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

Moore RA, Derry S, Moore M, McQuay HJ

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[Intervention Review]

Single dose oral tiaprofenic acid for acute postoperative pain in adults

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ABSTRACT

Background

Tiaprofenic acid is a a non-steroidal anti-inflammatory drug (NSAID). It is widely available around the world, with indications for osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, periarticular disorders, and strains and sprains. This review sought to evaluate the efficacy and safety of oral tiaprofenic acid 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 tiaprofenic acid in acute postoperative pain, and any associated adverse events.

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 tiaprofenic acid in adults with moderate to severe acute postoperative pain.

Data collection and analysis

Two review authors independently assessed trial quality and extracted data. We planned to use area under the "pain relief versus time" curve to derive the proportion of participants with tiaprofenic acid experiencing at least 50% pain relief over 4 to 6 hours, using validated equations; to use number needed to treat to benefit (NNT); the proportion of participants using rescue analgesia over a specified time period; time to use of rescue analgesia; information on adverse events and withdrawals.

Main results

Not one of eleven studies identified by the searches and examined in detail studied oral tiaprofenic acid against placebo in patients with established postoperative pain and therefore no results are available.

Authors' conclusions

In the absence of evidence of efficacy for oral tiaprofenic acid 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 tiaprofenic acid 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 no studies that tested oral tiaprofenic acid against placebo. It is possible that the studies were done, but not reported, because they were used only to register tiaprofenic acid 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 tiaprofenic acid 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).

Tiaprofenic acid

This review looks at tiaprofenic acid, a non-steroidal anti-inflammatory drug (NSAID). It is widely available around the world, with indications for osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, periarticular disorders, and strains and sprains. In England in 2006 only 11,000 prescriptions were issued in primary care. This compares with almost eight 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).

Tiaprofenic acid (trade names include Surgam, Artiflam, Flamirex, and variants of these) is a NSAID of the arylpropionic acid (profen) class. The typical adult dose is 300 mg twice daily. It is sparingly metabolised in the liver to two inactive metabolites. Most of the drug is eliminated unchanged in the urine (Davies 1996). Renal disease impairs excretion, and it should be used with caution in patients who have renal disease.

Long term use of tiaprofenic acid is associated with severe cystitis, roughly 100 times more commonly than with other NSAIDs. It is contraindicated in patients with cystitis (Crawford 1997; Buchbinder 2000), prostatitis, and urinary tract infections.

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

OBJECTIVES

To assess the efficacy and safety of single dose oral tiaprofenic acid for acute postoperative pain, using methods that permit comparison with other analgesics evaluated in the same way, using criteria of efficacy recommended by an in-depth study at the individual patient level (Moore 2005).

METHODS

Criteria for considering studies for this review

Types of studies

Studies would be included if they were double blind trials of single dose oral tiaprofenic acid 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. Multiple

dose studies would be included if appropriate data from the first dose were available. Cross-over studies would be eligible provided that data from the first arm were presented separately. No language restriction was applied to the search for studies.

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.

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

Types of participants

Studies of adult participants (> 15 years) with established postoperative pain of moderate to severe intensity 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

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

Types of outcome measures

Data was collected on the following outcomes:

- 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 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 CENTRAL search strategy.

Language

No language restrictions were applied.

Unpublished studies

Abstracts, conference proceedings and other grey literature were not searched. The manufacturing pharmaceutical company 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

The following calculations were planned. For each study, the mean TOTPAR, SPID, VAS TOTPAR or VAS SPID (Appendix 4) values for active and placebo would be 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 can be calculated using verified equations (Moore 1996; Moore 1997a; Moore 1997b), and these proportions 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 would be used to calculate relative benefit 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" would be used for the number of participants achieving at least 50% pain relief (Collins 2001).

The number of participants reporting treatment-emergent adverse effects would be extracted for each treatment group. Relative

benefit and relative risk estimates (RB and RR) would be calculated with 95% confidence intervals (CI) using a fixed-effect model (Morris 1995). NNT and number-needed-to-treat-to-harm (NNH) and 95% CI would be calculated using the pooled number of events by the method of Cook and Sackett (Cook 1995). A statistically significant difference from control is assumed when the 95% CI of the relative benefit or risk does not include the number one. Homogeneity would be examined visually using L'Abbé plots (L'Abbé 1987).

Sub-group analyses were planned to determine the effect of dose, presenting condition (pain model), and low versus high (two versus three or more) quality trials. A minimum of two trials and 200 participants must be available in any sensitivity analysis (Moore 1998). The z test (Tramér 1997) would be used to determine if there is a significant difference between NNTs for different groups in the sensitivity analyses when the 95% CIs do not overlap.

RESULTS

Description of studies

Results of the search

Eleven studies were examined in detail by reading abstracts and the full paper obtained in electronic or paper format.

Included studies

No studies were included.

