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

Moore RA, Derry S, McQuay HJ

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Single dose oral meloxicam for acute postoperative pain in adults.
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[Intervention Review]

Single dose oral meloxicam for acute postoperative pain in adults

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ABSTRACT

Background

Meloxicam is a non-steroidal anti-inflammatory drug (NSAID) used mainly in treating pain associated with arthritis. The usual oral dose for osteoarthritis is 15 mg daily, but lower doses of 7.5 mg are advised in older patients. This review sought to evaluate the efficacy and safety of oral meloxicam 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 meloxicam in acute postoperative pain, and any associated adverse events.

Search methods

We searched Cochrane CENTRAL (Issue 2, 2009), MEDLINE (June 2009); EMBASE (June 2009); the Oxford Pain Relief Database.

Selection criteria

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

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 meloxicam experiencing 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

No studies were identified by the searches that examined oral meloxicam in patients with established postoperative pain.

Authors' conclusions

In the absence of evidence of efficacy, at present, for oral meloxicam 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. Given the large number of available drugs of this and similar classes, there is no urgent research agenda.

PLAIN LANGUAGE SUMMARY

Single dose oral meloxicam 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 meloxicam against placebo. It is possible that the studies were done, but not reported, because they were used only to register meloxicam 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 meloxicam 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 2009), 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).

Meloxicam

This review looks at meloxicam. Meloxicam is used mainly in treating pain associated with arthritis and can be administered orally or rectally. The usual oral dose for osteoarthritis is 15 mg daily, but lower doses of 7.5 mg are advised in older patients. Meloxicam is available in a number of European counties, as well as Argentina, Australia, New Zealand, Hong Kong, India, Malaysia, Thailand, Singapore, Brazil, Chile, South Africa, Mexico, USA & Canada. In England in 2007 1.1 million 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 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).

Meloxicam has a number of trade names (Afamid, Anposel, Biofiac, Coxflam, Dormelox, Ecax, Exel, Fexidol, Flamtec, Flexicam, Hyflex, Inicox, Isox, Latonid, Leutrol, Lonaflam, Loxam, Loxibest, Loxitan, Loxitenk, Masflex, Mel-OD, Mellotec, Melodol, Melosterol, Meloxil, Meloxigran, Meraprin, Mevamox, Miogesil, Mobex, Mobic, Mobicox, Movacox, Movalis, Movatec, Movoxicam, Parocin, Telaroid, Tenaron, Skudal, Uticox, Zilutrol). Meloxicam is a NSAID and belongs to the class of drugs called the enolic acid group, structurally related to piroxicam. The plasma half life is 15 to 20 hours. The pharmacology and some clinical features of meloxicam have previously been reviewed (Gates 2005). Meloxicam has been claimed to be a preferential inhibitor of one form of cyclooxygenase, COX-2 (Davies 1999).

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

OBJECTIVES

To assess the efficacy and adverse effects of single dose oral meloxicam 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 would have been included if they were double blind trials of single dose oral meloxicam 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 have been 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 four 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 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).

Types of interventions

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

Types of outcome measures

Data was collected on 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 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 were sought from the reference lists of retrieved articles and reviews.

Language

No language restrictions 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.

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 2) 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 can then 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 found. Relative benefit and relative risk (RB and 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% 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. Any 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

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

Included studies

No studies were found matching the inclusion criteria.

Excluded studies

All the five studies examined were excluded. Two studies were excluded as they had no placebo arm (Calvo 2007; Yilmaz 2006), one because analgesic administration was pre-emptive to surgical intervention (Kurukahvecioglu 2007), another as there was no 4 or 6 hour data (Nekoofar 2003), and the fifth used rectal, as opposed to oral, administration (Thompson 2000).

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

Meloxicam 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.

Meloxicam is principally used for treating chronic musculoskeletal conditions. It is regarded as having better gastrointestinal safety than other NSAIDs, with some evidence of this from randomised trials (Schoenfeld 1999), though this may be due to the low dose used in those studies. A more recent review was sceptical about the efficacy of meloxicam in musculoskeletal conditions (Chen 2008).

AUTHORS' CONCLUSIONS

Implications for practice

In the absence of evidence of efficacy for oral meloxicam 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 to treat postoperative pain, there is no urgent research agenda.

