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Single dose oral fenbufen for acute postoperative pain in adults (Review)

Moore RA, Derry S, McQuay HJ

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[Intervention Review]

Single dose oral fenbufen for acute postoperative pain in adults

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ABSTRACT

Background

Fenbufen is a non-selective non-steroidal anti-inflammatory drug (NSAID), used to treat acute and chronic painful conditions. There is no known systematic review of its use in acute postoperative pain.

Objectives

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

Search methods

We searched Cochrane CENTRAL, MEDLINE, EMBASE and the Oxford Pain Relief database for studies to June 2009.

Selection criteria

Randomised, double blind, placebo-controlled trials of single dose orally administered fenbufen in adults with moderate to severe acute postoperative pain.

Data collection and analysis

Two review authors independently assessed trial quality and extracted data. Pain relief or pain intensity data were extracted and converted into the dichotomous outcome of number of participants with at least 50% pain relief over 4 to 6 hours, from which relative risk and number needed to treat to benefit (NNT) were calculated. Numbers of participants using rescue medication over specified time periods, and time to use of rescue medication, were sought as additional measures of efficacy. Information on adverse events and withdrawals were collected.

Main results

Searches identified only one study with (90 participants in total, 31 taking fenbufen). The study compared oral fenbufen 800 mg, fenbufen 400 mg, and placebo in participants with established postoperative pain. Fenbufen at both doses had apparent analgesic efficacy, but the numbers of participants was too small to allow sensible analysis. Gastrointestinal adverse events were noted in 4 of 15 participants taking fenbufen 800 mg.

Authors' conclusions

In the absence of evidence of efficacy for oral fenbufen in acute postoperative pain, its use in this indication is not justified at present. Because trials clearly demonstrating analgesic efficacy in the most basic of acute pain studies is lacking, use in other indications should be evaluated carefully. Given the large number of available drugs of this and similar classes which are effective, there is no urgent research agenda for this particular drug.

PLAIN LANGUAGE SUMMARY

Single dose oral fenbufen for acute postoperative pain in adults

Pain is commonly experienced after surgical procedures. The condition is usually used to test whether or not drugs are effective painkillers in participants with moderate or severe pain. In this case we could find only a single small study that tested oral fenbufen against placebo. It is possible that more studies were done, but not reported, because they were used only to register fenbufen with licensing authorities throughout the world. However, this leaves an important gap in our knowledge, and it means that we cannot be confident about using oral fenbufen for acute painful conditions.

BACKGROUND

Acute pain occurs as a result of tissue damage either accidentally, due to an injury, or as a result of surgery. Acute postoperative pain is a manifestation of inflammation due to tissue injury. The management of postoperative pain and inflammation is a critical component of patient care.

This is one of a series of reviews whose aim is to 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. Recently published reviews include paracetamol (Toms 2008), celecoxib (Derry 2008), naproxen (Derry C 2009a), parecoxib (Lloyd 2009), diclofenac (Derry P 2009), etoricoxib (Clarke 2009), ibuprofen (Derry C 2009b) and oxycodone (Gaskell 2009).

Acute pain trials

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

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

Knowing the relative efficacy of different analgesic drugs at various doses can be helpful. An example is the relative efficacy in the third molar extraction pain model (Barden 2004).

Fenbufen

This review looks at fenbufen. Fenbufen is available in various European countries, Israel, South Africa, and Thailand. Fenbufen is a non-steroidal anti-inflammatory drug (NSAID), generally prescribed for osteoarthritis, rheumatoid arthritis, acute musculoskeletal conditions such as lumbar sciatica, and for post-operative pain management, although licensed indications vary between countries. In England in 2006 only 3000 prescriptions were issued in primary care. This compares with almost 8 million prescriptions for naproxen and 4.5 million prescriptions for ibuprofen in the same period (PACT 2007).

Clinicians prescribe NSAIDs on a routine basis for a range of mild to moderate pain. NSAIDs are the most commonly prescribed analgesic medications worldwide, and their efficacy for treating acute pain has been well demonstrated (Moore 2003). They reversibly inhibit cyclooxygenase (prostaglandin endoperoxide synthase), the enzyme mediating production of prostaglandins (PGs) and thromboxane A2 (Fitzgerald 2001). PGs 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. However, relatively little is known about the mechanism of action of this class of compounds aside from their ability to inhibit cyclooxygenase-dependent prostanoid formation (Hawkey 1999).

