals (all-cause, adverse events).

Primary outcomes

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

Secondary outcomes

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

Search methods for identification of studies

A previous Cochrane review had recently searched for studies of single dose oral of analgesics (including ibuprofen) plus caffeine in postoperative pain (Derry 2014). That review had analysed analgesics plus caffeine compared with analgesics without caffeine. Its principal aim was to establish the analgesic effect of added caffeine. It did not examine analgesics plus caffeine compared with placebo. We used results of searches for that review as well as additional searching strategies.

Electronic searches

We searched the following databases.

- The Cochrane Central Register of Controlled Trials (CENTRAL; 2015, Issue 1).
- MEDLINE (via Ovid) 1946 to 1 February 2015.
- EMBASE (via Ovid) 1974 to 1 February 2015.
- The Oxford Pain Relief Database (Jadad 1996a).

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

Searching other resources

On 1 February 2015 we searched for additional studies in reference lists of retrieved articles and reviews. We also searched the ClinicalTrials database (www.clinicaltrials.gov) and the WHO International Clinical Trials Registry Platform (apps.who.int/trialsearch/) for otherwise unpublished trial results and information about ongoing studies.

We contacted Bayer Schering Pharma, the distributor of ActronPlus in Argentina and Actron Max in Mexico. No clinical trial data were available.

Data collection and analysis

Selection of studies

Two review authors independently assessed the search results and agreed on the studies to be included in the review. Disagreements would have been resolved by consensus or referral to a third review author, but this was not necessary.

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 Review Manager 5.3 (RevMan 2014).

Assessment of risk of bias in included studies

We used the Oxford Quality Score as the basis for study inclusion, limiting inclusion to studies that were randomised and double-blind as a minimum (Jadad 1996b).

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,* resolving any disagreements by discussion (Higgins 2011). We assessed the following for each study.

1. Random sequence generation (checking for possible selection bias). We assessed the method used to generate the allocation sequence as: low risk of bias (any truly random process: random number table; computer random number generator); unclear risk of bias (method used to generate sequence not clearly stated). We excluded studies using a non-random process, which were therefore at high risk of bias (odd or even date of birth; hospital or clinic record number).
2. Allocation concealment (checking for possible selection bias). The method used to conceal allocation to interventions before assignment determines whether the intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment. We assessed the methods as: low risk of bias (telephone or central randomisation; consecutively numbered sealed opaque envelopes); unclear risk of bias (method not clearly stated). We excluded studies that did not conceal allocation, which were therefore at high risk of bias (open list).
3. Blinding of outcome assessment (checking for possible detection bias). We assessed the methods used to blind study participants and outcome assessors from knowledge of which intervention a participant received. We assessed the methods as: low risk of bias (study stated that it was blinded and

described the method used to achieve blinding: identical tablets; matched in appearance and smell); unclear risk of bias (study stated that it was blinded but did not provide an adequate description of how blinding was achieved). We excluded studies that were not double-blind and therefore at high risk of bias.

4. Size (checking for possible biases confounded by small size). Small studies have been shown to overestimate treatment effects, probably because the conduct of small studies is more likely to be less rigorous, allowing critical criteria to be compromised (Dechartres 2013; Nüesch 2010). Studies were considered to be at low risk of bias if they had 200 participants or more, at unclear risk if they had 50 to 200 participants, and at high risk if they had fewer than 50 participants.

Measures of treatment effect

We used risk ratio (or relative risk, RR) to establish statistical difference, and numbers needed to treat to benefit (NNT) and pooled percentages as absolute measures of benefit or harm.

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

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

Unit of analysis issues

We accepted only randomisation of the individual patient.

Dealing with missing data

The only likely issue with missing data in these studies was 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 (Moore 2005).

Assessment of heterogeneity

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

Assessment of reporting biases

We assessed the number of trials of average size amongst the included studies, with a RR of one (no effect), that would be needed to reduce any statistically significant result to one that fails to meet statistical significance (following Moore 2008).

Data synthesis

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 the number of participants randomised to each treatment group who took the study medication. Results for different doses were analysed separately.

For each study we converted the mean total pain relief (TOTPAR), summed pain intensity difference (SPID), VAS TOTPAR, or VAS SPID (see Appendix 4) values for the active and placebo groups to %maxTOTPAR or %maxSPID by division into the calculated maximum value (Cooper 1991). We then calculated the proportion of participants in each treatment group who achieved at least 50%maxTOTPAR using verified equations (Moore 1996; Moore 1997a; Moore 1997b). We 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 groups to calculate RR and NNT.

We accepted the following pain measures for the calculation of TOTPAR or SPID (in order of priority: see Appendix 4).

- 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 were available, we used 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 (CIs) using a fixed-effect model (Morris 1995). We calculated NNT and NNH with 95% CIs using the pooled number of events and the method of Cook and Sackett (Cook 1995). We assumed a statistically significant difference from control when the 95% CI of the RR did not include the number one.

Subgroup analysis and investigation of heterogeneity

We planned subgroup analyses to determine the effect of dose of ibuprofen, formulation, and presenting condition (pain model: dental versus other postoperative pain (Barden 2004)).

Ibuprofen is available as a standard (acid) formulation, and a number of fast-acting formulations. Fast-acting formulations not only produce more rapid pain relief, but better overall results, and a longer duration of action (Moore 2014; Moore 2015). For this reason, subgroup analysis is planned according to formulation of ibuprofen.

There are also issues around the dose of caffeine; if there were sufficient data we planned to analyse according to low (≤ 65 mg), medium (70 mg to 150 mg) and high (≥ 160 mg) doses of caffeine, but only single studies used doses other than 100 mg caffeine (50 mg and 200 mg).

A minimum of two studies and 200 participants had to be available in any subgroup analysis (Moore 1998), which was restricted to the primary outcome (50% pain relief over four to six hours) and the dose with the greatest amount of data. We would have determined significant differences between NNT, NNTp, or NNH for different groups in subgroup and sensitivity analyses using the z test (Tramèr 1997), but this was not appropriate.

Sensitivity analysis

No sensitivity analyses were planned.