ACKNOWLEDGEMENTS

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

REFERENCES

References to studies excluded from this review

Calvo 2007 *{published data only}*

Calvo AM, Sakai VT, Giglio FP, Modena KC, Colombini BL, Benetello V, et al. Analgesic and anti-inflammatory dose-response relationship of 7.5 and 15 mg meloxicam after lower third molar removal: a double-blind, randomized, crossover study. *International Journal of Oral & Maxillofacial Surgery* 2007;**36**(1):26-31. [DOI: 10.1016/j.ijom.2006.09.006]

Kurukahvecioglu 2007 *{published data only}*

Kurukahvecioglu O, Karamercan A, Ege B, Koksal H, Anadol Z, Tezel E, et al. Effect of meloxicam on postoperative pain relief after inguinal hernia repair with local anaesthesia. *West Indian Medical Journal* 2007;**56**(6):530-3.

Nekoofar 2003 *{published data only}*

Nekoofar MH, Sadeghipanah M, Dehpour AR. Evaluation of meloxicam (A cox-2 inhibitor) for management of postoperative endodontic pain: a double-blind placebo-controlled study. *Journal of Endodontics* 2003;**29**(10):634-7.

Thompson 2000 *{published data only}*

Thompson JP, Sharpe P, Kiani S, Owen-Smith O. Effect of meloxicam on postoperative pain after abdominal hysterectomy. *British Journal of Anaesthesia* 2000;**84**(2):151-4.

Yilmaz 2006 *{published data only}*

Yilmaz I, Sener M, Yavuz H, Yilmazer C, Erkan AN, Cagici CA. Postoperative pain management in clinics of otolaryngology [Kulak burun bogaz kliniginde ameliyat sonrasi agri tedavisi]. *Kulak burun boğaz ihtisas dergisi : KBB = Journal of Ear, Nose, and Throat* 2006;**16**(1):1-6.

Additional references

Barden 2004

Barden J, Edwards JE, McQuay HJ, Wiffen PJ. Relative efficacy of oral analgesics after third molar extraction. *British Dental Journal* 2004;**197**(7):407-11.

Chen 2008

Chen YF, Jobanputra P, Barton P, Bryan S, Fry-Smith A, Harris G, et al. Cyclooxygenase-2 selective non-steroidal anti-inflammatory drugs (etodolac, meloxicam, celecoxib, rofecoxib, etoricoxib, valdecoxib and lumiracoxib) for osteoarthritis and rheumatoid arthritis: a systematic review and economic evaluation. Health Technology Assessment 2008; Vol. 12, issue 11:1-278, iii. [ISSN: 1366-5278]

Clarke 2009

Clarke R, Derry S, Moore RA, McQuay HJ. Single dose oral etoricoxib for acute postoperative pain in adults. *Cochrane Database of Systematic Reviews* 2009, Issue 2. [DOI: 10.1002/14651858.CD004309.pub2]

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Collins 2001

Collins SL, Edwards J, Moore RA, Smith LA, McQuay HJ. Seeking a simple measure of analgesia for mega-trials: is a single global assessment good enough?. *Pain* 2001;**91**(1-2):189-94.

Cook 1995

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Cooper 1991

Cooper SA. Single-dose analgesic studies: the upside and downside of assay sensitivity. The Design of Analgesic Clinical Trials. *Advances in Pain Research Therapy* 1991;**18**:117-24.

Davies 1999

Davies NM, Skjodt NM. Clinical pharmacokinetics of meloxicam. A cyclo-oxygenase-2 preferential nonsteroidal anti-inflammatory drug. *Clinical Pharmacokinetics* 1999;**36**(2):115-26.

Derry 2008

Derry S, Moore RA, McQuay HJ. Single dose oral celecoxib for acute postoperative pain. *Cochrane Database of Systematic Reviews* 2008, Issue 4. [DOI: 10.1002/14651858.CD004233]

Derry C 2009

Derry C, Derry S, Moore RA, McQuay HJ. Single dose oral naproxen and naproxen sodium for acute postoperative pain in adults. *Cochrane Database of Systematic Reviews* 2009, Issue 1. [DOI: 10.1002/14651858.CD004234.pub2]

Derry C 2009b

Derry C, Derry S, Moore RA, McQuay HJ. Single dose oral ibuprofen for acute postoperative pain in adults. *Cochrane Database of Systematic Reviews* 2009, Issue 3.

