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Single dose oral dexibuprofen [S(+)-ibuprofen] for acute postoperative pain in adults (Review)

Derry S, Best J, Moore RA

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[Intervention Review]

Single dose oral dexibuprofen [S(+)-ibuprofen] for acute postoperative pain in adults

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ABSTRACT

Background

This review is an update of a previously published review in The Cochrane Database of Systematic Reviews Issue 3, 2009 on single dose oral dexibuprofen (S(+)-ibuprofen) for acute postoperative pain in adults.

Dexibuprofen is a non-steroidal anti-inflammatory drug (NSAID) licensed for use in rheumatic disease and other musculoskeletal disorders in the UK, and widely available in other countries worldwide. It is an active isomer of ibuprofen. This review sought to evaluate the efficacy and safety of oral dexibuprofen in acute postoperative pain, using clinical studies in patients with established pain, and with outcomes measured primarily over four to six hours, using standard methods. This type of study has been used for many decades to establish that drugs have analgesic properties.

Objectives

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

Search methods

Searches were run for the original review in 2009 and subsequent searches have been run in August 2013. We did not find any new published studies as a result of the updated search.

We searched for randomised studies of dexibuprofen in acute postoperative pain in MEDLINE, EMBASE, and CENTRAL (*The Cochrane LIbrary*), and for clinical trial reports and synopses of published and unpublished studies from Internet sources.

Selection criteria

Randomised, double blind, placebo-controlled clinical studies of oral dexibuprofen for relief of acute postoperative pain in adults.

Data collection and analysis

Two review authors independently assessed study quality and extracted data. We extracted pain relief or pain intensity data and converted it into the dichotomous outcome of number of participants with at least 50% pain relief over four to six hours, from which relative risk and number needed to treat to benefit (NNT) were calculated. Numbers of participants using rescue medication over specified time periods, and time to use of rescue medication, were sought as additional measures of efficacy. We collected information on adverse events and withdrawals.

Main results

New data were identified for this update in one unpublished trial synopsis (BR1160 1995) in addition to the single study (Dionne 1998) that was included in the original review. In both studies dexibuprofen gave high levels of response, with 51/96 (53%) participants experiencing at least 50% pain relief with dexibuprofen 200 mg and 35/50 (70%) with dexibuprofen 400 mg, compared with 75/147 (51%) with racemic ibuprofen 400 mg, and 12/62 (13%) with placebo. The numbers of participants was too small to calculate NNTs with any meaning. The median time to additional analgesic use was greater than four hours for all active therapies, but about two hours for placebo.

Adverse events were generally of mild or moderate intensity and consistent with events normally associated with anaesthesia and surgery. There were no serious adverse events or deaths.

Additional data did not alter the conclusions from the earlier review.

Authors' conclusions

The information from these two studies in acute postoperative pain suggested that dexibuprofen may be a useful analgesic, but at doses not very different from racemic ibuprofen, for which considerably more evidence exists.

PLAIN LANGUAGE SUMMARY

Single dose oral dexibuprofen 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. People with pain are used to test pain killers. They have often had wisdom teeth removed. The pain is often treated with pain killers given by mouth. Results can be applied to other forms of acute pain.

A series of reviews looks at how good pain killers are. This review looks at a drug called dexibuprofen. This is a form of ibuprofen. It is thought to give the same pain relief at a lower dose.

We found two clinical trials with 313 people. Dexibuprofen at 200 mg or 400 mg single doses probably produced useful pain relief. The small number of studies, and of people in them, meant that no sensible results about benefit or harm after taking the drug were available.

SUMMARY OF FINDINGS

Summary of findings for the main comparison.

Dexibuprofen compared with placebo for acute postoperative pain

Patient or population: Adults with moderate or severe acute postoperative pain

Settings: Community or hospital

Intervention: Dexibuprofen 200 mg or 400 mg

Comparison: Placebo

Outcomes	Probable outcome with		NNT or NNH and/or relative effect (95% CI)	No of studies, attacks, events	Quality of the evidence (GRADE)	Comments
	comparator	intervention				
At least 50% of maximum pain relief over 4 to 6 hours	Insufficent data				Very low	Quality of evidence very low because of small numbers of studies and participants
Participants with at least 1 adverse event	No data				Very low	
Participants with a serious adverse event	No serious adverse events				Very low	
Deaths	No deaths				Very low	

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.

