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

Moore RA, Derry S, McQuay HJ

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[Intervention Review]

Single dose oral acemetacin for acute postoperative pain in adults

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ABSTRACT

Background

Acemetacin is a non-steroidal anti-inflammatory drug (NSAID) licensed for use in rheumatic disease and other musculoskeletal disorders in the UK, and widely available in other countries worldwide. This review sought to evaluate the efficacy and safety of oral acemetacin 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 acemetacin in acute postoperative pain, and any associated adverse events.

Search methods

We searched CENTRAL (Issue 2, 2009), MEDLINE via Ovid (1966 to May 2009); EMBASE via Ovid (1980 to May 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 acemetacin 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 acemetacin and placebo 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. 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

No study fulfilled the inclusion criteria.

Authors' conclusions

In the absence of randomised evidence of efficacy for oral acemetacin in acute postoperative pain, we cannot, at present, make any conclusions regarding its effectiveness. 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 kind and similar classes, there is no urgent research agenda for this drug.

PLAIN LANGUAGE SUMMARY

Single dose oral acemetacin for acute 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 no studies that tested oral acemetacin against placebo. It is possible that the studies were done, but not reported, because they were used only to register acemetacin with licensing authorities throughout the world. However, this leaves an important gap in our knowledge, and it means that we cannot be confident, at present, about using oral acemetacin 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.

Recent reviews include well established analgesics such as paracetamol (Toms 2008), naproxen (Derry C 2009a), diclofenac (Derry P 2009), and ibuprofen (Derry C 2009b), and newer cyclo-oxygenase-2 selective analgesics, such as lumiracoxib (Roy 2007), celecoxib (Derry 2008), etoricoxib (Clarke 2009), and parecoxib (Lloyd 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).

Acemetacin

This review looks at acemetacin. Acemetacin 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 low back pain and for postoperative pain and inflammation. Usual daily doses are 120 mg to 180 mg by mouth in divided doses of 60 mg. Acemetacin is available in many European counties, as well as Mexico and Singapore. Acemetacin is not used much in the UK, with only 15,500 prescriptions in England in 2007, compared with 4.5 million for ibuprofen and almost eight million for diclofenac (PACT 2007).

Clinicians prescribe non-steroidal anti-inflammatory drugs (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).

Acemetacin is a glycolic acid ester of indomethacin, and therefore acts as a prodrug. It is metabolized to indomethacin, which then acts as an inhibitor of cyclooxygenase, producing the anti-inflammatory effects (Chavez-Pina 2007). A hypothetical advantage of acemetacin is that it reduces gastric damage when compared to indomethacin, but there is a lack of good evidence. Three small and short endoscopy studies claim less gastrointestinal damage with acemetacin than indomethacin (Müller 1986a; Müller 1986b; Müller 1989).

Based on two small, short trials, 180 mg acemetacin daily is roughly equivalent to 400 mg celecoxib daily (Leeb 2004) and 75 mg indomethacin daily in osteoarthritis (Chou 2002). Based on one small short trial, 120 mg acemetacin daily is roughly equivalent to 100 mg indomethacin daily in rheumatoid arthritis (Saul 1991). This review will look at its efficacy in the setting of acute postoperative pain.

OBJECTIVES

To assess the efficacy and adverse effects of single dose oral acemetacin 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 were included if they are double blind trials of single dose oral acemetacin 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 were included if appropriate data from the first dose are 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 four hours duration or studies that fail to present data over 4 to 6 hours post-dose.

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

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 will be included. For studies using a visual analogue scale (VAS), pain of at least moderate intensity will be equated to greater than 30 mm (Collins 1997).

Types of interventions

Acemetacin 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 (to May 2009);
- EMBASE via Ovid (to May 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.

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

Language

No language restriction were applied.

Unpublished studies

No manufacturing or distributing pharmaceutical company was 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.

The scale used is as follows.

- Is the study randomised? If yes give one point.
- Is the randomisation procedure reported and is it appropriate? If yes add one point, if no deduct one point.
- Is the study double blind? If yes then add one point.
- Is the double blind method reported and is it appropriate? If yes add one point, if no deduct one point.
- Are the reasons for patient withdrawals and dropouts described? If yes add one point.

Data management

Data were extracted by two review authors and recorded on a standard data extraction form. Data suitable for pooling would be 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 will be calculated using verified equations (Moore 1996; Moore 1997a; Moore 1997b). These proportions were 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 treatment and placebo was 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 was 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" will 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. RB/RR estimates 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% CIs would be calculated using the pooled number of events using the method devised by Cook and Sackett (Cook 1995). A statistically significant difference from the control would be assumed when the 95% CI of the RR/RB did not include the number one. Homogeneity would be examined visually using L'Abbe 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 studies and 200 participants must be available in any sensitivity analysis (Moore 1998).