Derry P 2009

Derry P, Derry S, Moore RA, McQuay HJ. Single dose oral diclofenac for acute postoperative pain in adults. *Cochrane Database of Systematic Reviews* 2009, Issue 2. [DOI: 10.1002/14651858.CD004768.pub2]

Fitzgerald 2001

FitzGerald GA, Patrono C. The coxibs, selective inhibitors of cyclooxygenase-2. *New England Journal of Medicine* 2001;**345**(6):433-42.

Gaskell 2009

Gaskell H, Derry S, Moore RA, McQuay HJ. Single dose oral oxycodone and oxycodone plus paracetamol (acetaminophen) for acute postoperative pain in adults. *Cochrane Database of Systematic Reviews* 2009, Issue 3.

Gates 2005

Gates BJ, Nguyen TT, Setter SM, Davies NM. Meloxicam: a reappraisal of pharmacokinetics, efficacy and safety. *Expert Opinion on Pharmacotherapy* 2005;**6**(12):2117-40. [DOI: 10.1517/14656566.6.12.2117]

Hawkey 1999

Hawkey CJ. Cox-2 inhibitors. *Lancet* 1999;**353**(9149):307-14.

Jadad 1996a

Jadad AR, Carroll D, Moore RA, McQuay H. Developing a database of published reports of randomised clinical trials in pain research. *Pain* 1996;**66**(2-3):239-46.

Jadad 1996b

Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJM, Gavaghan DJ, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary?. *Controlled Clinical Trials* 1996;**17**:1-12.

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Lloyd 2009

Lloyd R, Derry S, Moore RA, McQuay HJ. Intravenous or intramuscular parecoxib for acute postoperative pain in adults. *Cochrane Database of Systematic Reviews* 2009, Issue 2. [DOI: 10.1002/14651858.CD004771.pub4]

McQuay 2005

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Moore 1996

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Moore 1997a

Moore A, McQuay H, Gavaghan D. Deriving dichotomous outcome measures from continuous data in randomised controlled trials of analgesics: verification from independent data. *Pain* 1997;**69**(1-2):127-30. [DOI: 10.1016/S0304-3959(96)03251-4]

Moore 1997b

Moore A, Moore O, McQuay H, Gavaghan D. Deriving dichotomous outcome measures from continuous data in randomised controlled trials of analgesics: use of pain intensity and visual analogue scales. *Pain* 1997;**69**(3):311-5. [DOI: 10.1016/S0304-3959(96)03306-4]

Moore 1997c

Moore RA, McQuay HJ. Single-patient data meta-analysis of 3453 postoperative patients: oral tramadol versus placebo, codeine and combination analgesics. *Pain* 1997;**69**(3):287-94. [DOI: 10.1016/S0304-3959(96)03291-5]

Moore 1998

Moore RA, Gavaghan D, Tramer MR, Collins SL, McQuay HJ. Size is everything-large amounts of information are needed to overcome random effects in estimating direction and magnitude of treatment effects. *Pain* 1998;**78**(3):209-16. [DOI: 10.1016/S0304-3959(98)00140-7]

Moore 2003

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Moore 2005

Moore RA, Edwards JE, McQuay HJ. Acute pain: individual patient meta-analysis shows the impact of different ways of analysing and presenting results. *Pain* 2005;**116**(3):322-31. [DOI: 10.1016/j.pain.2005.05.001]

Moore 2006

Moore A, McQuay H. Bandolier's Little Book of Making Sense of the Medical Evidence. Oxford: Oxford University Press, 2006. [ISBN: 0-19-856604-2]

Moore 2008

Moore RA, Barden J. Systematic review of dexketoprofen in acute and chronic pain. *BMC Clinical Pharmacology* 2008;**8**:11. [DOI: 10.1186/1472-6904-8-11]

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Morris JA, Gardner MJ. Calculating confidence intervals for relative risk, odds ratio and standardised ratios and rates. In: Gardner MJ, Altman DG editor(s). Statistics with Confidence - Confidence Intervals and Statistical Guidelines. London: British Medical Journal, 1995:50-63.

PACT 2007

Prescription Cost Analysis . England 2007. [ISBN: 978-1-84636-210-1]

Schoenfeld 1999

Schoenfeld P. Gastrointestinal safety profile of meloxicam: a meta-analysis and systematic review of randomized controlled trials. *The American Journal of Medicine* 1999;**107**(6A):48S-54S.

