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Single dose intravenous diclofenac for acute postoperative pain in adults (Protocol)

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[Intervention Protocol]

Single dose intravenous diclofenac for acute postoperative pain in adults

Ewan D McNicol[1,2,3], McKenzie C Ferguson[4], Roman Schumann[1]

[1]Department of Anesthesiology and Perioperative Medicine, Tufts Medical Center, Boston, Massachusetts, USA. [2]Department of Pharmacy, Tufts Medical Center, Boston, Massachusetts, USA. [3]Pain Research, Education and Policy (PREP) Program, Department of Public Health and Community Medicine, Tufts University School of Medicine, Boston, Massachusetts, USA. [4]Pharmacy Practice, Southern Illinois University Edwardsville, Edwardsville, USA

Contact address: Ewan D McNicol, Department of Anesthesiology and Perioperative Medicine, Tufts Medical Center, Boston, Massachusetts, USA. ewan.mcnicol@tufts.edu.

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To assess the analgesic efficacy and adverse effects of a single dose of intravenous diclofenac, compared with placebo or an active comparator, for moderate to severe postoperative pain in adults.

BACKGROUND

The proposed methodology and sections of the text in this protocol are derived from a series of reviews published in the Cochrane Library that assess single or combined analgesic agents for postoperative pain, and from suggested wording from the Pain, Palliative and Supportive Care Cochrane Review Group (PaPaS CRG) (Derry 2016).

Description of the condition

Patients frequently experience pain after surgery. Evidence indicates that around 80% of patients experience postoperative pain and that 75% of patients report pain of moderate or greater severity (Chou 2016). Many patients receive suboptimal perioperative analgesia, which affects quality of life, functioning, and time to recovery, and places them at risk for developing acute post-surgical complications and persistent post-surgical pain (Apfelbaum 2003; Chou 2016).

As noted, this review is based on a series of reviews published in the Cochrane Library, 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 person, but guides policy-making at the local level. The series covers all analgesics licensed for acute postoperative pain in the UK, and dipyrone, which is commonly used in Spain, Portugal, and Latin-American countries. The results have been examined in overviews of efficacy and harm (Moore 2015a; Moore 2015b), and related individual reviews include ibuprofen (Derry 2009), paracetamol (acetaminophen) (Toms 2008), keto-

profen and dexketoprofen (Barden 2009), codeine (Derry 2010), and combinations such as ibuprofen plus paracetamol (Derry 2013a), ibuprofen plus codeine (Derry 2013b), and paracetamol plus codeine (Toms 2009).

Description of the intervention

Acute pain trials

Single-dose trials in acute pain are commonly short in duration, rarely lasting longer than 12 hours. The numbers of participants are 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 addressed 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 one hour. This is reasonable, because not all participants given an analgesic will have significant pain relief. Approximately 18% of participants given placebo will have significant pain relief (Moore 2006), and up to 50% may have inadequate analgesia with active medicines. Hence, the use of additional or rescue analgesia is important for all participants in the trials.

Clinical trials measuring the efficacy of analgesics in acute pain have been standardized over many years (McQuay 2012). Trials have to be randomized 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 four to six 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 (Moore 2011). 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 four to six hours (Moore 2005). Patients usually remain in the hospital or clinic for at least the first six 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 (Moore 2015b).

Recommendations for nonsteroidal anti-inflammatory drug use in postoperative guidelines

Treatment guidelines for acute pain developed by major professional organizations recommend a multimodal approach to analgesia, which routinely includes administration of both an opioid and one or more nonopioids, the latter of which frequently includes a nonsteroidal anti-inflammatory drug (NSAID) (Chou 2016, Macintyre 2010). Postoperative administration of NSAIDs has been shown to reduce patient requirements for opioids and, in turn, to reduce the incidence and severity of opioid-induced adverse events (Cepeda 2005). Parenteral analgesics are required postoperatively if patients are unable to tolerate oral medications. Until recently, the only parenteral NSAID available in the US and many other countries was ketorolac. Parenteral ketorolac has demonstrated efficacy in reducing pain and opioid requirements (Cepeda 2005). However, its acute safety profile includes increased risk of gastrointestinal bleeding and renal events, particularly with use beyond five days and in at-risk populations, thought to be due to in part to its selectivity for the cyclooxygenase-1 (COX-1) enzyme (Feldman 1997; Strom 1996). Parenteral formulations of the commonly used NSAIDs ibuprofen and diclofenac have been developed, expanding the menu of NSAID agents for treating postoperative pain in patients who require intravenous (IV) analgesia (Daniels 2016; Scott 2012).