RESULTS

Description of studies

Results of the search

One study was examined in detail by reading abstracts and the full paper obtained in electronic or paper format. It was excluded because it did not use a placebo and had no 6 hour data (Szabados 1986). Two Japanese studies (Kamiya 1981; Tsuyama 1981) may have contained relevant information, but no copy of the papers could be obtained and translated.

Included studies

No studies were found matching the inclusion criteria.

Excluded studies

The one study examined was excluded.

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

Acemetacin is a widely available NSAID in some parts of the world taken by oral, rectal, intravenous or intramuscular injection. It is disappointing that no classical analgesic studies have been published of efficacy of oral acemetacin compared with placebo 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.

There is a limited literature concerning the analgesic efficacy of acemetacin in acute or chronic conditions, and such trials as there are tend to be small. This probably reflects the fact that acemetacin is a pro-drug for indomethacin.

AUTHORS' CONCLUSIONS

Implications for practice

In the absence of included studies for this drug, we could not calculate evidence of efficacy for oral acemetacin in acute postoperative pain, we therefore cannot justify, at present, its use for postoperative pain. 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 PaPaS CRG for help with searching.

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References to studies awaiting assessment

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Tsuyama 1981 *{published data only}*

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Derry C 2009b

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Derry P 2009

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CHARACTERISTICS OF STUDIES

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

Study	Reason for exclusion
Szabados 1986	No 6 hour data available. No placebo

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

Kamiya 1981

Methods	
Participants	
Interventions	
Outcomes	
Notes	Unobtainable

Tsuyama 1981

Methods	
Participants	
Interventions	
Outcomes	
Notes	Unobtainable

APPENDICES

Appendix 1. MEDLINE search strategy (via OVID)

1. (acemetcin OR).ti,ab,kw.
2. Pain, postoperative.sh
3. ((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.
4. ((post-surgical adj4 pain$) or ("post surgical" adj4 pain$) or (post-surgery adj4 pain$)).ti,ab,kw.
5. (("pain-relief after surg$") or ("pain following surg$") or ("pain control after")).ti,ab,kw.

6. (("post surg$" or post-surg$) AND (pain$ or discomfort)).ti,ab,kw.
7. ((pain$ adj4 "after surg$") or (pain$ adj4 "after operat$") or (pain$ adj4 "follow$ operat$") or (pain$ adj4 "follow$ surg$")).ti,ab,kw.
8. ((analgesi$ adj4 "after surg$") or (analgesi$ adj4 "after operat$") or (analgesi$ adj4 "follow$ operat$") or (analgesi$ adj4 "follow$ surg $")).ti,ab,kw.
9. OR/2-8
10. randomized controlled trial.pt.
11. controlled clinical trial.pt.
12. randomized.ab.
13. placebo.ab.
14. drug therapy.fs.
15. randomly.ab.
16. trial.ab.
17. groups.ab.
18. OR/10-17
19. humans.sh.
20. 18 AND 19
21. 1 AND 9 AND 20

Appendix 2. Search strategy for EMBASE (via Ovid)

1. Acemetacin.sh.
2. (acemetacin OR altren or analgel or bay F 4975 or emflex or rantudil or solart or tilur or tvx 1322).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. (acemetacin OR altren or analgel or bay F 4975 or emflex or rantudil or solart or tilur or tvx 1322):ti,ab,kw.
2. MESH descriptor Pain, Postoperative.
3. ((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$")):ti,ab,kw.
4. ((post-surgical adj4 pain$) or ("post surgical" adj4 pain$) or (post-surgery adj4 pain$)):ti,ab,kw.
5. (("pain-relief after surg$") or ("pain following surg$") or ("pain control after")):ti,ab,kw.
6. (("post surg$" or post-surg$) AND (pain$ or discomfort)):ti,ab,kw.
7. ((pain$ adj4 "after surg$") or (pain$ adj4 "after operat$") or (pain$ adj4 "follow$ operat$") or (pain$ adj4 "follow$ surg$")):ti,ab,kw.

8. ((analgesi$ adj4 "after surg$") or (analgesi$ adj4 "after operat$") or (analgesi$ adj4 "follow$ operat$") or (analgesi$ adj4 "follow$ surg $")):ti,ab,kw.
9. OR/2-8
10. Clinical trial:pt.
11. Controlled Clinical Trial:pt.
12. Randomized Controlled Trial:pt.
13. MeSH descriptor Double-Blind Method
14. (clin$ adj25 trial$):ti,ab,kw.
15. ((doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)):ti,ab,kw.
16. placebo$:ti,ab,kw.
17. random$:ti,ab,kw.
18. OR/10-17
19. 1 AND 9 AND 18

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.

Date	Event	Description
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 writing. SD will be responsible for conducting any updates 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.

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

MeSH check words

Adult; Humans