RESULTS

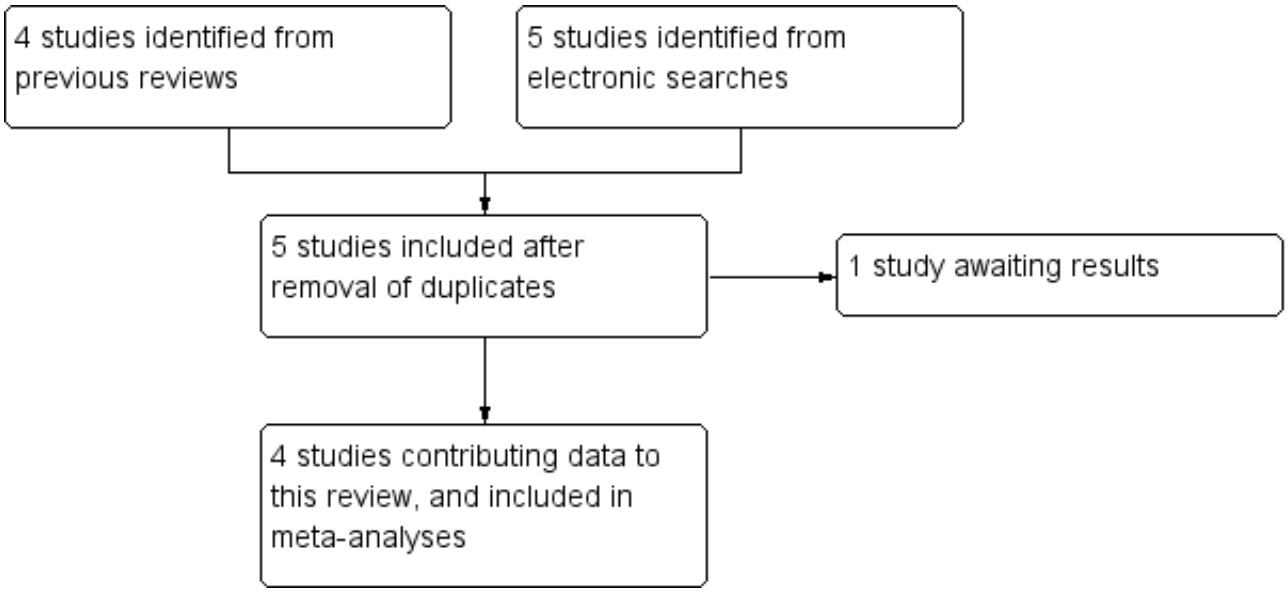
Description of studies

Results of the search

We identified five studies with 1501 participants fulfilling the inclusion criteria (Forbes 1991; Jain 1988; McQuay 1996; Sunshine 1996; NCT01929031). Four published studies (940 participants) were identified from the Cochrane review of caffeine as an analgesic adjuvant (Derry 2014) and current electronic searches (Forbes 1991; Jain 1988; McQuay 1996; Sunshine 1996). Details of individual studies are in the Characteristics of included studies table. One study (561 participants estimated) was scheduled to complete in March 2014 but remains unpublished and with no results posted on line (NCT01929031). Details are in the Characteristics of studies awaiting classification table.

See Figure 1 (Liberati 2009).

Figure 1. Flow diagram.



Included studies

We collected information on participant characteristics. Two of the included studies recruited men and women with pain following dental surgery (Forbes 1991; McQuay 1996), and two recruited women following episiotomy (Jain 1988; Sunshine 1996). The mean age in the studies was 25 years or less. Participants were required to be in good general health, and were excluded if they had a history of gastrointestinal disturbance, renal or hepatic disease, psychiatric disorder, or required medication that might interfere with the study results. In all studies participants took their medication when baseline pain reached moderate or severe intensity. Pain intensity and pain relief were measured at set time intervals after dosing on standard four- and five-point scales respectively, or 100 mm VAS.

All four of the included studies used placebo, and ibuprofen as an active comparator. A number of different treatments were administered.

- Ibuprofen 100 mg + caffeine 100 mg, n = 99 (two studies).
- Ibuprofen 200 mg + caffeine 100 mg, n = 174 (four studies).
- Ibuprofen 200 mg + caffeine 50 mg, n = 30 (one study).
- Ibuprofen 200 mg + caffeine 200 mg, n = 29 (one study).
- Ibuprofen at 50 mg to 400 mg, n = 448 (four studies).
- Placebo, n = 160 (four studies).

None of the studies specified the formulation of ibuprofen used, but none indicated that a fast-acting formulation was being used.

Excluded studies

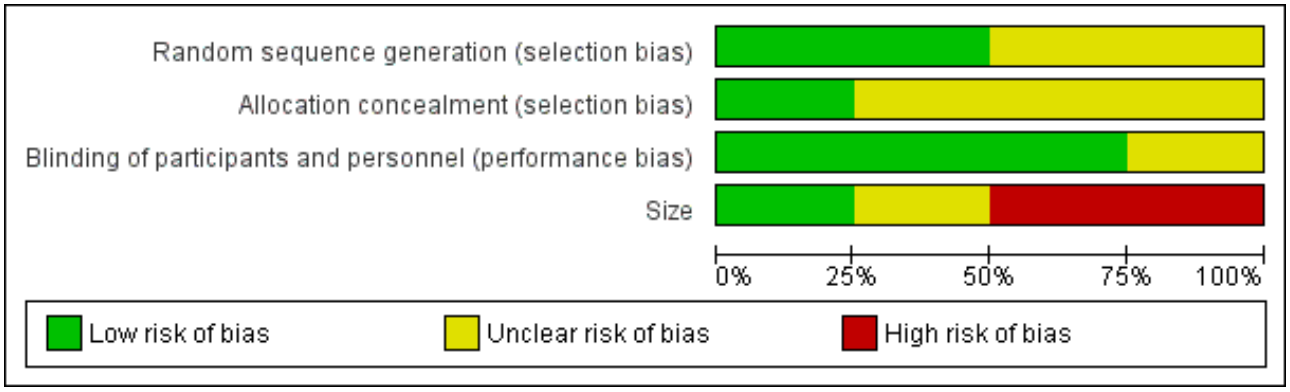
Excluded studies had been identified in other reviews (Derry 2009; Derry 2014), but the excluded studies in those reviews were checked to ensure that none might have included useful information for this review.

Risk of bias in included studies

All included studies were randomised and double-blind; one study scored 5/5 on the Oxford Quality Scale (McQuay 1996), and the remaining three scored 4/5 or 3/5 due to failure to report the method used to generate the randomisation schedule or blinding. It is likely that this was a failure of reporting rather than a flaw in the methods.

We assessed the risk of bias using the 'Risk of bias' tool (Figure 2). Details for each study are in the Characteristics of included studies table.

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



Allocation

All studies reported that they were randomised, but only one properly described the method used to generate the schedule and described the method used to conceal the random allocation (McQuay 1996), while in the other studies this was not described.