BACKGROUND

Description of the condition

This review is an update of a previously published review in The Cochrane Database of Systematic Reviews Issue 3, 2009 on Single dose oral dexibuprofen [S(+)-ibuprofen] for acute postoperative pain in adults (Moore 2009).

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 studies 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 studies

Single dose studies 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 studies.

Clinical studies measuring the efficacy of analgesics in acute pain have been standardised over many years (McQuay 2012). They 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 studies 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). Participants 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 studies of longer duration.

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

Dexibuprofen

Dexibuprofen is a non-steroidal anti-inflammatory drug (NSAID), sporadically available in different countries, and with no consistent licensed indications. In England in 2012 only 4500 prescriptions were issued in primary care, for 300 mg and 400 mg tablets. This compares with almost 5.7 million prescriptions for naproxen and 4.6 million prescriptions for ibuprofen in the same period (PACT 2013).

Dexibuprofen (trade names Deltaran and Seractil) is the single pharmacologically active enantiomer of racemic ibuprofen. Half doses of dexibuprofen are not entirely equivalent to full doses of ibuprofen (Gabard 1995), since there is hepatic conversion of some of the inactive enantiomer to the active form when the racemic mixture is given (Lee 1985). In general, the dexibuprofen dose given is half that of ibuprofen, although this may not be the case in some ethnic groups, particularly the Chinese (Zheng 2008). In arthritis, daily doses of 800 mg dexibuprofen produced as much analgesia as 200 mg celecoxib (Hawel 2003), and 1200 mg dexibuprofen as much as 2400 mg ibuprofen (Singer 2000). A review by Phleps 2001 reported clinical efficacy in rheumatoid arthritis, ankylosing spondylitis, osteoarthritis of the hip, osteoarthritis of the knee, lumbar vertebral syndrome, distortion of the ankle joint and dysmenorrhoea.

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.

Why it is important to do this review

We could find no systematic review on the efficacy of dexibuprofen in acute pain. While a number of studies have reported equivalent efficacy for reduced doses of dexibuprofen compared with racemic ibuprofen (or other NSAIDs) in chronic musculoskeletal pain, it is not known whether the same is found in acute pain. Lower doses of NSAIDs may result in better tolerability. This update was prompted by the availability of an unpublished clinical trial synopsis.

OBJECTIVES

To assess the efficacy and adverse effects of single dose oral dexibuprofen for acute postoperative pain using methods that permit comparison with other analgesics evaluated in standardised studies 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 dexibuprofen 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 phase were presented separately.

We excluded:

- 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), pain of at least moderate intensity would be equated to greater than 30 mm (Collins 1997).

Types of interventions

Dexibuprofen administered as a single oral dose, compared with matched placebo or racemic ibuprofen, given for relief of postoperative pain.

Types of outcome measures

We collected the following data where available:

- participant characteristics;
- patient reported pain at baseline (physician, nurse or carer reported pain were 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 event).

Search methods for identification of studies

Electronic searches

We searched the following electronic databases:

- The Cochrane Central Register of Controlled Trials (CENTRAL) on *The Cochrane Library*, (Issue 2, 2009 for the original review and Issue 7, 2013 for this update);
- MEDLINE via Ovid (to May 2009 for the original review and from 2008 to 19 August 2013 for this update);
- EMBASE via Ovid (to May 2009 for the original review and from 2008 to 19 August 2013 for this update).
- Oxford Pain Relief Database (Jadad 1996a).

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

Searching other resources

We searched for additional studies in reference lists of retrieved articles and reviews. We also searched the PhRMA clinical study results 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.

The unpublished clinical trial synopsis included in this update was made available by Reckitt Benckiser.