Parenteral diclofenac

Diclofenac, first introduced in Europe in 1973, has an established role in the treatment of acute and chronic pain (Daniels 2016; Hoy 2016; Todd 1988). It has analgesic, antipyretic and anti-inflammatory properties. In its oral formulation, it has demonstrated limited efficacy in the treatment of acute postoperative pain (Derry 2015). A parenteral formulation of diclofenac has been available outside of the US for several decades (Gan 2012). Due to diclofenac's poor solubility, this formulation contains the solubilizing agents benzyl alcohol and propylene glycol. The use of these solubilizers further necessitates that the drug be administered intramuscularly; or if administered intravenously, that it be further diluted and buffered (with sodium bicarbonate) before administration via slow infusion over 30 to 120 minutes, in order to prevent venous irritation. These added steps may delay analgesia, potentially limiting this formulation's role in acute postoperative pain management. Recently developed formulations of parenteral diclofenac employ hydroxypropyl-β-cyclodextrin (HPβCD) as a solubility enhancer. These formulations do not require further dilution or buffering and may be administered as bolus intravenous (Dyloject®) or subcutaneous (Akis®, Dicloin®) injections (Hoy 2016).

How the intervention might work

NSAIDs inhibit COX isoenzymes 1 and 2, thereby reducing the formation of prostaglandins that are responsible for pain and inflammation at a site of injury or disease (FitzGerald 2001). In addition to their peripheral effects, NSAIDs act in the spinal cord and central nervous system to reduce pain even when inflammation is not present. They also act upon inflammatory pathways other than those involving COX. Diclofenac shares these properties, and additionally is thought to increase β-endorphin levels and inhibit the N-methyl-D-aspartate (NMDA) pathway (Gan 2010).

Inhibition of COX may also play a role in the adverse event profile of NSAIDs. NSAIDs account for more reports of drug toxicity than any other agents (Hawkey 2002). Risk factors for toxicity include dose, duration of therapy, patient age and pre-existing renal impairment. At least two forms of COX are expressed in tissues: COX-1 is responsible for the production of prostaglandins that play a predominately protective role in the GI tract, vascular system, and kidneys, and for the production of thromboxane A2, responsible for platelet aggregation and vasoconstriction (FitzGerald 2004); COX-2 is expressed constitutively only in the CNS and kidneys but in other organs it is induced after trauma (including surgery) and inflammation. Inhibition of the production of protective prostaglandins and thromboxane may lead to gastrointestinal, hematological, cardiovascular and renal adverse events. Postoperative patients are at greater risk of developing NSAID-induced acute kidney injury as they may be volume depleted, as are the elderly, who rely on prostaglandins to maintain renal function. NSAIDs that selectively inhibit the COX-2 isoenzyme or that have a balanced COX-1/COX-2 profile may reduce the incidence of gastrointestinal bleeding and interfere less with platelet aggregation in comparison to NSAIDs that are selective for COX-1 (such as ketorolac) (FitzGerald 2001; FitzGerald 2004). Conversely, NSAIDs that are selective for COX-2 may increase the risk of a cardiovascular event. NSAIDs may also occasionally produce liver damage, particularly with long-term use (APS 2008).

Why it is important to do this review

The recent reformulation of parenteral diclofenac has led to a renewed interest in the use of this agent in the perioperative setting. The newer formulation may provide a more rapid onset of analgesia than traditional formulations. In theory, diclofenac's balanced COX-1/COX-2 profile may reduce the risk of development of acute postoperative adverse events as observed with ketorolac, such as gastrointestinal bleeding. Studies in healthy volunteers have suggested a reduced risk of platelet dysfunction compared with COX-1 selective NSAIDs (Bauer 2010), and pooled analyses of safety data from clinical trials have demonstrated a reduction in the rate of thrombophlebitis versus traditional formulations of parenteral diclofenac, and similar rates of renal dysfunction to placebo (Colucci 2009; Daniels 2016). However, there are no systematic reviews to date that have assessed the efficacy or safety of this agent.

OBJECTIVES

To assess the analgesic efficacy and adverse effects of a single dose of intravenous diclofenac, compared with placebo or an active comparator, for moderate to severe postoperative pain in adults.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomized controlled trials (RCTs), with at least 10 participants randomly allocated to each treatment group, and double-blind assessment of participant outcomes. We will include multiple dose studies if appropriate data from the first dose are available, and cross-over studies provided that data from the first phase are presented separately or can be obtained.