Fenbufen (trade names - Cepal, Cinopal, Cybufen, Lederfen, and Reugast) is a prodrug with no intrinsic effect on cyclooxygenase activity, whereas its major metabolite, biphenylacetic acid, is a potent inhibitor of prostaglandin synthesis, acting in part through the non-selective inhibition of cyclo-oxygenase-1 and -2 to produce analgesic and antipyretic effects (Berg 1999). Doses are usually 900 mg daily by mouth, divided either as 450 mg in the morning and evening, or 300 mg in the morning with 600 mg in the evening. Fenbufen is absorbed from the gastrointestinal tract and peak plasma concentrations are reached in about 70 minutes. It is over 99% bound to plasma proteins. Fenbufen and its metabolites are reported to have plasma half-lives of about 10 to 17 hours and are mainly eliminated as conjugates in the urine (Brogden 1981; Brogden 1986; Kerwar 1983).

We could find no systematic review on the efficacy of fenbufen in acute pain. This review looks at the efficacy of fenbufen in the setting of acute postoperative pain.

OBJECTIVES

To evaluate the analgesic efficacy and safety of oral fenbufen in the treatment of acute postoperative pain, using criteria of efficacy recommended by an in-depth study at the individual patient level (Moore 2005), and methods that allow comparison with other analgesics evaluated in the same way.

METHODS

Criteria for considering studies for this review

Types of studies

Studies were included if they were full publications of double blind trials of a single dose oral fenbufen against placebo for the treatment of moderate to severe postoperative pain in adults, with at least 10 participants randomly allocated to each treatment group. Multiple dose studies were included if appropriate data from the first dose were available, and cross-over studies were included provided that data from the first arm were presented separately.

Studies were excluded if they were:

- posters or abstracts not followed up by full publication;
- reports of trials concerned with pain other than postoperative pain (including experimental pain);
- studies using healthy volunteers;
- studies where pain relief was assessed by clinicians, nurses or carers (i.e. not patient-reported);
- studies of less than 4 hours' duration or which failed to present data over 4 to 6 hours post-dose.

Types of participants

Studies of adult participants (15 years old or above) with established moderate to severe postoperative pain were included. For studies using a visual analogue scale (VAS), pain of at least moderate intensity was assumed when the VAS score was greater than 30 mm (Collins 1997). Studies of participants with postpartum pain were included provided the pain investigated resulted from episiotomy or Caesarean section (with or without uterine cramp). Studies investigating participants with pain due to uterine cramps alone were excluded.

Types of interventions

Fenbufen or matched placebo administered as a single oral dose for postoperative pain.

Types of outcome measures

Data collected included the following:

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

Search methods for identification of studies

To identify studies for inclusion in this review, the following electronic databases were searched:

- Cochrane CENTRAL (issue 2, 2009);
- MEDLINE via Ovid (June 2009);
- EMBASE via Ovid (June 2009);
- Oxford Pain Relief Database (Jadad 1996a).

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

Additional studies will be sought from the reference lists of retrieved articles and reviews.

Language

No language restriction was applied.

Unpublished studies

The manufacturing pharmaceutical company producing this drug were not contacted for unpublished trial data.

Data collection and analysis

Selection of studies

Two review authors independently assessed and agreed the search results for studies that were included in the review.

Quality assessment

Two review authors independently assessed the included studies for quality using a five-point scale (Jadad 1996b) that considers randomisation, blinding, and study withdrawals and dropouts.

Data management

Data was extracted by two review authors and recorded on a standard data extraction form. Data suitable for pooling was entered into RevMan 5.

Data analysis

For each study, the mean TOTPAR, SPID, VAS TOTPAR or VAS SPID (Appendix 4) values for active and placebo were converted to %maxTOTPAR or %maxSPID by division into the calculated maximum value (Cooper 1991). The proportion of participants in each treatment group who achieved at least 50%maxTOTPAR was calculated using verified equations (Moore 1996; Moore 1997a; Moore 1997b). These proportions were then converted into the number of participants achieving at least 50%maxTOTPAR by multiplying by the total number of participants in the treatment group. Information on the number of participants with at least 50%maxTOTPAR for active and placebo were then used to calculate relative benefit (RB)/relative risk (RR), and number needed to treat to benefit (NNT).

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

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

If none of these measures were available, 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" could be used for the number of participants achieving at least 50% pain relief (Collins 2001).