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 into RevMan 5.2 (RevMan 2012).

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.

We also completed a Risk of bias in included studies 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 participant.

Assessment of heterogeneity

We planned to examine 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 planned 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 no subgroup analysis as the data set was known to be small. We required a minimum of two studies and 200 participants to be available in any subgroup analysis (Moore 1998).

Sensitivity analysis

We planned no sensitivity analysis as the data set was known to be small. We required a minimum of two studies and 200 participants to be available in any sensitivity analysis (Moore 1998).

RESULTS

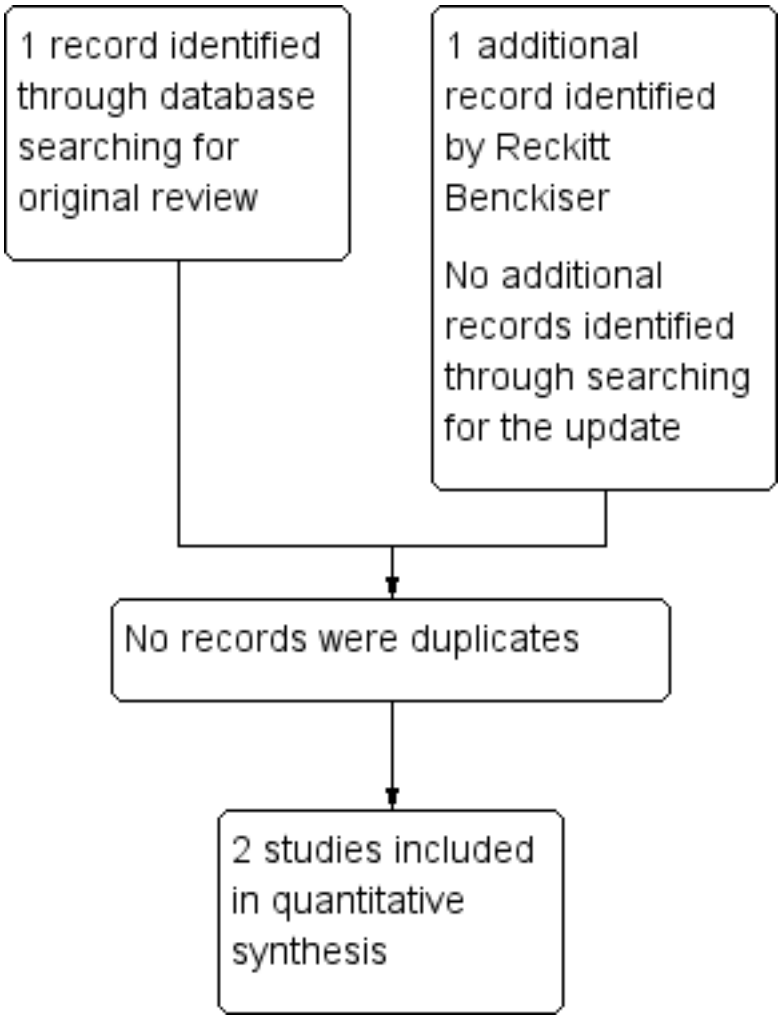
Description of studies

This is an update of a review first published in 2009 (Moore 2009).

Results of the search

No new studies were found through an updated search. Reckitt Benckiser provided a clinical trial synopsis of a previously unpublished study (BR1160 1995) that did not appear on any search, including clinicaltrials.gov or the WHO portal. Figure 1 shows the flow diagram for included studies.

Figure 1. Study flow diagram.



Included studies

Two studies satisfied inclusion criteria. One study (Dionne 1998) was published in a peer review journal and included in the earlier review. The other (BR1160 1995) was available only as a clinical trial synopsis; this new study increased the total number of participants by 137.

Both studies recruited participants with pain following third molar extraction, aged 16 years or older (mean age 22 and 25 years), and the majority were female (65%). There was a washout period for analgesics or other drugs likely to influence pain perception of 24 or 48 hours. Study medication was administered when pain was of moderate or severe intensity. Dionne 1998 used standard pain intensity (4-point) and pain relief (5-point) scales, but BR1160 1995 measured only pain intensity using a non-standard 9-point scale.