Blinding

All studies were double-blind and three adequately described how this was achieved (Forbes 1991; McQuay 1996; Sunshine 1996).

Other potential sources of bias

Treatment group size was an issue. None of the treatment groups in this review were large enough to be confident that bias would be avoided; studies had treatment group sizes that put them at high risk of bias, or with participant numbers in treatment arms that were on the borderline between high and unclear risk of bias.

Effects of interventions

See: **Summary of findings for the main comparison**

The small numbers of participants in most of these treatment groups meant that analysis was limited to the combinations of ibuprofen 200 mg + caffeine 100 mg and ibuprofen 100 mg + caffeine 100 mg. Comparisons of ibuprofen + caffeine with the same dose of ibuprofen alone have been done in a separate review on the effects of caffeine as an analgesic adjuvant (Derry 2014). Results for individual studies are provided in Appendix 5 (analgesia and use of rescue medication) and Appendix 6 (adverse events and withdrawals).

Participants with at least 50% pain relief

Ibuprofen 200 mg + caffeine 100 mg versus placebo

Four studies (334 participants) included comparisons of ibuprofen 200 mg + caffeine 100 mg (Forbes 1991; Jain 1988; McQuay 1996; Sunshine 1996).

- The proportion of participants with at least 50% pain relief with ibuprofen 200 mg + caffeine 100 mg was 59% (103/174, range 47% to 72%).
- The proportion of participants with at least 50% pain relief with placebo was 10% (16/160, range 0% to 33%).
- The relative benefit of treatment compared with placebo was 5.5 (95% CI 3.5 to 8.7); the NNT for one additional patient to benefit compared with placebo was 2.1 (1.8 to 2.5) (Analysis 1.1; Figure 3). Figure 4 shows the scatter plot for the individual studies.

Figure 3. Forest plot of comparison 1: Ibuprofen 200 mg + caffeine 100 mg versus placebo, outcome: 1.1 At least 50% maximum pain relief.

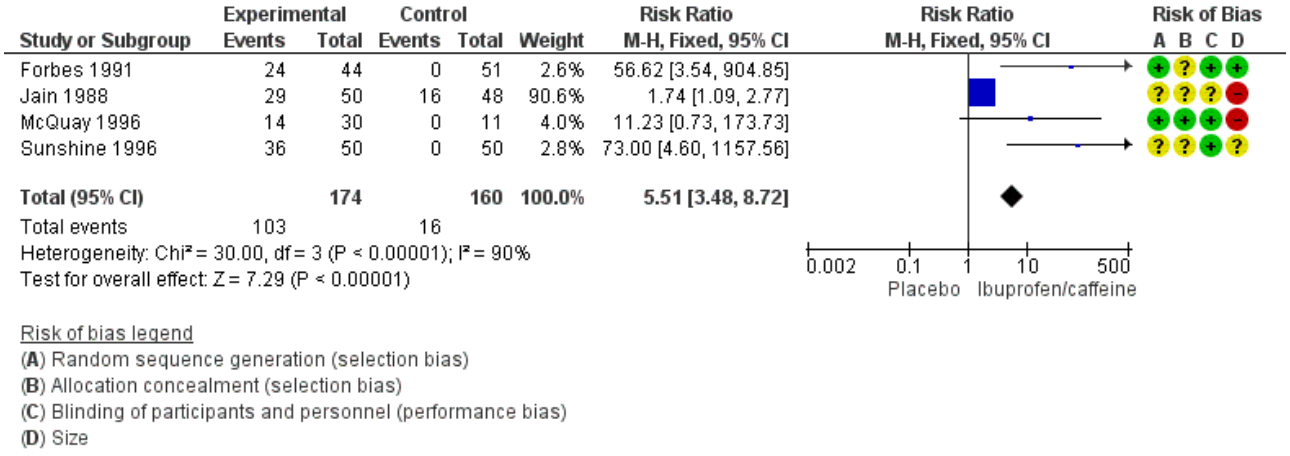
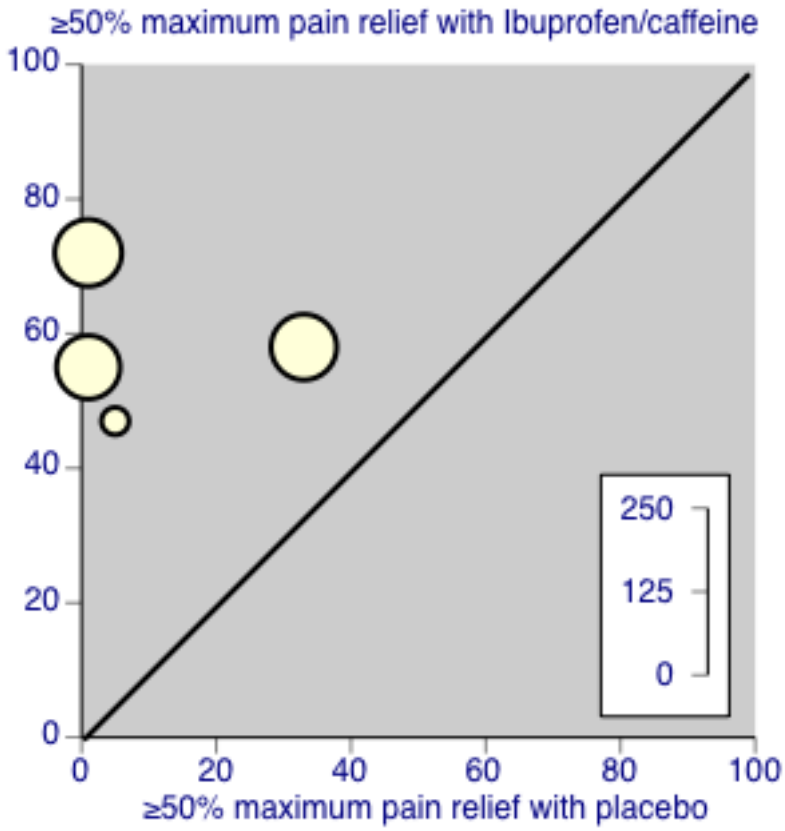


Figure 4. Studies comparing ibuprofen 200 mg + caffeine 100 mg with placebo.



Ibuprofen 100 mg + caffeine 100 mg versus placebo

Two studies (200 participants) included comparisons of ibuprofen 100 mg + caffeine 100 mg (Forbes 1991; Sunshine 1996).