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.pub2]

Tramér 1997

Tramèr MR, Reynolds DJM, Moore RA, McQuay HJ. Impact of covert duplicate results on meta-analysis: a case study. *BMJ* 1997;**315**:635-9.

CHARACTERISTICS OF STUDIES

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

Study	Reason for exclusion
Calvo 2007	No placebo arm
Kurukahvecioglu 2007	Pre-emptive administration
Nekoofar 2003	No 4 or 6 hour data, baseline pain assessed before procedure and medication given immediately after procedure
Thompson 2000	Rectal administration, no oral route
Yilmaz 2006	No placebo arm

APPENDICES

Appendix 1. MEDLINE search strategy (via OVID)

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

1 meloxicam*.mp.
2 (Mesoxicam or Metacam or Mobec or Mobic or Movalis or Movicox or Parocin).mp.
3 (flexidol or loxitenk or merapiran or miogesil or mobic or skudal or telaroid or tenaron or movalis or alivian or bioflac or diatec or dormelox or flamatec or flexican or inicox or leutrol or lonaflam or loxam or loxiflan or melotec or meloxigran or meloxil or mevamox or movacox or movatec or movoxicam or mobicox or anposel or ecax or hyflex or isox or melodol or mobex or tenaron or zix or mobec or loxitan or mel-od or aflamid or exel or loxibest or masflex or melosterel or mobicox or movicox or ziloxican or coxflam or parocin or uticox or latonid or zilutrol).mp.
4 1 or 3 or 2
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. Search strategy for EMBASE (via Ovid)

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

1 meloxicam/
2 meloxicam*.mp.
3 (Mesoxicam or Metacam or Mobec or Mobic or Movalis or Movicox or Parocin).mp.
4 (flexidol or loxitenk or merapiran or miogesil or mobic or skudal or telaroid or tenaron or movalis or alivian or bioflac or diatec or dormelox or flamatec or flexican or inicox or leutrol or lonaflam or loxam or loxiflan or melotec or meloxigran or meloxil or mevamox or movacox or movatec or movoxicam or mobicox or anposel or ecax or hyflex or isox or melodol or mobex or tenaron or zix or mobec or loxitan or mel-od or aflamid or exel or loxibest or masflex or melosterel or mobicox or movicox or ziloxican or coxflam or parocin or uticox or latonid or zilutrol).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. Search strategy for Cochrane CENTRAL

#1 MESH descriptor meloxicam.
#2 meloxicam*.ti,ab,kw.
#3 Mesoxicam or Metacam or Mobec or Mobic or Movalis or Movicox or Parocin.ti,ab,kw.
#4 flexidol or loxitenk or merapiran or miogesil or mobic or skudal or telaroid or tenaron or movalis or alivian or bioflac or diatec or dormelox or flamatec or flexican or inicox or leutrol or lonaflam or loxam or loxiflan or melotec or meloxigran or meloxil or mevamox or movacox or movatec or movoxicam or mobicox or anposel or ecax or hyflex or isox or melodol or mobex or tenaron or zix or mobec or loxitan or mel-od or aflamid or exel or loxibest or masflex or melosterel or mobicox or movicox or ziloxican or coxflam or parocin or uticox or latonid or zilutrol).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.
11 October 2017	Review declared as stable	No new studies likely to change the conclusions are expected.

HISTORY

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

Date	Event	Description
3 April 2017	Review declared as stable	See Published notes.
15 September 2011	Review declared as stable	The authors of this review scanned the literature during August 2011 and are confident that there will be no need to bring the search up to date before at least January 2015.
8 February 2011	Amended	Contact details updated.
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 review. SD will be responsible for any update.

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

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External sources

- 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

A restricted search in March 2017 did not identify any potentially relevant studies likely to change the conclusions. Therefore, this review has now been stabilised following discussion with the authors and editors. If appropriate, we will update the review if new evidence likely to change the conclusions is published, or if standards change substantially which necessitate major revisions.

INDEX TERMS

Medical Subject Headings (MeSH)

Acute Disease; Administration, Oral; Analgesics [*administration & dosage]; Cyclooxygenase Inhibitors [*administration & dosage]; Meloxicam; Pain, Postoperative [*drug therapy]; Thiazines [*administration & dosage]; Thiazoles [*administration & dosage]

MeSH check words

Adult; Humans