The number of participants reporting treatment-emergent adverse effects was extracted for each treatment group. RB or RR estimates were calculated with 95% confidence intervals (CI) using a fixed-effect model (Morris 1995). NNT and number needed to treat to harm (NNH) and 95% CIs were calculated from the pooled number of events using the method devised by Cook and Sackett (Cook 1995). A statistically significant difference from control was assumed when the 95% CI of the RR/RB did include the number one. Homogeneity was examined visually using L'Abbé plots (L'Abbe 1987).

Sub-group analyses were planned to determine the effect of dose, presenting condition (pain model), and high versus low (two or fewer versus three or more) quality trials. A minimum of two trials and 200 participants had to be available in any sensitivity analysis (Moore 1998).

RESULTS

Description of studies

Results of the search

Four potential studies were found (Coutinho 1976; Henrikson 1979; Nishida 1986; Sunshine 1975).

Included studies

Only a single study could be included (Coutinho 1976). This single study examined participants undergoing a variety of urogenital procedures with moderate or severe postoperative pain, and with measurements over the first 6 hours after dosing. There were 90 participants divided between six oral therapies, including placebo and fenbufen 400 mg and 800 mg. Only 31 participants took fenbufen.

Excluded studies

Three studies were examined for possible inclusion, but had to be excluded because participants were not in established pain (Henrikson 1979), there was no 4 to 6 hour pain data (Nishida 1986), or because the condition examined was not solely postoperative pain (Sunshine 1975).

Risk of bias in included studies

The study was properly randomised and double blind, and had a quality score of 5/5, indicating little risk of bias.

Effects of interventions

In the single included trial, 14/16 participants had at least 50% pain relief over 5 hours with fenbufen 800 mg, 11/15 with fenbufen 400 mg, and 6/15 with placebo.

The number needing additional analgesia within 5 hours was 2/16 with fenbufen 800 mg, 4/15 with fenbufen 400 mg, and 6/15 with placebo.

Three participants taking fenbufen 800 mg complained of mild heartburn (described as "pyrosis"), and one participant complained of nausea.

DISCUSSION

Fenbufen is neither a widely available nor widely used NSAID, but it is disappointing that only a single small classical analgesic study has been published of efficacy of oral fenbufen compared with placebo in participants with established postoperative pain.

It is almost certain that such studies have been performed, as they would have been required for registration purposes. Previously, large numbers of unpublished trials of this design have been included in systematic reviews of tramadol (Moore 1997c), and large numbers of analgesic trials of many designs with dexketoprofen (Moore 2008a). Obtaining unpublished clinical trial data is, however, a long and complicated process, made more difficult by drugs being older, and with original trial data hard to find.

The single study we have available for analysis (Coutinho 1976) has so few participants that no conclusions could be drawn. While both 400 mg and 800 mg doses showed some analgesic effect, of concern was that 4/15 participants taking 800 mg had a gastrointestinal adverse event - a common problem with NSAIDs, where more severe gastrointestinal events involving severe bleeding (Moore 2007) and low level bleeding (Moore 2008b) are relatively common.

No review of fenbufen in acute or chronic pain has been published for almost three decades (Brogden 1981), and no randomised placebo controlled trials in acute or chronic painful conditions using this drug for over two decades.

AUTHORS' CONCLUSIONS

Implications for practice

In the absence of evidence of efficacy for oral fenbufen in acute postoperative pain, its use in this indication is at present not justified. Because trials clearly demonstrating analgesic efficacy in the most basic of acute pain studies is lacking, use in other indications should be evaluated carefully.

Implications for research

Given the large number of available drugs of this and similar classes to treat postoperative pain, there is no urgent research agenda.

REFERENCES

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References to studies excluded from this review

Henrikson 1979 *{published data only}*

Henrikson PA, Tjernberg A, Ahlstrom U, Peterson LE. Analgesic efficacy and safety of Fenbufen following surgical removal of a lower wisdom tooth: a comparison with acetylsalicylic acid and placebo. *Journal of International Medical Research* 1979;**7**(2):107-16.