- The proportion of participants with at least 50% pain relief with ibuprofen 100 mg + caffeine 100 mg was 43% (43/99, range 38% to 49%).
- The proportion of participants with at least 50% pain relief with placebo was 0% (0/101).
- The relative benefit of treatment compared with placebo was 45 (6.3 to 319); the NNT for one additional participant to benefit compared with placebo was 2.4 (1.9 to 3.1) (Analysis 2.1).

Use of rescue medication: Median (or mean) time to use of rescue medication

Only one study reported data for this outcome (Forbes 1991). The time to use of rescue medication was longer for all active treatments than placebo, but there were too few data for analysis.

Use of rescue medication: Participants remedicating

Ibuprofen 200 mg + caffeine 100 mg versus placebo

The number of participants remedicating was typically measured within six or eight hours.

Three studies (293 participants) included comparisons of ibuprofen 200 mg + caffeine 100 mg (Forbes 1991; Jain 1988; Sunshine 1996).

- The proportion of participants remedicating with ibuprofen 200 mg + caffeine 100 mg was 26% (38/144, range 2% to 57%).
- The proportion of participants remedicating with placebo was 60% (90/149, range 38% to 94%).
- The RR of treatment compared with placebo was 0.5 (0.4 to 0.6); the NNTp for one fewer participant to remedicate compared with placebo was 2.9 (2.2 to 4.3) (Analysis 1.2).

Ibuprofen 100 mg + caffeine 100 mg versus placebo

Two studies (200 participants) included comparisons of ibuprofen 100 mg + caffeine 100 mg (Forbes 1991; Sunshine 1996).

- The proportion of participants remedicating with ibuprofen 100 mg + caffeine 100 mg was 34% (34/99, range 0% to 68%).
- The proportion of participants remedicating with placebo was 66% (67/101, range 38% to 94%).
- The RR of treatment compared with placebo was 0.5 (0.4 to 0.7); the NNTp for one fewer participant to remedicate compared with placebo was 3.1 (2.2 to 5.3) (Analysis 2.2).

Adverse events

All studies reported the number of participants experiencing any adverse event.

Ibuprofen 200 mg + caffeine 100 mg versus placebo

Four studies (336 participants) included comparisons of ibuprofen 200 mg + caffeine 100 mg (Forbes 1991; Jain 1988; McQuay 1996; Sunshine 1996).

- The proportion of participants experiencing an adverse event with ibuprofen 200 mg + caffeine 100 mg was 11% (19/174, range 7% to 18%).
- The proportion of participants experiencing an adverse event with placebo was 6.2% (10/162, range 0% to 15%).
- The RR of treatment compared with placebo was 1.9 (0.91 to 3.8); the NNH was not calculated (Analysis 1.3).

Ibuprofen 100 mg + caffeine 100 mg versus placebo

Two studies (200 participants) included comparisons of ibuprofen 100 mg + caffeine 100 mg (Forbes 1991; Sunshine 1996).

- The proportion of participants experiencing an adverse event with ibuprofen 100 mg + caffeine 100 mg was 14% (14/99, range 4% to 24%).
- The proportion of participants experiencing an adverse event with placebo was 8% (8/101, range 0% to 15%).
- The RR of treatment compared with placebo was 1.8 (0.8 to 3.9); the NNH was not calculated (Analysis 2.3).

Serious adverse events

No study reported that there were serious adverse events, and three specifically reported that no serious adverse events occurred.

Withdrawals

Withdrawals due to lack of efficacy have been considered under 'Use of rescue medication' (above) and were not consistently reported.

There were no adverse event withdrawals, or other withdrawals.

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 aim was to assess the analgesic efficacy of ibuprofen and caffeine combination analgesics because caffeine is a known analgesic adjuvant for acute pain at doses of about 100 mg (Derry 2014). Ibuprofen combined with caffeine is not commonly available except in some South American countries, but the combination is easily achieved by taking ibuprofen tablets with caffeine tablets, a reasonably strong cup of coffee, or perhaps some other caffeine-containing drinks.

Summary of main results

Ibuprofen plus caffeine was effective when taken in combination as a single oral dose for treatment of established moderate or severe postoperative pain. NNT values for ibuprofen 200 mg + caffeine 100 mg of 2.1 (1.8 to 2.5) and for ibuprofen 100 mg + caffeine 100 mg of 2.4 (1.9 to 3.1) are amongst the lowest (best) values for analgesics in this pain model (Moore 2011a). These results for the proportion of participants achieving at least 50% of maximum pain relief were supported by similar low NNT values for remedication.

Moreover, these measured NNT values are close to the values predicted by a model for acute pain combinations (Moore 2012). It predicts that the absolute benefit increase for a combination will be the sum of the benefit increases of two different drugs. Using absolute benefit increases for appropriate doses of ibuprofen and caffeine from Cochrane reviews produces predicted NNT values in the range of 2.0 to 2.2 for ibuprofen 200 mg + caffeine 100 mg and 3.0 to 3.2 for ibuprofen 100 mg + caffeine 100 mg. The prediction is very accurate for ibuprofen 200 mg + caffeine 100 mg where there was most information, but somewhat less so for ibuprofen 100 mg + caffeine 100 mg where there was limited information for the combination here, and for ibuprofen 100 mg alone (Derry 2009).

As best we know, all four contributing studies used a standard ibuprofen acid formulation. Standard acid formulation ibuprofen has an NNT of 2.9 for 200 mg and 2.5 for 400 mg. Fast-acting formulations have NNTs of 2.1 for 200 mg and 400 mg (Moore 2014). The result for a standard acid formulation of ibuprofen combined with caffeine is therefore not unimportant, as it produces a more effective analgesic response from a less effective formulation. Moreover, it is at least possible that this can be accomplished by a low technology and low cost intervention, namely a caffeinated drink. Whether adding caffeine to a fast-acting formulation would achieve similar additional benefit is not known.

Overall completeness and applicability of evidence

The main limitation of the review was the small number of studies and participants. However, the general results are in accord with those known for ibuprofen in combination with codeine and paracetamol (Derry 2013a; Derry 2013b), for caffeine as an analgesic adjuvant (Derry 2014), and for combination drugs in acute pain (Moore 2011b; Moore 2012). The additional effect of caffeine (here with ibuprofen) is about the same magnitude as that found when doubling the dose of the analgesic (Derry 2014; Moore 2012).

The limited number of studies and participants did not allow for any sensible assessment of common or rare adverse events, although both ibuprofen and caffeine are widely studied.

Quality of the evidence

The studies themselves were of high quality but sample sizes were somewhat limited. Older studies in postpartum and dental pain tended historically to be small and meta-analyses of small trials are susceptible to overestimation of effects (Dechartres 2013; Nüesch 2010). The small study size explains the high I^2 values for some heterogeneity tests, though the spread of data was consistent between studies (Figure 4).