Excluded studies

All the eleven studies examined were excluded. Seven studies had no placebo arm (Burguet 1989; Cutting 1980; Giudice 1987; Lecointre 1991; Ormiston 1981; Salvato 1992; van der Aa 1984); one had no 6 hour data (Bornfleth 1981); one used a peri-operative therapeutic plan (2 days before and 6 days after operation) (Massin 1985); one used an intramuscular dose during surgery (van der Westhuijzen 1994); and one used a non-standard scale in patients who were not stated to have at least moderate pain at baseline (Trop 1983).

Risk of bias in included studies

There were no included studies, so bias could not be evaluated.

Effects of interventions

There were no included studies, so effects could not be evaluated.

DISCUSSION

Tiaprofenic acid is a widely available NSAID in many parts of the world, and it is disappointing that no classical analgesic studies were found in patients with established 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 2008). 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.

Tiaprofenic acid is principally used for treating chronic musculoskeletal conditions. Long term use is associated with severe cystitis, roughly 100 times more commonly than with other NSAIDs. It is contraindicated in patients with cystitis (Buchbinder 2000; Crawford 1997), prostatitis, and urinary tract infections.

AUTHORS' CONCLUSIONS

Implications for practice

In the absence of evidence of efficacy for oral tiaprofenic acid in acute postoperative pain, its use in this indication is 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, there is no urgent research agenda.

ACKNOWLEDGEMENTS

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

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CHARACTERISTICS OF STUDIES

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

Study	Reason for exclusion
Bornfleth 1981	No 6 hour data
Burguet 1989	No placebo arm, not single dose
Cutting 1980	Not postoperative pain, no placebo arm
Giudice 1987	No placebo arm
Lecointre 1991	No placebo arm (tiaprofenic acid versus paracetamol)
Massin 1985	Peri-operative therapeutic plan (2 days before and 6 days after operation)
Ormiston 1981	No placebo arm
Salvato 1992	No placebo arm. Open design
Trop 1983	Not standard scale, and patients not necessarily with at least moderate pain
van der Aa 1984	No placebo arm (tiaprofenic acid vs indomethacin)
van der Westhuijzen 1994	Intramuscular injection during surgery

APPENDICES

Appendix 1. MEDLINE search strategy (via OVID)

[mp=title, original title, abstract, name of substance word, subject heading word]

1 tiaprofenic acid/

2 tiaprofen*.mp.

3 Ru 15060 or Suralgan or Surgam or Surgam Forte or Surgamic or Surgamyl or Thiaprofenic Acid or Tiaprofen or surgam or artiflam or "albert tiafen" or surgamyl or flamirex or flanid or lindotab or artroreuma or suralgan or tiaprofen or tiaprorex or surdolin or derilate or surgamic or anafen or fengam or gasam.mp.

4 1 or 2 or 3

5 Pain, Postoperative/

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.

7 ((post-surgical adj4 pain*) or ("post surgical" adj4 pain*) or (post-surgery adj4 pain*)).mp.

8 ("pain-relief after surg*" or "pain following surg*" or "pain control after").mp.

9 (("post surg*" or post-surg*) and (pain* or discomfort)).mp.

10 ((pain* adj4 "after surg*") or (pain* adj4 "after operat*") or (pain* adj4 "follow* operat*") or (pain* adj4 "follow* surg*")).mp.

11 ((analgesi* adj4 "after surg*") or (analgesi* adj4 "after operat*") or (analgesi* adj4 "follow* operat*") or (analgesi* adj4 "follow* surg*")).mp.

12 or/5-11

13 exp Surgical Procedures, Operative/

14 12 or 13

15 randomized controlled trial.pt.

16 controlled clinical trial.pt.

17 randomized.ab.

18 placebo.ab.

19 drug therapy.fs.

20 randomly.ab.

21 trial.ab.

22 groups.ab.

23 or/15-22

24 humans.sh.

25 23 and 24

26 25 and 4 and 14

Cochrane highly sensitive search strategy for identifying randomized trials in MEDLINE: sensitivity-maximizing version (2008 revision); Ovid format

1. randomized controlled trial.pt.
2. controlled clinical trial.pt.
3. randomized.ab.
4. placebo.ab.
5. drug therapy.fs.
6. randomly.ab.
7. trial.ab.
8. groups.ab.
9. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10. humans.sh.
11. 9 and 10

Appendix 2. EMBASE search strategy (via OVID)

[mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]

1 tiaprofenic acid/

2 tiaprofen*.mp.

3 Ru 15060 or Suralgan or Surgam or Surgam Forte or Surgamic or Surgamyl or Thiaprofenic Acid or Tiaprofen.mp.

4 surgam or artiflam or "albert tiafen" or surgamyl or flamirex or flanid or lindotab or artroreuma or suralgan or tiaprofen or tiaprorex or surdolin or derilate or surgamic or anafen or fengam or gasam).mp.

5 1 or 2 or 3 or 4

6 Pain, Postoperative/

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.

8 ((post-surgical adj4 pain*) or ("post surgical" adj4 pain*) or (post-surgery adj4 pain*)).mp.

9 ("pain-relief after surg*" or "pain following surg*" or "pain control after").mp.