There were 318 participants in total, of whom 313 provided data for analysis; 97 received dexibuprofen (S(+) ibuprofen) 200 mg, 50 received dexibuprofen 400 mg, 101 received racemic ibuprofen 400 mg, and 65 received placebo.

Full details are in the Characteristics of included studies table.

Excluded studies

One study excluded in the original review was a pharmacokinetic study without pain measures (Jamali 1999). Details are in Characteristics of excluded studies table.

Risk of bias in included studies

Included studies were both randomised and double-blind and provided information about withdrawals and dropouts. The methodological quality of the studies was determined using the Oxford Quality Scale. BR1160 1995 scored 5/5 points whereas Dionne 1998 only scored 4/5 as it did not adequately describe sequence generation. Details for individual studies are provided in the Characteristics of included studies table.

In addition we created a Risk of bias in included studies table which considered random sequence generation, allocation concealment, blinding, and study size (Figure 2; Figure 3).

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

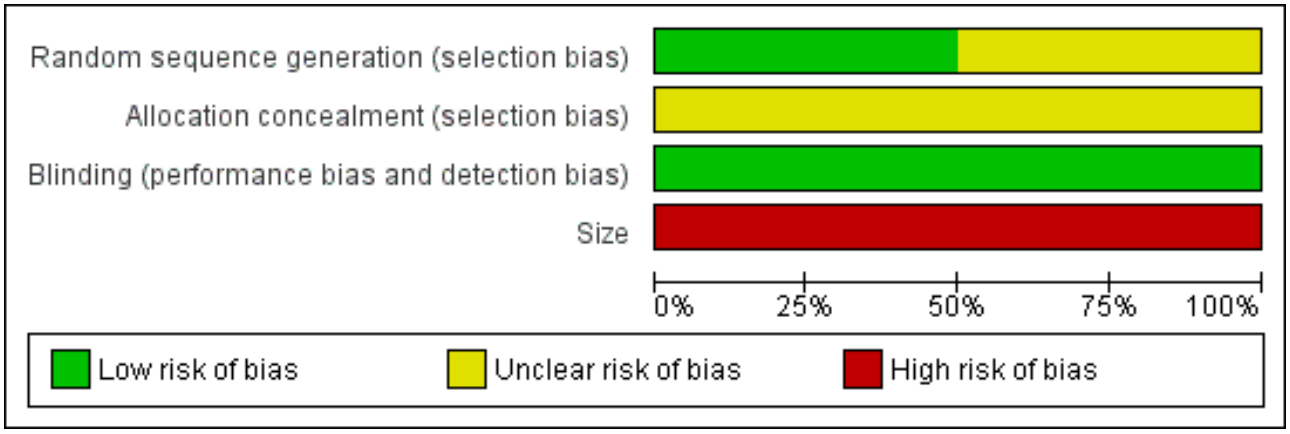


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

Allocation

Both studies reported that they were randomised. Only one (BR1160 1995) adequately described the method used to generate the sequence and to conceal the random allocation.

Blinding

Both 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. Both studies had treatment group sizes that put them at high risk of bias.

Effects of interventions

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

Number of participants achieving at least 50% pain relief

Dexibuprofen 200 mg vs placebo

Both studies reported on this dose; 51/96 (53%) participants achieved this outcome with dexibuprofen 200 mg compared with 12/62 (13%) with placebo. There were insufficient data for statistical analysis.

Dexibuprofen 400 mg vs placebo

One study (Dionne 1998) reported on this dose; 35/50 (70%) achieved this outcome with dexibuprofen 400 mg compared with 12/62 (13%) with placebo. There were insufficient data for statistical analysis.

Dexibuprofen 200 mg vs racemic ibuprofen 400 mg

Both studies reported on this dose; 51/96 (53%) achieved this outcome with dexibuprofen 200 mg compared with 49/97 (51%) with racemic ibuprofen 400 mg. There were insufficient data for statistical analysis.