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 200 mg + caffeine 100 mg, an additional 938 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).

A large number of clinical trials relating to caffeine as an analgesic adjunct for acute pain have only been published in part, or in reviews, or without full publication or clinical trial reports made available. In one review, only four of 30 studies had previously

been published, and no additional information on unpublished studies was available in that review (Laska 1984). However, there is considerable evidence that a positive effect of caffeine occurs in these studies (Laska 1984; Sawynok 1993). In this circumstance it is unlikely that publication bias would play any role in changing either the direction or magnitude of the result.

Agreements and disagreements with other studies or reviews

A review of ibuprofen + caffeine in postsurgical pain did not calculate the beneficial effect of combinations compared with placebo (Li Wan Po 1998). A previous review had indicated that the addition of caffeine to analgesic drugs for acute pain produced a significant increase in the number of people achieving good levels of pain relief (Derry 2014). We know of no previous reviews with the analyses reported here.

AUTHORS' CONCLUSIONS

Implications for practice

For people with moderate-to-severe acute pain

A single tablet of ibuprofen 200 mg taken with a dose of up to 100 mg of caffeine produces a strong analgesic effect. Better pain relief can come at a lower dose of drug. In the absence of medicines with a fixed dose combination of ibuprofen + caffeine, a single tablet of ibuprofen 200 mg taken with a strong cup of coffee or a caffeinated drink containing about 100 mg of caffeine produces analgesia as good as or better than taking two tablets of ibuprofen 200 mg without the coffee or drink.

For clinicians

Especially for people who have frequent acute pain, or where it may be important to limit exposure to NSAIDs, the use of a lower dose of ibuprofen together with a source of caffeine amounting to 100 mg can produce very good levels of pain relief.

For policy-makers

Population exposure to NSAIDs is a potential public health risk. Risks are largely dose related, and advice about the concomitant use of low dose ibuprofen together with caffeine potentially reduces population exposure and risk.

For funders

This is potentially a low cost way of achieving good pain relief. Ideally, fixed dose formulations would achieve that, but in their absence there are alternative ways to deliver good pain relief at low cost.

Implications for research

General

Very considerable research has been done on analgesic effects of ibuprofen in single dose analgesic trials to test its analgesic efficacy. Often it is used as a standard analgesic at the 400 mg dose. This may be why the current total of participants in comparisons of ibuprofen 400 mg with placebo amounts to some 6000, with another 2000 in comparisons of ibuprofen 200 mg with placebo. By contrast, only 334 participants contributed to the main analysis of ibuprofen 200 mg + caffeine 100 mg and placebo.

This is barely adequate to measure the NNT accurately, and quite inadequate for any assessment of adverse events.

Given the very good pain relieving effects of the combination, and the potential to minimise population exposure to NSAIDs (as with fast-acting ibuprofen formulations), as well as to minimise exposure to NSAID and opioid combinations, research on this combination of ibuprofen plus caffeine in acute pain should have a higher priority.

Generalisability could be confirmed by including older participants in future studies, although we know of no reason why age should influence the result.

Design

The current design of acute pain studies is well understood, and has proven to be robust.

Measurement (endpoints)

Endpoints in these studies have been extensively validated, as have standard pain scoring systems. The main outcome used is one valued by patients with pain, and has economic benefits in most circumstances.

Comparison between active treatments

The standardised nature of the study design means that indirect comparisons with placebo are valid, as evidenced by independent research on the topic. There is, however, a very large body of information amenable to network meta-analysis. While unlikely to provide much in the way of new insights, it could prove an invaluable tool for testing network meta-analytical methods.

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CHARACTERISTICS OF STUDIES

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

Forbes 1991

Methods	Multicentre, randomised, double-blind, placebo-controlled, parallel group study, with a single oral dose administered at the onset of moderate or severe pain Eight-hour study period, with assessments at baseline, 0.5, one, two, three, four, five, six, seven, and eight hours post-dose
Participants	Dental surgery - third molar removal Caffeine-containing foods and beverages were prohibited for four hours before taking study medication and for the following 8-hour study period Patients were at least 15 years of age N = 362 (298 for efficacy) M: 121, F: 177 Mean age: 22 years
Interventions	Ibuprofen 100 mg + caffeine 100 mg, n = 49 for efficacy Ibuprofen 100 mg, n = 49 for efficacy Ibuprofen 200 mg + caffeine 100 mg, n = 44 for efficacy Ibuprofen 200 mg, n = 48 for efficacy Ibuprofen 50 mg, n = 57 for efficacy Placebo, n = 51 for efficacy
Outcomes	PI: standard 4-point scale PR: standard 5-point scale PGE: standard 5-point scale Withdrawals and dropouts Serious adverse events
Notes	Oxford Quality Score: R1, DB2, W1. Total = 4

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Gives reference to methods in earlier reports that are low risk
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"identically appearing capsules"

Forbes 1991 *(Continued)*

Size	Low risk	< 50 participants in relevant treatment groups

Jain 1988

Methods	Single-centre, randomised, double-blind, placebo-controlled, parallel group study, with a single oral dose administered after the onset of moderate or severe pain Six-hour study period, with assessments at baseline, 0.5, one, two, three, four, five, and six hours post-dose
Participants	Women with moderate or severe pain following episiotomy N = 150 (147 for efficacy) Mean age 23 years
Interventions	Ibuprofen 200 mg + caffeine 100 mg, n = 50 Ibuprofen 400 mg, n = 49 Placebo, n = 48
Outcomes	PI: standard 4-point scale PR: 5-point scale marked with 0 to 100% relief at different points 0-4 Time of meaningful relief PGE: standard 5-point scale Withdrawals and dropouts Serious adverse events
Notes	Oxford Quality Score: R1, DB1, W1. Total = 3

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No details of randomisation method given
Allocation concealment (selection bias)	Unclear risk	No details of concealment method given
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No details of blinding method given
Size	High risk	49 and 50 participants in relevant treatment groups