Nishida 1986 *{published data only}*

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CHARACTERISTICS OF STUDIES

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

Coutinho 1976

Methods	RCT, DB, single oral dose, 6 parallel groups

Coutinho 1976 *(Continued)*

	Medication administered when baseline pain reached a moderate to severe intensity Pain assessed at 0, 30, 60 mins, then hourly to 5 hours
Participants	Variety of urogenital surgical procedures N = 90 M = 72, F = 18 Mean age about 38 years (note that placebo mean age 34 years, fenbufen 400 mg 38 years, and fenbufen 800 mg 46 years)
Interventions	Fenbufen 400 mg, n = 15 Fenbufen 800 mg, n = 16 Aspirin 600 mg, n = 15 Codeine 30 mg, n = 14 Propoxyphene 66 mg, n = 15 Placebo, n = 15
Outcomes	PI: standard 4 point scale PR: standard 5 point scale Number using rescue medication
Notes	Oxford Quality Score: R2, DB2, W1 Participants asked to refrain from using rescue medication for 4 hours

DB - double blind; F - female; M - male; N - total number in study; n - number in treatment arm; PI - pain intensity; PR - pain relief; R - randomised; RCT - randomised controlled trial; W - withdrawals

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

Study	Reason for exclusion
Henrikson 1979	Not established pain
Nishida 1986	No 0 to 6 hour data
Sunshine 1975	Not postoperative pain

APPENDICES

Appendix 1. MEDLINE search strategy (via OVID)

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1950 to Present>

---

1 Fenbufen/ (0)
2 fenbufen.mp. (253)
3 (lederfen or cinopal or reugast or cepal).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (13)

4 (Bifene or (Biphenylylcarbonyl adj3 Propionic Acid) or Bufemid or Cinopal or Cl 82204 or Cl82204 or Lederfen or Reugast).mp. (11)
5 1 or 2 or 3 or 4 (256)
6 Pain, Postoperative/ (19481)
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. [mp=title, original title, abstract, name of substance word, subject heading word] (32630)
8 ((post-surgical adj4 pain*) or ("post surgical" adj4 pain*) or (post-surgery adj4 pain*)).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (182)
9 ("pain-relief after surg*" or "pain following surg*" or "pain control after").mp. [mp=title, original title, abstract, name of substance word, subject heading word] (385)
10 (("post surg*" or post-surg*) and (pain* or discomfort)).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (682)
11 ((pain* adj4 "after surg*") or (pain* adj4 "after operat*") or (pain* adj4 "follow* operat*") or (pain* adj4 "follow* surg*")).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (1831)
12 ((analgesi* adj4 "after surg*") or (analgesi* adj4 "after operat*") or (analgesi* adj4 "follow* operat*") or (analgesi* adj4 "follow* surg*")).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (426)
13 or/6-12 (34021)
14 exp Surgical Procedures, Operative/ (1812522)
15 13 or 14 (1826452)
16 randomized controlled trial.pt. (269889)
17 controlled clinical trial.pt. (79129)
18 randomized.ab. (190830)
19 placebo.ab. (116206)
20 drug therapy.fs. (1302339)
21 randomly.ab. (141193)
22 trial.ab. (198055)
23 groups.ab. (956958)
24 or/16-23 (2456370)
25 humans.sh. (10663713)
26 24 and 25 (1939160)
27 26 and 15 (250563)
28 5 and 27 (8)

Appendix 2. EMBASE search strategy (via OVID)

Database: EMBASE <1980 to 2009 Week 17>
---
1 Fenbufen/ (852)
2 fenbufen.mp. (868)
3 (lederfen or cinopal or reugast or cepal).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (127)
4 (Bifene or (Biphenylylcarbonyl adj3 Propionic Acid) or Bufemid or Cinopal or Cl 82204 or Cl82204 or Lederfen or Reugast).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (130)
5 1 or 2 or 3 or 4 (868)
6 Pain, Postoperative/ (19611)
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. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (37987)
8 ((post-surgical adj4 pain*) or ("post surgical" adj4 pain*) or (post-surgery adj4 pain*)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (204)
9 ("pain-relief after surg*" or "pain following surg*" or "pain control after").mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (333)
10 (("post surg*" or post-surg*) and (pain* or discomfort)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (671)
11 ((pain* adj4 "after surg*") or (pain* adj4 "after operat*") or (pain* adj4 "follow* operat*") or (pain* adj4 "follow* surg*")).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (1588)
12 ((analgesi* adj4 "after surg*") or (analgesi* adj4 "after operat*") or (analgesi* adj4 "follow* operat*") or (analgesi* adj4 "follow* surg*")).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (391)
13 or/6-12 (39075)
14 exp Surgical Procedures, Operative/ (1512019)
15 13 or 14 (1521438)