We will exclude:

- review articles, case reports, and clinical observations;
- studies of experimental pain;
- studies of less than four hours' duration or studies that do not present data over four to six hours post dose;
- studies where pain is not patient-reported.

For postpartum pain, we will include studies if the pain investigated is due to episiotomy or Caesarean section irrespective of the presence of uterine cramps; we will exclude studies investigating pain due to uterine cramps alone.

We will require full journal publication, with the exception of online clinical trial results, summaries of otherwise unpublished clinical trials, and abstracts with sufficient data for analysis.

Types of participants

We will include studies of adults (aged 18 years and above) with established postoperative pain of moderate to severe intensity following day surgery or inpatient surgery. For studies using a visual analog scale (VAS) (see Glossary: Appendix 1), we will consider that pain intensity of greater than 30 mm equates to pain of at least moderate intensity (Collins 1997).

Types of interventions

Diclofenac, administered as a single intravenous dose, for the relief of acute postoperative pain, and compared to placebo or any active comparator.

Types of outcome measures

Primary outcomes

- Participants achieving at least 50% pain relief over a four to six hour period.

Secondary outcomes

- Median (or mean) time to use of rescue medication.
- Number of participants using rescue medication over a four- to six-hour period.
- Withdrawals due to lack of efficacy, adverse events, and for any cause.
- Participants experiencing any adverse event.
- Participants experiencing any serious adverse event. Serious adverse events typically include any untoward medical occurrence or effect that at any dose results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, is a congenital anomaly or birth defect, is an 'important medical event' that may jeopardize the patient, or may require an intervention to prevent one of the above characteristics or consequences.
- Specific adverse events, particularly renal dysfunction, cardiovascular events, bleeding, and thrombophlebitis.

Search methods for identification of studies

Electronic searches

We will search the following databases without language restrictions.

- The Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library.
- MEDLINE (via Ovid).
- Embase (via Ovid).

MeSH or equivalent and text word terms will be used. Searches will be tailored to individual databases. The search strategy for MEDLINE is in Appendix 2.

Searching other resources

We will search ClinicalTrials.gov and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (apps.who.int/trialsearch/) for ongoing or completed trials. In addition, we will check reference lists of reviews and retrieved articles for additional studies and perform citation searches on key articles. We will contact experts in the field for unpublished and ongoing trials. We will contact study authors where necessary for additional information.

Data collection and analysis

Selection of studies

We will perform each stage of study selection in duplicate and will check for agreement between us. We will determine eligibility by reading the abstract of each study identified by the search. We will eliminate studies that clearly do not satisfy the inclusion criteria, and we will obtain full copies of the remaining studies. Two review authors (a combination of two of EM, MF and RS) will read these studies independently and reach agreement by discussion. Where agreement cannot be reached, the third author will adjudicate. We will not anonymize the studies in any way before assessment.
We will include a PRISMA flow chart in the full review, which will show the status of identified studies (Moher 2009), as recommended in Section 11.2.1 of the *Cochrane Handbook for Systematic Reviews of Intervention* (Higgins 2011). We will include studies in the review irrespective of whether measured outcome data are reported in a 'usable' way.

Data extraction and management

Two review authors (a combination of two of EM, MF and RS) will independently extract data using a standard form and check for agreement before entry into Review Manager 5 (RevMan 2014). We will collate multiple reports of the same study, so that each study, rather than each report, is the unit of interest in the review. We will collect information about the included studies (e.g. study methods, study population, baseline pain intensity) in sufficient detail to complete a table of 'Characteristics of included studies' in the full review.

Assessment of risk of bias in included studies

Two review authors (a combination of EM, MF and RS) will independently assess risk of bias for each study, using applicable criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Chapter 8, Higgins 2011), and adapted from those used by the Cochrane Pregnancy and Childbirth Group, with any disagreements resolved by discussion. We will complete a 'Risk of bias' table for each included study using the 'Risk of bias' tool in Review Manager 5 (RevMan 2014).
We will assess the following for each study.

- Random sequence generation (checking for possible selection bias). We will assess the method used to generate the allocation sequence as: low risk of bias (any truly random process, e.g. random number table; computer random number generator); unclear risk of bias (method used to generate sequence not clearly stated). We will exclude studies using a non-random process (e.g. odd or even date of birth; hospital or clinic record number).