Dexibuprofen 400 mg vs racemic ibuprofen 400 mg

One study reported on this dose (Dionne 1998); 35/50 (70%) achieved this outcome with dexibuprofen 400 mg compared with 26/50 (52%) with racemic ibuprofen 400 mg. There were insufficient data for statistical analysis.

Rescue medication

Median time to use of rescue medication

One study (Dionne 1998) reported a median time to remedication of 5.8 hours with dexibuprofen 200 mg, 6.1 hours with dexibuprofen 400 mg, and 5.4 hours with racemic ibuprofen compared with 1.8 hours with placebo.

The other study (BR1160 1995) reported median time to remedication in excess of 4.0 hours for dexibuprofen 200 mg and racemic ibuprofen compared to 2.5 hours with placebo.

Number of participants using rescue medication

One study (BR1160 1995) reported that 16/45, 17/47, 24/37 participants used rescue medication with dexibuprofen 200 mg, racemic ibuprofen 400 mg, and placebo respectively.

Adverse events

The adverse events most commonly reported in Dionne 1998 were drowsiness, nausea and headache with ibuprofen, and headache with placebo. In BR1160 1995 nausea with racemic ibuprofen 400 mg and vomiting with dexibuprofen 200 mg and placebo were reported. These events are commonly associated with surgery and anaesthesia and there were no obvious differences between treatment groups. All adverse events were reported as mild to moderate in intensity, and were most likely to be related to the anaesthetic or surgical procedure.

Neither study reported the number of participants who experienced one or more adverse event. There were no serious adverse events reported in either study.

Withdrawals

Withdawal due to lack of efficacy is considered under use of rescue medication. Withdrawals for other reasons were infrequent and balanced across treatment arms. Two adverse event withdrawals were reported, both in the study BR1160 1995, in the placebo group, both due to vomiting. Dionne 1998 reported no withdrawals due to adverse events but four participants were excluded as impaction was neither partial nor bony at the time of surgery. One further participant was excluded as remedication was administered within one hour of the study drug. Eleven participants were excluded from BR1160 1995 due to protocol violation and a further eight due to loss to follow-up.

DISCUSSION

Dexibuprofen is not a widely available NSAID, and there is no large literature describing its use in clinical pain conditions, although in a review by Phleps 2001 clinical efficacy of dexibuprofen was reported in rheumatoid arthritis, ankylosing spondylitis, osteoarthritis of the hip, osteoarthritis of the knee, lumbar vertebral syndrome, distortion of the ankle joint and dysmenorrhoea. The information from the two studies in acute postoperative pain suggests it to be a useful analgesic, but at doses not very different from racemic ibuprofen. Published randomised trials indicate reasonable efficacy of dexibuprofen in relatively short studies in osteoarthritis (Hawel 2003; Singer 2000), and in single doses in dysmenorrhoea (Kollenz 2009).

As with many other analgesics in acute and chronic pain, dexibuprofen produces good pain relief in some but not all patients (Moore 2013a). With NSAIDs, formulations that produce faster absorption (soluble salts, or liquigel, for example) also produce faster and often better overall pain relief, as with ibuprofen (Moore 2013b). For dexibuprofen in this review, only standard formulations were reported upon.

Summary of main results

Data from one new study synopsis were available for this updated review in addition to the original study but the conclusions remained unchanged. Incuded studies involved 313 participants of whom 97 received dexibuprofen 200 mg, 50 received dexibuprofen

400 mg, 101 received racemic ibuprofen 400 mg, and 76 received placebo. Dexibuprofen at 200 mg and 400 mg single doses produced more participants with good pain relief than did placebo, and roughly the same proportion as with the same or double doses (in mg) of racemic ibuprofen. No analyses of the available data were sensible given the small numbers, and the high likelihood of false conclusions being arrived at by chance (Moore 1998).