16 random*.ti,ab. (396274)
17 factorial*.ti,ab. (8252)
18 (crossover* or cross over* or cross-over*).ti,ab. (39585)
19 placebo*.ti,ab. (110475)
20 (doubl* adj blind*).ti,ab. (85078)
21 (singl* adj blind*).ti,ab. (7497)
22 assign*.ti,ab. (109080)
23 allocat*.ti,ab. (34524)
24 volunteer*.ti,ab. (99462)
25 CROSSOVER PROCEDURE.sh. (21239)
26 DOUBLE-BLIND PROCEDURE.sh. (72216)
27 RANDOMIZED CONTROLLED TRIAL.sh. (168246)
28 SINGLE BLIND PROCEDURE.sh. (8128)
29 or/16-28 (663334)
30 ANIMAL/ or NONHUMAN/ or ANIMAL EXPERIMENT/ (3450348)
31 HUMAN/ (6469375)
32 30 and 31 (538433)
33 30 not 32 (2911915)
34 29 not 33 (577725)
35 15 and 34 (95996)
36 35 and 5 (2)

Appendix 3. CENTRAL search strategy

1. MESH descriptor Fenbufen

2. fenbufen.ti,ab,kw.

3. OR/1-2

4. MESH descriptor Pain, Postoperative

5. ((postoperative adj4 pain$) or (post-operative adj4 pain$) or post-operative-pain$ or (post$ NEAR pain$) or (postoperative adj4 analgesi$) or (post-operative adj4 analgesi$) or ("post-operative analgesi$")):ti,ab,kw.

6. ((post-surgical adj4 pain$) or ("post surgical" adj4 pain$) or (post-surgery adj4 pain$)):ti,ab,kw.

7. (("pain-relief after surg$") or ("pain following surg$") or ("pain control after")):ti,ab,kw.

8. (("post surg$" or post-surg$) AND (pain$ or discomfort)):ti,ab,kw.

9. ((pain$ adj4 "after surg$") or (pain$ adj4 "after operat$") or (pain$ adj4 "follow$ operat$") or (pain$ adj4 "follow$ surg$")):ti,ab,kw.

10. ((analgesi$ adj4 "after surg$") or (analgesi$ adj4 "after operat$") or (analgesi$ adj4 "follow$ operat$") or (analgesi$ adj4 "follow$ surg$")):ti,ab,kw.

11. OR/4-10

12. Clinical trials:pt.

13. Controlled Clinical Trial:pt.

14. Randomized Controlled Trial.pt.

15. MESH descriptor Double-Blind Method

16. (clin$ adj25 trial$):ti,ab,kw.

17. ((doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)):ti,ab,kw.

18. placebo$:ti,ab,kw.

19. random$:ti,ab,kw.

20. OR/12-19

21. 3 AND 11 AND 20

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 6 hours, they would have a 6-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).

WHAT'S NEW

Date	Event	Description
29 May 2019	Amended	Contact details updated.
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'.

HISTORY

Protocol first published: Issue 1, 2009
Review first published: Issue 4, 2009

Date	Event	Description
8 February 2011	Amended	Contact details updated.
6 October 2010	Amended	Contact details updated.

CONTRIBUTIONS OF AUTHORS

RAM and SD carried out the searches, selected studies for inclusion, and carried out the data extraction. RAM and SD carried out the analysis. HJM helped with analysis and acted as arbitrator. All review authors contributed to the writing. SD will be responsible for any future update.

DECLARATIONS OF INTEREST

SD, RAM & HJM have received research support from charities, government and industry sources at various times, this work was supported by an NHS Cochrane Collaboration Grant and NIHR Biomedical Research Centre Programme. RAM and HJM have consulted for various pharmaceutical companies. RAM and HJM have received lecture fees from pharmaceutical companies related to analgesics and other healthcare interventions.

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Internal sources

- Oxford Pain Research Funds, UK.

External sources

- NHS Cochrane Collaboration Grant, UK.
- European Union Biomed 2 Grant no. BMH4 CT95 0172, UK.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

There are no differences between the protocol and the review.

NOTES

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'.

INDEX TERMS

Medical Subject Headings (MeSH)

Acute Disease; Administration, Oral; Analgesics [*administration & dosage]; Cyclooxygenase Inhibitors [*administration & dosage]; Pain, Postoperative [*drug therapy]; Phenylbutyrates [*administration & dosage]; Randomized Controlled Trials as Topic

MeSH check words

Adult; Humans