10 (("post surg*" or post-surg*) and (pain* or discomfort)).mp.

11 ((pain* adj4 "after surg*") or (pain* adj4 "after operat*") or (pain* adj4 "follow* operat*") or (pain* adj4 "follow* surg*")).mp.

12 ((analgesi* adj4 "after surg*") or (analgesi* adj4 "after operat*") or (analgesi* adj4 "follow* operat*") or (analgesi* adj4 "follow* surg*")).mp.

13 or/6-12

14 exp Surgical Procedures, Operative/

15 13 or 14

16 random*.ti,ab.

17 factorial*.ti,ab.

18 (crossover* or cross over* or cross-over*).ti,ab.

19 placebo*.ti,ab.

20 (doubl* adj blind*).ti,ab.

21 (singl* adj blind*).ti,ab.

22 assign*.ti,ab.

23 allocat*.ti,ab.

24 volunteer*.ti,ab.

25 CROSSOVER PROCEDURE.sh.

26 DOUBLE-BLIND PROCEDURE.sh.

27 RANDOMIZED CONTROLLED TRIAL.sh.

28 SINGLE BLIND PROCEDURE.sh.

29 or/16-28 (667297)

30 ANIMAL/ or NONHUMAN/ or ANIMAL EXPERIMENT/

31 HUMAN/

32 30 and 31

33 30 not 32

34 29 not 33

35 34 and 15 and 5

Search filter for EMBASE (Ovid format) 2008

1. random*.ti,ab.
2. factorial*.ti,ab.
3. (crossover* or cross over* or cross-over*).ti,ab.
4. placebo*.ti,ab.
5. (doubl* adj blind*).ti,ab.
6. (singl* adj blind*).ti,ab.
7. assign*.ti,ab.
8. allocat*.ti,ab.
9. volunteer*.ti,ab.
10. CROSSOVER PROCEDURE.sh.
11. DOUBLE-BLIND PROCEDURE.sh.
12. RANDOMIZED CONTROLLED TRIAL.sh.
13. SINGLE BLIND PROCEDURE.sh.
14. or/1-13
15. ANIMAL/ or NONHUMAN/ or ANIMAL EXPERIMENT/
16. HUMAN/
17. 15 and 16
18. 15 not 17
19. 14 not 18

Appendix 3. CENTRAL search strategy

#1 MESH descriptor tiaprofenic acid.
#2 tiaprofen*.ti,ab,kw.
#3 Ru 15060 or Suralgan or Surgam or Surgam Forte or Surgamic or Surgamyl or Thiaprofenic Acid or Tiaprofen.ti,ab,kw.
#4 surgam or artiflam or "albert tiafen" or surgamyl or flamirex or flanid or lindotab or artroreuma or suralgan or tiaprofen or tiaprorex or surdolin or derilate or surgamic or anafen or fengam or gasam.ti,ab,kw.
#5 1 or 2 or 3 or 4
#6 MESH descriptor Pain, postoperative
#7((postoperative near/4 pain$) or (post-operative near/4 pain$) or post-operative-pain$ or (post$ NEAR pain$) or (postoperative near/4 analgesi$) or (post-operative near/4 analgesi$) or ("post-operative analgesi$")):ti,ab,kw.
#8 ((post-surgical near/4 pain$) or ("post surgical" near/4 pain$) or (post-surgery near/4 pain$)):ti,ab,kw.
#9(("pain-relief after surg$") or ("pain following surg$") or ("pain control after")):ti,ab,kw.
#10(("post surg$" or post-surg$) AND (pain$ or discomfort)):ti,ab,kw.
#11 ((pain$ near/4 "after surg$") or (pain$ near/4 "after operat$") or (pain$ near/4 "follow$ operat$") or (pain$ near/4 "follow$ surg $")):ti,ab,kw.
#12 ((analgesi$ near/4 "after surg$") or (analgesi$ near/4 "after operat$") or (analgesi$ near/4 "follow$ operat$") or (analgesi$ near/4 "follow$ surg$")):ti,ab,kw.
#13 OR/6-12
#14 #5 and #13
#15 Limit #14 to Clinical Trials (CENTRAL)

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 4, 2009

Date	Event	Description
8 February 2011	Amended	Contact details updated.
24 September 2010	Amended	Contact details updated.

CONTRIBUTIONS OF AUTHORS

MM, RAM, and SD performed searching, data extraction, and analysis, including assessment of study quality. HJM helped with analysis and act as arbitrator. All review authors contributed to the writing of the protocol and will contribute to the writing of the final review. SD will be responsible for conducting the update of this 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.

SOURCES OF SUPPORT

Internal sources

- Oxford Pain Research Funds, UK.

External sources

- NHS Cochrane Collaboration Grant, UK.
- NIHR Biomedical Research Centre Programme, 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]; Anti-Inflammatory Agents, Non-Steroidal [*administration & dosage]; Pain, Postoperative [*drug therapy]; Propionates [*administration & dosage]

MeSH check words

Adult; Humans