McQuay 1996

Methods	Single-centre, randomised, double-blind, placebo-controlled, parallel group study, with a single oral dose administered after onset of moderate or severe pain Eight-hour study period with first two hours in hospital. Time points of individual assessments not reported
Participants	Dental surgery - third molar removal. No caffeine-containing products from midnight on the evening before surgery and no other analgesics in the 12 hours before surgery N = 164 (161 for efficacy) M: 59, F: 102 Mean age: 25 years
Interventions	Ibuprofen 200 mg + caffeine 50 mg, n = 30 for efficacy Ibuprofen 200 mg + caffeine 100 mg, n = 30 for efficacy Ibuprofen 200 mg + caffeine 200 mg, n = 29 for efficacy Ibuprofen 200 mg, n = 31 for efficacy Ibuprofen 400 mg, n = 30 for efficacy Placebo, n = 11 for efficacy
Outcomes	PI: standard 4-point scale, an 8-word scale (randomly placed words ranging from 'no pain' to 'excruciating', scored 0 - 7), and a 100 mm VAS PR: standard 5-point scale and a 100 mm VAS PGE: standard 5-point scale Withdrawals and dropouts Serious adverse events
Notes	Oxford Quality Score: R2, DB2, W1. Total = 5

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised using a random number computer program
Allocation concealment (selection bias)	Low risk	Remote packaging, labelled only with treatment number
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"identical matching capsules"
Size	High risk	< 50 participants in relevant treatment groups

Sunshine 1996

Methods	Single-centre, randomised, double-blind, placebo-controlled, parallel group study, with a single oral dose administered after the onset of severe pain Six-hour study period, with assessments at baseline, 0.5, one, two, three, four, five, and six hours post-dose
Participants	Postepisiotomy pain No medications that might confound the interpretation of efficacy, or caffeine-containing food and beverages were permitted during the six hours before and after dosing Participants aged 18 years or older N = 305 (302 for efficacy) All F Mean age 24 years
Interventions	Ibuprofen 100 mg + caffeine 100 mg, n = 50 Ibuprofen 100 mg, n = 51 Ibuprofen 200 mg + caffeine 100 mg, n = 50 Ibuprofen 200 mg, n = 50 Ibuprofen 50 mg, n = 51 Placebo, n = 50
Outcomes	PI: standard 4-point scale PR: standard 5-point scale PGE: 4-point categorical scale (0 = poor, 1 = fair, 2 = good, 3 = excellent) Withdrawals and dropouts Serious adverse events
Notes	Oxford Quality Score: R1, DB2, W1. Total = 4

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"All medications were dispensed as capsules"
Size	Unclear risk	50 participants in relevant treatment groups

DB: double-blind; F: female; N - number of participants in study; n: number of participants in treatment arm; PGE: Patient Global Evaluation of treatment; PI: pain intensity; PR: pain relief; R: randomised; VAS: visual analogue scale

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

NCT01929031

Methods	Randomised, double-blind, placebo-controlled, parallel group study
Participants	Surgical extraction of 3 - 4 impacted third molar(s), with a minimum of two mandibular extractions Age: 18 - 55 years Pain ≥ 5/10 within 4.5 hours of end of surgery N = 561
Interventions	Ibuprofen 400 mg + caffeine 100 mg Ibuprofen 400 mg Caffeine 100 mg Placebo
Outcomes	Time-weighted sum of pain relief (PAR) and pain intensity difference (PID) from 0 to 8 hours (SPRID0-8h) 2 hours SPRID Time to rescue Time to meaningful relief
Notes	Completed March 2014 but results not yet available

N: number of participants in study

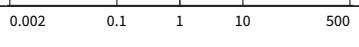
DATA AND ANALYSES

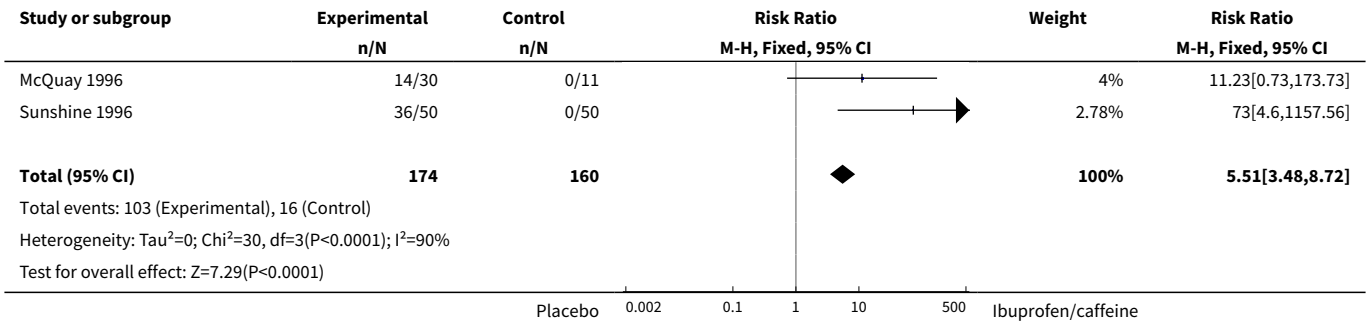
Comparison 1. Ibuprofen 200 mg + caffeine 100 mg versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 At least 50% of maximum pain relief	4	334	Risk Ratio (M-H, Fixed, 95% CI)	5.51 [3.48, 8.72]
2 Remedication	3	293	Risk Ratio (M-H, Fixed, 95% CI)	0.46 [0.35, 0.60]
3 Adverse events	4	336	Risk Ratio (M-H, Fixed, 95% CI)	1.86 [0.91, 3.79]

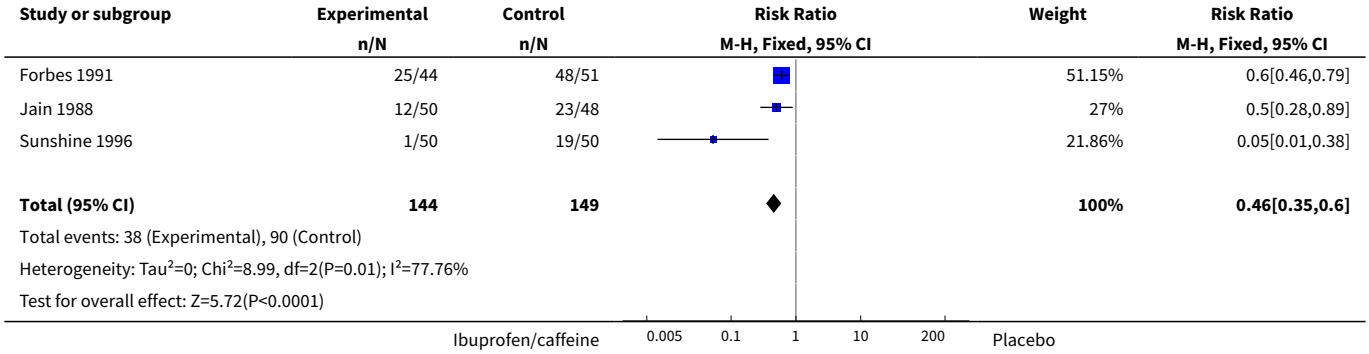
Analysis 1.1. Comparison 1 Ibuprofen 200 mg + caffeine 100 mg versus placebo, Outcome 1 At least 50% of maximum pain relief.

