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Single dose oral aceclofenac for postoperative pain in adults (Review)

Moore RA, Derry S, McQuay HJ

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[Intervention Review]

Single dose oral aceclofenac for postoperative pain in adults

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ABSTRACT

Background

Aceclofenac is the prodrug of the non-steroidal anti-inflammatory drug (NSAID) diclofenac, widely used to treat acute and chronic pain. There are no known systematic reviews of its analgesic efficacy in acute postoperative pain. This review sought to evaluate the efficacy and safety of oral aceclofenac in acute postoperative pain, using clinical studies of patients with established pain, and with outcomes measured primarily over 6 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 of single dose oral aceclofenac in acute postoperative pain, and any associated adverse events.

Search methods

We searched *The Cochrane Library* (Issue 1, 2009), MEDLINE via Ovid (1966 to March 2009); EMBASE via Ovid (1980 to March 2009); the Oxford Pain Relief Database (1950 to 1994); and reference lists of articles.

Selection criteria

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

Data collection and analysis

Two review authors independently assessed trial quality and extracted data. The area under the "pain relief versus time" curve was used to derive the proportion of participants with paracetamol plus codeine and placebo or paracetamol alone experiencing least 50% pain relief over 4 to 6 hours, using validated equations. The number needed to treat to benefit (NNT) was calculated using 95% confidence intervals (CI). The proportion of participants using rescue analgesia over a specified time period, and time to use of rescue analgesia, were sought as additional measures of efficacy. Information on adverse events and withdrawals was also collected.

Main results

Searches identified only one study (217 participants total), which used oral aceclofenac 150 mg in patients with established postoperative pain. Aceclofenac 150 mg could not be distinguished from placebo, though ibuprofen 400 mg was distinguished from placebo.

Authors' conclusions

In the absence of evidence of efficacy for oral aceclofenac in acute postoperative pain (at least at 150 mg single dose), its use in this indication is not justified. Because trials clearly demonstrating analgesic efficacy in the most basic of acute pain studies are lacking, use in

other indications should be evaluated carefully. Given the large number of effective drugs available in this and similar classes of analgesics, there is no urgent research agenda required to demonstrate the effective dose of aceclofenac in acute postoperative pain.

PLAIN LANGUAGE SUMMARY

Single dose oral aceclofenac for postoperative pain in adults

Pain is commonly experienced after surgical procedures. Acute postoperative pain of moderate or severe intensity is often used (as a model) to test whether or not drugs are effective painkillers. In this case we could find only a single study testing oral aceclofenac 150 mg against placebo, and aceclofenac was not statistically better than placebo. It is possible that other studies were done, possibly at larger or more effective doses, but not reported because they were used only to register aceclofenac 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 aceclofenac 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 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), diclofenac (Derry P 2009) and etoricoxib (Clarke 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. Hence, the use of additional or rescue analgesia is 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 2004a).

Aceclofenac

This review looked at aceclofenac. Aceclofenac is available in the UK as a prescription-only drug, and is used for the relief of pain and inflammation in rheumatoid arthritis, osteoarthritis and ankylosing spondylitis. The oral dose is 100 mg twice daily. Aceclofenac is widely available in many European counties, as well as in some Middle Eastern, and South and Central American countries. Aceclofenac is not used much in the UK, with only 48,000 prescriptions in England in 2007, but is more widely used in other countries in Europe. Aceclofenac works by being metabolised to the non-steroidal anti-inflammatory drug (NSAID) diclofenac (Hinz 2003; Hinz 2004).

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).

Aceclofenac (trade names include Aceclofar, Beofenac, Bristaflam, Preservex, and Sovipan) acts through the non-selective inhibition of cyclo-oxygenase-1 and -2 to produce analgesic and antipyretic effects (Berg 1999), though the level of cyclooxygenase-1 inhibition is questioned (Hinz 2004). Maximal plasma concentrations are reached after 1 to 2 hours for the standard oral preparations, with 100% absorption. Aceclofenac has a half life of 4 hours, and is metabolised to mainly hydroxy metabolites appearing in the urine.

The literature on aceclofenac is sparse. Adverse events of aceclofenac are likely to be similar to those of diclofenac to which it is metabolised.

OBJECTIVES

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

METHODS

Criteria for considering studies for this review

Types of studies

Studies were included if they were double blind trials of single dose oral aceclofenac compared with placebo for the treatment of moderate to severe postoperative pain in adults with at least ten participants randomly allocated to each treatment group. Multiple dose studies were included if appropriate data from the first dose

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

The following were 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 4 hours duration or studies that fail to present data over 4 to 6 hours post-dose.