It was also unclear if the median time to rescue medication varied between studies because there was a difference in study duration. Dionne 1998 lasted six hours; the median time to remedicate was five or six hours for active therapies (dexibuprofen and ibuprofen). BR1160 1995) lasted only for four hours; the median time to remedicate was over four hours for both active treatments (dexibuprofen and ibuprofen). Therefore no pooling of results was possible.

Neither study reported serious adverse events, including death.

Overall completeness and applicability of evidence

Both studies included in this update enrolled participants with dental pain following extraction of at least one impacted third molar. These individuals are generally in their early 20s, and are otherwise fit and healthy. They are not representative of the range of individuals who might need analgesia for acute postoperative pain. Although there is no reason why analgesic response in these individuals should differ in any systematic way from a more generalised population, it is entirely possible that adverse events (gastrointestinal in particular) may be more frequent, intense, or severe in older patients, and those with comorbidities. Neither study provided information on numbers of participants experiencing adverse events, but it was unlikely to be a significant problem as both were single-dose studies.

Quality of the evidence

The studies were of adequate methodological quality with (Dionne 1998) scoring 4/5 and (BR1160 1995) scoring 5/5 on the Oxford Quality Scale, although they were both judged to be at high risk of bias from the small sizes of their treatment groups. Both studies administered the medication when pain levels were moderate or severe, ensuring that the study was sensitive to detect a 50% reduction (Moore 2013a).

Potential biases in the review process

We are unaware of any potential biases in the review process.

Agreements and disagreements with other studies or reviews

We are not aware of any other systematic reviews of dexibuprofen in treating acute postoperative pain.

AUTHORS' CONCLUSIONS

Implications for practice

Additional information has not changed the conclusions. There are no implications for practice because there is insufficient information at present to draw conclusions about efficacy or harm of dexibuprofen, or to make any sensible comparisons with racemic ibuprofen or other analgesics.

Implications for research

A considerable additional body of clinical trial results would be needed to know whether dexibuprofen has any advantages in efficacy, or faster analgesic onset, or safety over racemic ibuprofen. There seems little need for this research, as emerging evidence is that formulation is likely to be more important than chirality for NSAIDs in acute pain.

ACKNOWLEDGEMENTS

Henry McQuay was an author on the original review. The earlier review was supported by an NHS Cochrane Collaboration Grant and NIHR Biomedical Research Centre Programme. We thank Reckitt Benckiser for making available data from the unpublished study.

REFERENCES

References to studies included in this review

BR1160 1995 *{unpublished data only}*

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CHARACTERISTICS OF STUDIES

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

BR1160 1995

Methods	RCT, DB, single oral dose, parallel groups Medication administered when pain was of moderate or severe intensity Pain assessed at 0, 15, 30, 45, 60 minutes, then hourly to 4 hours
Participants	Third molar extraction N = 137 M = 55, F = 82 Mean age 25 years
Interventions	Dexibuprofen (S(+)-Ibuprofen) 200 mg, n = 46 Racemic ibuprofen 400 mg, n = 51 Placebo, n = 40
Outcomes	PI: non-std 9 point scale Use of rescue medication Withdrawals
Notes	Oxford Quality Score: R2, DB2, W1 Rescue medication permitted after 1 hour

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomisation list generated by the Statistics Section of Boots Pharmaceuticals"
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding (performance bias and detection bias) All outcomes	Low risk	"Double-dummy method"
Size	High risk	< 50 participants per treatment group

Dionne 1998

Methods	RCT, DB, single oral dose, 4 parallel groups Medication administered when baseline pain was of moderate to severe intensity Pain assessed at 0, 15, 30, 45, 60 minutes, then hourly to 6 hours
Participants	Third molar extraction N = 181 (176 analysed for efficacy) M = 50, F = 126 Mean age 22 years
Interventions	Dexibuprofen (S(+)-Ibuprofen) 200 mg, n = 51 Dexibuprofen (S(+)-Ibuprofen) 400 mg, n = 50 Ibuprofen (racemic) 400 mg, n = 50 Placebo, n = 25
Outcomes	PI: std 4 point scale and 100 mm VAS PR: std 5 point scale and 100 mm VAS Time to use of rescue medication Withdrawals
Notes	Oxford Quality Score: R1, DB2, W1 Rescue medication permitted - no further details