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Forbes 1991	24/44	0/51		2.58%	56.62[3.54,904.85]
Jain 1988	29/50	16/48		90.65%	1.74[1.09,2.77]

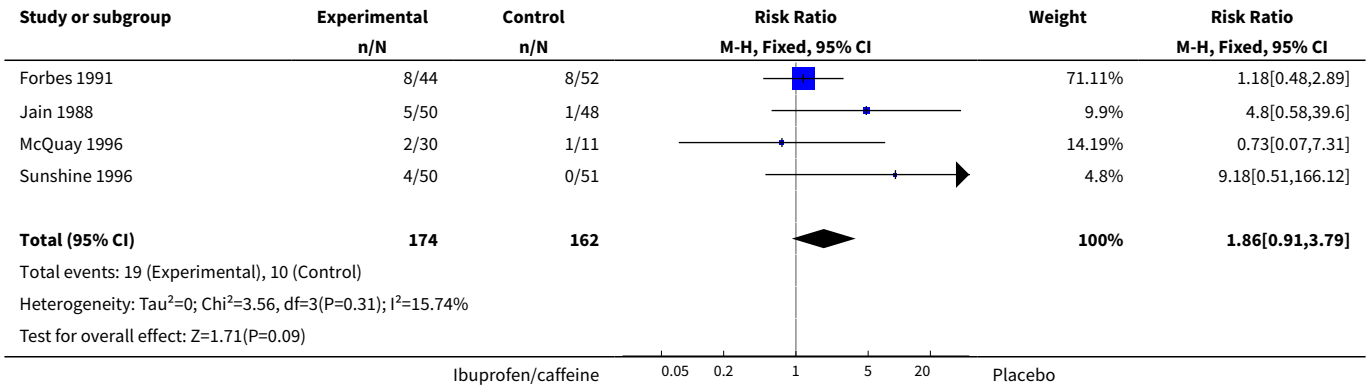




Analysis 1.2. Comparison 1 Ibuprofen 200 mg + caffeine 100 mg versus placebo, Outcome 2 Remedication.



Analysis 1.3. Comparison 1 Ibuprofen 200 mg + caffeine 100 mg versus placebo, Outcome 3 Adverse events.



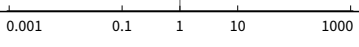
Comparison 2. Ibuprofen 100 mg + caffeine 100 mg versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 At least 50% of maximum pain relief	2	200	Risk Ratio (M-H, Fixed, 95% CI)	44.82 [6.29, 319.49]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Remedication	2	200	Risk Ratio (M-H, Fixed, 95% CI)	0.53 [0.41, 0.67]
3 Adverse events	2	201	Risk Ratio (M-H, Fixed, 95% CI)	1.80 [0.83, 3.90]

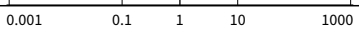
Analysis 2.1. Comparison 2 Ibuprofen 100 mg + caffeine 100 mg versus placebo, Outcome 1 At least 50% of maximum pain relief.

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Forbes 1991	19/49	0/51		49.5%	40.56[2.52,653.88]
Sunshine 1996	24/50	0/50		50.5%	49[3.06,784.26]
Total (95% CI)	**99**	**101**		**100%**	**44.82[6.29,319.49]**
Total events: 43 (Experimental), 0 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.01, df=1(P=0.92); I^2=0%					
Test for overall effect: Z=3.79(P=0)					



Analysis 2.2. Comparison 2 Ibuprofen 100 mg + caffeine 100 mg versus placebo, Outcome 2 Remedication.

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Forbes 1991	34/49	48/51		70.69%	0.74[0.6,0.9]
Sunshine 1996	0/50	19/50		29.31%	0.03[0,0.41]
Total (95% CI)	**99**	**101**		**100%**	**0.53[0.41,0.67]**
Total events: 34 (Experimental), 67 (Control)					
Heterogeneity: Tau^2=0; Chi^2=15.36, df=1(P<0.0001); I^2=93.49%					
Test for overall effect: Z=5.12(P<0.0001)					



Analysis 2.3. Comparison 2 Ibuprofen 100 mg + caffeine 100 mg versus placebo, Outcome 3 Adverse events.

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Forbes 1991	12/49	8/52		93.95%	1.59[0.71,3.56]
Sunshine 1996	2/50	0/50		6.05%	5[0.25,101.58]
Total (95% CI)	**99**	**102**		**100%**	**1.8[0.83,3.9]**
Total events: 14 (Experimental), 8 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.53, df=1(P=0.47); I^2=0%					
Test for overall effect: Z=1.49(P=0.14)					

APPENDICES

Appendix 1. Search strategy for CENTRAL

1. MeSH descriptor: Ibuprofen this term only
2. (ibuprofen or brufen or propionic acid or "isobutylphenyl propionic acid")
3. MeSH descriptor: Caffeine this term only
4. Caffeine:ti,ab,kw
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*")):ti,ab,kw
10. ((post-surgical near/4 pain*) or ("post surgical" near/4 pain*) or (post-surgery near/4 pain*)):ti,ab,kw
11. ("pain-relief after surg*" or "pain following surg*" or "pain control after"):ti,ab,kw
12. (("post surg*" or post-surg*) and (pain* or discomfort)):ti,ab,kw
13. ((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
14. ((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
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 2. Search strategy for MEDLINE (via OVID)

1. Ibuprofen/ or (ibuprofen or brufen or propionic acid or isobutylphenyl propionic acid).mp.
2. Caffeine/ or caffeine.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 3. Search strategy for EMBASE (via Ovid)

1. Ibuprofen/ or (ibuprofen or brufen or propionic acid or isobutylphenyl propionic acid).mp.
2. Caffeine/ or caffeine.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 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.

Visual analogue scale (VAS): 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 co-ordination are needed, which can be difficult postoperatively or with neurological disorders.

Total pain relief (TOTPAR): 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.