- Allocation concealment (checking for possible selection bias). The method used to conceal allocation to interventions prior to assignment determines whether intervention allocation could have been foreseen in advance of, or during, recruitment, or changed after assignment. We will assess the methods as: low risk of bias (e.g. telephone or central randomization; consecutively numbered sealed opaque envelopes); unclear risk of bias (method not clearly stated). We will exclude studies that do not conceal allocation (e.g. open list).
- Blinding of participants and personnel (checking for possible performance bias). We will assess the methods used to blind study participants and personnel from knowledge of which intervention a participant received. We will assess methods as: low risk of bias (study states that it was blinded and describes the method used to achieve blinding, such as identical tablets matched in appearance or smell, or a double-dummy technique); unclear risk of bias (study states that it was blinded but does not provide an adequate description of how it was achieved). We will exclude studies that were not double-blind.
- Blinding of outcome assessment (checking for possible detection bias). In this review, pain-related outcomes will be self-assessed, so that the same considerations apply to detection bias as performance bias.
- Incomplete outcome data (checking for possible attrition bias due to the amount, nature and handling of incomplete outcome data). We will assess the methods used to deal with incomplete data as: low risk (< 10% of participants did not complete the study and/or used 'baseline observation carried forward' analysis); unclear risk of bias (used 'last observation carried forward' analysis); high risk of bias (used 'completer' analysis).
- Selective reporting (checking for reporting bias). We will assess whether primary and secondary outcome measures were pre-specified and whether these were consistent with those reported. We will assess reporting of results as having low risk of bias (e.g. the study protocol was available and all of the study's prespecified outcomes of interest in the review were reported in the prespecified way; the study protocol was not available but it is clear that published reports included all expected outcomes, including those that were prespecified); high risk of bias (e.g. not all of the study's prespecified primary outcomes were reported; one or more primary outcomes were reported using measurements, analysis methods or subsets of data that were not prespecified); or unclear risk of bias (information insufficient to permit judgement of 'low risk' or 'high risk').
- Size of study (checking for possible biases confounded by small size). We will assess studies as being at low risk of bias (200 participants or more per treatment arm); unclear risk of bias (50 to 199 participants per treatment arm); high risk of bias (fewer than 50 participants per treatment arm).

Measures of treatment effect

We will use risk ratio (RR) to establish statistical difference, and number needed to treat for an additional beneficial outcome (NNT) and pooled percentages as absolute measures of effect. We will use the following terms to describe adverse outcomes in terms of harm or prevention of harm.

- When significantly fewer adverse outcomes occur with treatment than with control (placebo or active) we will use the term 'the number needed to treat to prevent one additional harmful event' (NNTp).
- When significantly more adverse outcomes occur with treatment compared with control (placebo or active) we will use the term 'the number needed for one additional harmful event' (NNH).

Unit of analysis issues

We will accept only randomization of the individual participant. When two or more active treatment arms are compared with a placebo arm within the same meta-analysis, we will avoid double-counting of participants in the placebo arm by splitting the total number between the active arms. If we identify multiple-dose studies, we will use data for the most commonly used dose only; and for cross-over studies, we will use data from the first treatment phase.

Dealing with missing data

The only likely issue with missing data in these studies will be from imputation using last observation carried forward when a participant requests rescue medication. It has previously been shown that this does not affect results for up to six hours after taking study medication (Moore 2005). Where large amounts of data were missing, we will report this in our review and assess such results with caution. Where papers report results using more than one method of imputation, we will analyze data using the primary method reported and perform sensitivity analysis by entering data from secondary methods. We will also attempt to assess differences between intervention groups in reasons for missing data and how these differences might bias results.

Assessment of heterogeneity

We will assess statistical heterogeneity by visually examining forest plots and quantify it by using the I^2 statistic. The I^2 statistic is a reliable and robust test to quantify heterogeneity, since it does not depend on the number of trials or on the between-study variance. I^2 measures the extent of inconsistency among studies' results, and can be interpreted as the proportion of total variation in study estimates that is due to heterogeneity rather than sampling error. An I^2 value of greater than 50% is considered to indicate substantial heterogeneity (Deeks 2011).