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not specified
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding (performance bias and detection bias) All outcomes	Low risk	"Double-dummy method"
Size	High risk	< 50 participants per treatment group

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

Study	Reason for exclusion
Jamali 1999	Fewer than 10 per group Pharmacokinetic study - no pain measures

APPENDICES

Appendix 1. MEDLINE search strategy (via OVID)

1. (dexibuprofen).mp. (15)
2. (deltaran or seractil).mp. (2)
3. 1 or 2 (17)
4. Pain, Postoperative/ (6191)
5. exp Surgical Procedures, Operative/ (399388)
6. ((postoperative adj4 pain*) or (post-operative adj4 pain*) or post-operative-pain* or (post* adj4 pain*) or (postoperative adj4 analgesi*) or (post-operative adj4 analgesi*) or "post-operative analgesi*").mp. (10296)
7. ((post-surgical adj4 pain*) or ("post surgical" adj4 pain*) or (post-surgery adj4 pain*)).mp. (100)
8. ("pain-relief after surg*" or "pain following surg*" or "pain control after").mp. (132)
9. (("post surg*" or post-surg*) and (pain* or discomfort)).mp. (388)
10. ((pain* adj4 "after surg*") or (pain* adj4 "after operat*") or (pain* adj4 "follow* operat*") or (pain* adj4 "follow* surg*")).mp. (650)
11. ((analgesi* adj4 "after surg*") or (analgesi* adj4 "after operat*") or (analgesi* adj4 "follow* operat*") or (analgesi* adj4 "follow* surg*")).mp. (97)
12. or/4-11 (402335)
13. randomized controlled trial.pt. (82601)
14. controlled clinical trial.pt. (7435)
15. randomized.ab. (74425)
16. placebo.ab. (27937)
17. drug therapy.fs. (320336)
18. randomly.ab. (49540)
19. trial.ab. (74386)
20. groups.ab. (27566)
21. or/13-20 (65141)
22. 3 and 12 and 21 (2)

Appendix 2. Search strategy for EMBASE (via Ovid)

1. Dexibuprofen/ (102)
2. (dexibuprofen).mp. (104)
3. (deltaran or seractil).mp. (15)
4. 1 or 2 or 3 (105)
5. Pain, Postoperative/ (16657)
6. exp Surgical Procedures, Operative/ (1089731)
7. ((postoperative adj4 pain*) or (post-operative adj4 pain*) or post-operative-pain* or (post* adj4 pain*) or (postoperative adj4 analgesi*) or (post-operative adj4 analgesi*) or "post-operative analgesi*").mp. (34142)
8. ((post-surgical adj4 pain*) or ("post surgical" adj4 pain*) or (post-surgery adj4 pain*)).mp. (371)
9. ("pain-relief after surg*" or "pain following surg*" or "pain control after").mp. (330)
10. (("post surg*" or post-surg*) and (pain* or discomfort)).mp. (1140)
11. ((pain* adj4 "after surg*") or (pain* adj4 "after operat*") or (pain* adj4 "follow* operat*") or (pain* adj4 "follow* surg*")).mp. (1558)
12. ((analgesi* adj4 "after surg*") or (analgesi* adj4 "after operat*") or (analgesi* adj4 "follow* operat*") or (analgesi* adj4 "follow* surg*")).mp. (225)
13. or/5-12 (1098653)
14. clinical trials.sh. (219621)
15. controlled clinical trial.sh. (95337)
16. randomized controlled trial.sh. (127951)
17. double-blind procedure.sh. (33503)
18. (clin* adj25 trial*).mp (374809)
19. ((doubl* or trebl* or tripl*) adj25 (blind* or mask*)).mp (55272)
20. placebo*.mp (120870)

21.random*.mp (425810)
22.or/14-21 (678206)
23.4 and 13 and 22 (11)