Types of participants

Studies of adult participants (> 15 yrs) with established postoperative pain of moderate to severe intensity following day surgery or in-patient surgery were included. For studies using a visual analogue scale (VAS), pain of at least moderate intensity was equated to greater than 30 mm (Collins 1997). Studies of participants with postpartum pain were included provided the pain investigated resulted from episiotomy or Caesarean section (with or without uterine cramp). Studies investigating participants with pain due to uterine cramps alone were excluded.

Types of interventions

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

Types of outcome measures

Data collected included the following:

- participant characteristics;
- patient reported pain at baseline (physician, nurse or carer reported pain will not be included in the analysis);
- patient reported pain relief expressed at least hourly over 4 to 6 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

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

- Cochrane CENTRAL (Issue 1, 2009);
- MEDLINE via Ovid (March 2009);
- EMBASE via Ovid (March 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 were 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 might be 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 were extracted by two review authors and recorded on a standard data extraction form. Data suitable for pooling was entered into RevMan 5.0.

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 1997). 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

Five potential studies were found.

Included studies

Only a single study could be included, a randomised, double blind comparison of aceclofenac 150 mg and ibuprofen 400 mg with placebo after third molar extraction surgery with 217 participants in total, 71 of whom received aceclofenac 150 mg (Seymour 1998).

Excluded studies

Four studies were examined for possible inclusion, but as none had a placebo control group, these were excluded (Yscla 1988; Movilia 1989; Chalini 2005; Presser Lima 2006). One was additionally not described as randomised (Yscla 1988).

Risk of bias in included studies

The included study had a quality score of 4/5 on the Oxford Quality Scale, indicating little possibility of bias. Details are in the 'Characteristics of included studies' table.

Effects of interventions

Information available from the study was limited because data were reported on fewer participants than were originally randomised, without explanation. Based on a single trial with distinct limitations, aceclofenac 150 mg was not distinguished from placebo, while ibuprofen 400 mg was (Table 1).

DISCUSSION

This single study showed sensitivity, with a significant difference between placebo and ibuprofen 400 mg, with a wealth of good information of analgesic efficacy (Derry C 2009b). Aceclofenac 150 mg showed no analgesic efficacy in the same study.

This apparent failure could be due to the random play of chance, though the number of patients studied make this unlikely (Moore 1998). With no other placebo controlled trials the conclusion must be that, at 150 mg, aceclofenac has no measurable analgesic efficacy in a standard model of acute pain. None of the four excluded studies had designs and results that were in any way helpful in providing evidence to measure aceclofenac efficacy compared with placebo.

Aceclofenac does show analgesic efficacy in other pain conditions. For example, a small 170 participant six-week randomised study claimed superiority of aceclofenac 200 mg daily over paracetamol 3000 mg daily (Batlle-Gualda 2007). Another in osteoarthritis claimed equivalence of aceclofenac 200 mg daily with diclofenac 150 mg daily (Pareek 2006). Aceclofenac 100 mg daily was superior to placebo and equivalent to naproxen 500 mg in dysmenorrhoea (Letzel 2006).

The reason for the failure of aceclofenac to show efficacy in a third molar extraction model of postoperative pain is unclear. Third molar extraction is the most common model of postoperative pain used, and is acknowledged to provide good sensitivity with low placebo response (Barden 2004b). Random play of chance where numbers of participants are limited cannot be excluded as a cause of a negative result (Moore 1998). There is, however, no evidence that aceclofenac 150 mg is effective for treating acute postoperative pain according to this one study.

AUTHORS' CONCLUSIONS

Implications for practice

In the absence of evidence of efficacy for oral aceclofenac in acute postoperative pain (at least at 150 mg single dose), its use in this indication is not justified. Because trials clearly demonstrating analgesic efficacy in the most basic of acute pain studies are lacking, use in other indications should be evaluated carefully.

Implications for research

Given the large number of available drugs of this and similar classes which have good evidence of efficacy in acute postoperative pain, there is no urgent research agenda for this drug. This review should not require updating unless a substantial body of new clinical trials on aceclofenac appears, an unlikely eventuality.

ACKNOWLEDGEMENTS

We wish to thank Caroline Struthers at the PaPaS Cochrane Review Group for help with searching.

REFERENCES

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Chalini S, Raman U. Comparative efficacy of aceclofenac and etoricoxib in post extraction pain control: randomized control trial. *Indian journal of Dental Research* 2005;**16**(2):47-50.