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

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

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

Appendix 5. Results for individual studies: efficacy

Study ID	Condition	Treatment	Efficacy outcome	Participants with outcome	Remedication	Time to remedication (h)
Forbes 1991	Dental	(1) Ibuprofen 100 mg + caffeine 100 mg, n = 49 (2) Ibuprofen 100 mg, n = 49 (3) Ibuprofen 200 mg + caffeine 100 mg, n = 44 (4) Ibuprofen 200 mg, n = 48 (5) Placebo, n = 51	TOTPAR 6 hours: (1) 8.95 (2) 6.67 (3) 12.1 (4) 8.65 (5) 2.21	≥ 50% max PR: (1) 19/49 (2) 13/49 (3) 24/44 (4) 17/48 (5) 0/51	By 8 hours (1) 34/49 (2) 38/49 (3) 25/44 (4) 38/48 (5) 48/51	Mean: (1) 5.4 (2) 4.8 (3) 6.1 (4) 5.1 (5) 3.0 Note remedication after 8 hours censored at 8 hours
Jain 1988	Postepisiotomy	(1) Ibuprofen 200 mg + caffeine 100 mg, n = 50 (2) Ibuprofen 400 mg, n = 49 (3) Placebo, n = 48	TOTPAR 6 hours: (1) 13.9 (2) 14.4 (3) 8.6	(1) 29/50 (2) 30/49 (3) 16/48	(1) 12/50 (2) 10/49 (3) 23/48	No data
McQuay 1996	Dental	(1) Ibuprofen 200 mg + caffeine 50 mg, n = 30 (2) Ibuprofen 200 mg + caffeine 100 mg, n = 30 (3) Ibuprofen 200 mg + caffeine 200 mg, n = 29 (4) Ibuprofen 200 mg, n = 31 (5) Ibuprofen 400 mg, n = 30 (6) Placebo, n = 11	TOTPAR 6 hours: (1) 7.0 (2) 10.3 (3) 9.5 (4) 3.0 (5) 5.5 (6) 0	≥ 50% max PR: (1) 8/30 (2) 14/30 (3) 12/29 (4) 2/31 (5) 5/30 (6) 0/11	No data	No data
Sunshine 1996	Postepisiotomy	(1) Ibuprofen 100 mg + caffeine 100 mg, n = 50 (2) Ibuprofen 100 mg, n = 51 (3) Ibuprofen 200 mg + caffeine 100 mg, n = 50 (4) Ibuprofen 200 mg, n = 50 (5) Placebo, n = 50	TOTPAR 6 hours: (1) 10.9 (2) 8.2 (3) 14.9 (4) 13.9 (5) 2.2	≥ 50% max PR: (1) 24/50 (2) 17/51 (3) 36/50 (4) 33/50 (5) 0/50	(1) 0/50 (2) 0/51 (3) 1/50 (4) 0/50 (5) 19/51	No data

PR: pain relief; TOTPAR: total pain relief

Appendix 6. Results for individual studies: adverse events

Study ID	Condition	Treatment	Any adverse events	Serious adverse events
Forbes 1991	Dental	(1) Ibuprofen 100 mg + caffeine 100 mg, n = 49 (2) Ibuprofen 100 mg, n = 49 (3) Ibuprofen 200 mg + caffeine 100 mg, n = 44 (4) Ibuprofen 200 mg, n = 48 (5) Placebo, n = 51	(1) 12/49 (2) 5/49 (3) 8/44 (4) 6/48 (5) 8/52	None
Jain 1988	Postepisiotomy	Ibuprofen 200 mg + caffeine 100 mg, n = 50 Ibuprofen 400 mg, n = 49 Placebo, n = 48	(1) 5/50 (2) 2/49 (3) 1/48	Not mentioned
McQuay 1996	Dental	(1) Ibuprofen 200 mg + caffeine 50 mg, n = 30 (2) Ibuprofen 200 mg + caffeine 100 mg, n = 30 (3) Ibuprofen 200 mg + caffeine 200 mg, n = 29 (4) Ibuprofen 200 mg, n = 31 (5) Ibuprofen 400 mg, n = 30 (6) Placebo, n = 11	(1) 1/30 (2) 2/30 (3) 0/29 (4) 4/31 (5) 2/30 (6) 1/11	None
Sunshine 1996	Postepisiotomy	(1) Ibuprofen 100 mg + caffeine 100 mg, n = 50 (2) Ibuprofen 100 mg, n = 51 (3) Ibuprofen 200 mg + caffeine 100 mg, n = 50 (4) Ibuprofen 200 mg, n = 50 (5) Placebo, n = 50	(1) 2/50 (2) 4/51 (3) 4/50 (4) 1/50 (5) 0/51	None

WHAT'S NEW

Date	Event	Description
29 May 2019	Amended	Contact details updated.
11 October 2017	Review declared as stable	No new studies likely to change the conclusions are expected.

HISTORY

Protocol first published: Issue 2, 2015
Review first published: Issue 7, 2015

Date	Event	Description
27 February 2017	Review declared as stable	See Published notes.

CONTRIBUTIONS OF AUTHORS

SD and RAM wrote the protocol. RAM and SD carried out searches, assessed studies for inclusion, and extracted data. PW acted as arbitrator. All authors were involved in writing the review. RAM will be responsible for updating the review.

DECLARATIONS OF INTEREST

SD has no conflicts relating to this review or any similar product.

PW has no conflicts relating to this review or any similar product.

RAM has no conflicts relating to this review or any similar product.

For transparency, SD, PW, and RAM have received research support from charities, government, and industry sources at various times, but none relate to this review. SD, PW, and RAM are funded by the NIHR for work on a series of reviews informing the unmet need of chronic pain and providing the evidence for treatments of pain.

SOURCES OF SUPPORT

Internal sources

- Oxford Pain Relief Trust, UK.

  General institutional support

External sources

- No sources of support supplied

NOTES

In February 2017, the review authors ran restricted searches and found one new study in clinicaltrials.gov (NCT01929031). They had been notified by the new study's authors in November 2016 that the first results were available online. The study uses a different dose of ibuprofen plus caffeine from that in the Cochrane review, and does not report data that easily allow calculation of the review's primary outcome. However, it does appear to confirm the findings.

The review authors have requested information that would allow calculation of the review's primary outcome, and will consider updating the review if that becomes available and is likely to change the conclusions. This review is currently considered up to date.

INDEX TERMS

Medical Subject Headings (MeSH)

Acute Pain [*drug therapy]; Analgesics, Non-Narcotic [*administration & dosage] [adverse effects]; Caffeine [*administration & dosage] [adverse effects]; Drug Combinations; Ibuprofen [*administration & dosage] [adverse effects]; Numbers Needed To Treat; Pain, Postoperative [*drug therapy]; Randomized Controlled Trials as Topic

MeSH check words

Adult; Humans