Appendix 3. Search strategy for Cochrane CENTRAL

1. (Dexibuprofen or Deltaran or Seractil):ti,ab,kw (26)
2. MeSH descriptor: [Pain, Postoperative] this term only (8842)
3. MeSH descriptor: [Surgical Procedures, Operative] explode all trees (89806)
4. 2 or 3 (91999)
5. 4 and 6 (3)
6. Limit 5 to Trials (1)

Appendix 4. Glossary

Categorical rating scale:

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

VAS:

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

TOTPAR:

Total pain relief (TOTPAR) is calculated as the sum of pain relief scores over a period of time. If a patient had complete pain relief immediately after taking an analgesic, and maintained that level of pain relief for six hours, they would have a six-hour TOTPAR of the maximum of 24. Differences between pain relief values at the start and end of a measurement period are dealt with by the composite trapezoidal rule. This is a simple method that approximately calculates the definite integral of the area under the pain relief curve by calculating the sum of the areas of several trapezoids that together closely approximate to the area under the curve.

SPID:

Summed pain intensity difference (SPID) is calculated as the sum of the differences between the pain scores over a period of time. Differences between pain intensity values at the start and end of a measurement period are dealt with by the 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**	**Median time to use (h)**	**Number using**
Dionne 1998	1) Ibuprofen (s(+)-) 200mg n= 51 2) Ibuprofen (s(+)-) 400mg	TOTPAR 6: 1) 12.96 2) 14.85	1) 31/51 2) 35/50	1) 5.8 2) 6.1	No data

(Continued)

	n=50 3) Ibuprofen (racemic) 400mg n=50 4) Placebo n= 25	3) 11.52 4) 3.45	3) 26/50 4) 2/25	3) 5.4 4) 1.8	
BR1160 1995	1)Ibuprofen s(+) 200mg n=46 2)racemic ibuprofen 400mg n=51 3)Placebo n=40	This was converted to 100mm for 4 hours. SPID 4 1) 86.66 2) 91.51 3) 58.04	1) 20/45 2) 23/47 3) 10/37	1) >4 2) >4 3) 2.5	1) 16/45 2) 17/47 3) 24/37

PI = pain intensity; PR = pain relief; TOTPAR = total pain relief; SPID = summed pain intensity difference

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 1, 2009
Review first published: Issue 3, 2009

Date	Event	Description
26 February 2014	Review declared as stable	This review will be assessed for updating in 2018.
20 August 2013	New search has been performed	New data identified in one unpublished trial synopsis and included in review (BR1160 1995) with 137 participants. New searches carried out for published studies on the 19 August 2013.
20 August 2013	New citation required but conclusions have not changed	Additional data do not alter the conclusions from the previous publication. There are still too few data to determine whether dexibuprofen has any advantages in efficacy or safety over racemic ibuprofen. No clinical trials have been published since 1998, and this review can probably be made stable for 5 to 10 years.
10 November 2010	Review declared as stable	The authors declare that there is unlikely to be any further studies to be included in this review and so it should be published as a 'stable review'.
24 September 2010	Amended	Contact details updated.

CONTRIBUTIONS OF AUTHORS

For the original review, SD and RAM performed searching, data extraction, and analysis, including assessment of study quality. HJM helped with analysis and acted as arbitrator. All review authors contributed to writing.

For the update, JB and SD carried out searching, data extraction and analysis, and risk of bias assessments. All review authors were involved with writing.

DECLARATIONS OF INTEREST

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

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

For the update we have added a Risk of bias table and Summary of findings table.

NOTES

The authors believe that there are unlikely to be any further studies for inclusion in this review, so it should be published as a 'stable review'.

INDEX TERMS

Medical Subject Headings (MeSH)

Acute Pain [*drug therapy]; Administration, Oral; Analgesics, Non-Narcotic [*administration & dosage]; Anti-Inflammatory Agents, Non-Steroidal [*administration & dosage]; Ibuprofen [administration & dosage] [*analogs & derivatives]; Pain, Postoperative [*drug therapy]; Randomized Controlled Trials as Topic

MeSH check words

Adult; Humans