Movilia 1989 *{published data only}*

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Presser Lima 2006 *{published data only}*

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Yscla 1988 *{published data only}*

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Pareek 2006

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Toms 2008

Toms L, McQuay HJ, Derry S, Moore RA. Single dose oral paracetamol (acetaminophen) for postoperative pain in adults. *Cochrane Database of Systematic Reviews* 2008, Issue 4. [DOI: 10.1002/14651858.CD004602]

CHARACTERISTICS OF STUDIES

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

Seymour 1998

Methods	RCT, DB, DD, single oral dose, 3 parallel groups Medication administered when baseline pain was of least moderate intensity (> 30 mm on 100 mm VAS scale) Pain assessed at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4 and 6 hours.
Participants	Third molar extraction N = 217 M = 102, F = 115

Seymour 1998 *(Continued)*	Mean age 25 years
Interventions	Aceclofenac 150 mg, n = 71 Ibuprofen 400 mg, n = 76 Placebo, n = 70
Outcomes	PI: std 100 mm VAS PR: std 100 mm VAS Global assessment of pain relief: std 5 point scale Numbers of participants using rescue medication Time to use of rescue medication Numbers with any adverse event Withdrawals
Notes	Oxford Quality Score: R1, DB2, W1

DB - double blind; DD - double dummy; PGE - patient global evaluation of efficacy; PI - pain intensity; PR - pain relief; R - randomised; RCT - randomised controlled trial; std - standard; W - withdrawals

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

Study	Reason for exclusion
Chalini 2005	No placebo.
Movilia 1989	No placebo.
Presser Lima 2006	No placebo.
Yscla 1988	No placebo. Not described as randomized.

ADDITIONAL TABLES

Table 1. Summary of outcomes: analgesia and rescue medication

		Analgesia			Rescue medication	
Study ID	**Treatment**	**PI or PR**	**Number with 50% PR**	**PGE: v good or excellent**	**Median time to use (h)**	**% using**
Seymour 1998	1. Aceclofenac 150 mg 2. Ibuprofen 400 mg 3. Placebo incomplete data		Pain relief complete or good: 1. 21/69 2. 38/76 3. 12/68	1. 2.08 2. 3.52 3. 1.58	1. 72 2. 55 3. 86	no data

APPENDICES

Appendix 1. Search strategy for MEDLINE (via OVID)

1. aceclofenac.sh
2. aceclofenac.ti,ab,kw.
3. OR/1-2
4. PAIN, POSTOPERATIVE.sh
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. randomized controlled trial.pt.
13. controlled clinical trial.pt.
14. randomized.ab.
15. placebo.ab.
16. drug therapy.fs.
17. randomly.ab.
18. trial.ab.
19. groups.ab.
20. OR/12-19
21. 3 AND 11 AND 20

Appendix 2. Search strategy for EMBASE (via Ovid)

1. aceclofenac.sh.
2. aceclofenac.ti,ab,kw.
3. OR/1-2
4. postoperative pain.sh.
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 $")).ti,ab,kw.
11. OR/4-10
12. clinical trials.sh
13. controlled clinical trials.sh
14. randomized controlled trial.sh
15. double-blind procedure.sh
16. (clin$ adj25 trial$).ab.
17. ((doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ab.
18. placebo$.ab.
19. random$.ab.
20. OR/12-19
21. 3 AND 11 AND 20

Appendix 3. Search strategy for Cochrane CENTRAL

1. MESH descriptor Aceclofenac.
2. aceclofenac: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 $")):ti,ab,kw.
11. OR/4-10
12. Clinical trial:pt.
13. Controlled Clinical Trial:pt.
14. Randomized Controlled Trial:pt.
15. MeSH descriptor Double-Blind Method
16. (clin$ 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 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).

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 3, 2009

Date	Event	Description
24 September 2010	Amended	Contact details updated.

CONTRIBUTIONS OF AUTHORS

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 the writing of the final review.

DECLARATIONS OF INTEREST

SD, RAM & HJM have received research support from charities, government and industry sources at various times. RAM and HJM have consulted for various pharmaceutical companies. RAM, and HJM have received lecture fees from pharmaceutical companies related to analgesics and other healthcare interventions. Support for this review came from Oxford Pain Research, the NHS Cochrane Collaboration Programme Grant Scheme, and NIHR Biomedical Research Centre Programme.

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Internal sources

- Oxford Pain Research Funds, UK.

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- NHS Cochrane Collaboration Grant, UK.
- NIHR Biomedical Research Centre Programme, UK.

Support for RAM

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; Anti-Inflammatory Agents, Non-Steroidal [*administration & dosage]; Diclofenac [administration & dosage] [*analogs & derivatives]; Pain, Postoperative [*drug therapy]

MeSH check words

Adult; Humans