Assessment of reporting biases

To assess the impact of reporting bias we will consider the number of additional participants needed in studies with zero effect (relative benefit of one) required to change the NNT for all statistically significant outcomes to an unacceptably high level (in this case the arbitrary NNT of 10) (Moore 2008). Where this number is less than 400 (equivalent to four studies with 100 participants per comparison, or 50 participants per group), we will consider the results to be susceptible to publication bias and therefore unreliable (low quality evidence).

We will also attempt to mitigate the potential for publication bias by searching clinical trial websites, as noted above, and by contacting the manufacturers of parenteral diclofenac for an internal reference list of completed studies.

Data synthesis

For efficacy analyses, we will use the number of participants in each treatment group who were randomized, received medication, and provided at least one post-baseline assessment. For safety analyses, we will use the number of participants randomized to each treatment group who took the study medication.

For each study, we will convert the mean total pain relief (TOTPAR), or summed pain intensity difference (SPID), VAS TOTPAR, or VAS SPID (see Glossary: Appendix 1) values for the active and placebo groups to %maxTOTPAR or %maxSPID by division into the calculated maximum value (Cooper 1991). We will then calculate the proportion of participants in each treatment group who achieved at least 50%maxTOTPAR using verified equations (Moore 1996; Moore 1997a; Moore 1997b), and convert these proportions into the number of participants achieving at least 50%maxTOTPAR by multiplying by the total number of participants in the treatment group. We will use this information on the number of participants with at least 50%maxTOTPAR for active and placebo groups to calculate RR and NNT.

We will accept the following pain measures for the calculation of TOTPAR or SPID (in order of priority: see Appendix 1).

- 5-point categorical pain relief (PR) scales with comparable wording to 'none', 'slight', 'moderate', 'good', and 'complete'.
- 4-point categorical pain intensity (PI) scales with comparable wording to 'none', 'mild', 'moderate', and 'severe'.
- VAS for pain relief.
- VAS for pain intensity.

If none of these measures is available, we plan to use the number of participants reporting 'very good or excellent' on a 5-point categorical global scale with the wording 'poor', 'fair', 'good', 'very good', and 'excellent' for the number of participants achieving at least 50% pain relief (Collins 2001).

For each treatment group, we will extract the number of participants using rescue medication and the number reporting treatment-emergent adverse events.

If there are sufficient data, we will calculate RR estimates with 95% confidence intervals (CIs) using the Mantel-Haenszel method and a fixed-effect model in Review Manager 5 (RevMan 2014). We will calculate NNT and NNH with 95% CIs using the pooled number of events and the method of Cook and Sackett (Cook 1995). We will assume a statistically significant difference from control when the 95% CI of the RR does not include the number one.

Quality of evidence

Two review authors (EM, MF) will independently rate the quality of evidence for each outcome. We will use the GRADE approach to assess the quality of evidence using the GRADEprofiler Guideline Development Tool software (GRADEpro GDT 2015), and the guidelines provided in Chapter 12.2 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) (Appendix 3). We will report our judgement on the quality of evidence in the 'Summary of findings' table.

We will pay particular attention to:

1. inconsistency, where point estimates vary widely across studies or confidence intervals (CIs) of studies show minimal or no overlap (Guyatt 2011);
2. potential for publication bias, based on the amount of unpublished data required to make the result clinically irrelevant (Moore 2008).

In addition, there may be circumstances where the overall rating for a particular outcome needs to be adjusted as recommended by GRADE guidelines (Guyatt 2013a). For example, if there are so few data that the results are highly susceptible to the random play of chance, or if studies use 'last observation carried forward' (LOCF) imputation in circumstances where there are substantial differences in adverse event withdrawals, one would have no confidence in the result, and would need to downgrade the quality of the evidence by 3 levels, to very low quality. In circumstances where there were no data reported for an outcome, we would report the level of evidence as very low quality (Guyatt 2013b).

Summary of findings table

We will include 'Summary of findings' tables as set out in the PaPaS author guide (PaPaS 2012), and recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Chapter 11, Higgins 2011), to present the main findings in a transparent and simple tabular format. In particular, we will include key information concerning the quality of evidence (using GRADE), the magnitude of effect of the interventions examined, and the sum of available data on the outcomes of at least 50% of maximum pain relief over four to six hours, median (or mean) time to use of rescue medication, participants using rescue medication within four to six hours, participants with at least one adverse event, and participants with a serious adverse event.

Subgroup analysis and investigation of heterogeneity

We plan to analyze different doses separately, if there are sufficient data. We also plan to analyze different formulations of parenteral diclofenac separately. We will determine significant differences between different doses or formulations using the z test (Tramèr 1997), if appropriate.

Sensitivity analysis

For meta-analyses with an I^2 score of greater than 50% we will re-analyze data using a random-effects model.

ACKNOWLEDGEMENTS

This protocol was based on a series of reviews published in the Cochrane Library that assess single or combined analgesic agents for postoperative pain, and from suggested wording from the Pain, Palliative and Supportive Care Cochrane Review Group (PaPaS CRG).

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. Glossary

Categorical rating scale: the most common are the four-category scale for pain intensity (none, mild, moderate, and severe) and the five-category scale for pain relief (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 participants are then combined to produce means (rarely medians) and measures of dispersion (usually standard errors of means). The validity of converting categories into numerical scores is checked by comparison with concurrent visual analog scale measurements. Good correlation is 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.

Visual analog scale (VAS): for pain intensity, lines with left end labeled 'no pain' and right end labeled 'worst pain imaginable', and for pain relief lines with left end labeled 'no relief of pain' and right end labeled 'complete relief of pain', seem to overcome the limitation of forcing participant descriptors into particular categories. Participants mark the line at the point that corresponds to their pain or pain relief. The scores are obtained by measuring the distance between the 'no relief of pain' end and the participant's mark, usually in millimeters. 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 co-ordination are needed, which can be difficult postoperatively or with neurological disorders.

Total pain relief (TOTPAR): TOTPAR is calculated as the sum of pain relief scores over a period of time. If a participant had complete pain relief (as measured on a 5-point categorical scale) 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 (6 x 4). Differences between pain relief values at the start and end of a measurement period are dealt with by the 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.

Summed pain intensity difference (SPID): SPID is calculated as the sum of the differences between the pain scores and baseline pain score 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 analog versions of TOTPAR and SPID.

See 'Measuring pain' in *Bandolier's Little Book of Pain* (Moore 2003).

Appendix 2. MEDLINE search strategy

1. (diclofenac or dichlofenal or diclonate or feloran or novapirina or orthofen or orthophen or voltaren or voltarol or ortofen or dyloject).tw.
2. Diclofenac/
3. 1 or 2
4. exp Pain, Postoperative/
5. pain.tw.
6. 4 or 5
7. randomized controlled trial.pt.
8. controlled clinical trial.pt.
9. randomized.ab.
10. placebo.ab.
11. drug therapy.fs.

12. randomly.ab.
13. trial.ab.
14. groups.ab.
15. 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14
16. exp animals/ not humans.sh.
17. 15 not 16
18. 3 and 6 and 17

Appendix 3. GRADE: criteria for assigning grade of evidence

The GRADE system uses the following criteria for assigning a quality level to a body of evidence (Chapter 12, Higgins 2011).

- **High**: randomized trials; or double-upgraded observational studies.
- **Moderate**: downgraded randomized trials; or upgraded observational studies.
- **Low**: double-downgraded randomized trials; or observational studies.
- **Very low**: triple-downgraded randomized trials; or downgraded observational studies; or case series/case reports.

Factors that may decrease the quality level of a body of evidence are:

- limitations in the design and implementation of available studies suggesting high likelihood of bias;
- indirectness of evidence (indirect population, intervention, control, outcomes);
- unexplained heterogeneity or inconsistency of results (including problems with subgroup analyses);
- imprecision of results (wide confidence intervals);
- high probability of publication bias.

Factors that may increase the quality level of a body of evidence are:

- large magnitude of effect;
- all plausible confounding would reduce a demonstrated effect or suggest a spurious effect when results show no effect;
- dose-response gradient.

CONTRIBUTIONS OF AUTHORS

The contributions of the three authors will be as follows.

Draft the protocol	EM, MF, RS
Develop and run the search strategy	EM PaPaS Information Specialist to provide support
Obtain copies of studies	EM
Select which studies to include	EM, MF, RS
Extract data from studies	EM, MF, RS
Enter data into RevMan	EM
Carry out the analysis	EM, MF
Interpret the analysis	EM, MF, RS

(*Continued*)

Draft the final review	EM, MF, RS
Update the review	EM, MF, RS

DECLARATIONS OF INTEREST

Ewan D McNicol (EM): none known. EM is a pharmacist with a Master's degree in Pain Research, Education and Policy, and manages patients with acute pain.

McKenzie Ferguson (MF): none known.

Roman Schumann (RS): none known. RS is an anesthesiologist whose practice includes acute perioperative pain management.

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