Systematic review: The effectiveness and safety of diclofenac for the pain management after cesarean

ABSTRACT
This is the protocol of systematic review and there is no abstract. The objective is to evaluate the effectiveness and safety of diclofenac for the pain management after cesarean.

BACKGROUND
Cesarean delivery, as a surgical operation, could help maternity and infants when there’s difficulty in vaginal delivery. Recently, many countries reported the rate of cesarean delivery was increasing year by year. Taking US as an example, the rate was 20.7% in 1996\(^1\), and increased to 32.8% in 2012\(^2\). However the Pain management is focused after cesarean because wound pain and uterine cramp pain could affect breastfeeding\(^3\) and infant-mother attachment as well. Morphine and its derivatives could manage pain after operation through oral or intramuscular medication. Besides, Patient Controlled Epidural Analgesia (PCEA) or Patient Controlled Intravenous Analgesia (PCIA) with opioids and local anesthetics were reported to be effective in the pain management of post-operation. But all of them cost highly, and the opioids’ using is restricted due to some side effects, such as potential addiction, consciousness, nausea and vomiting, respiratory depression and bowel paralysis.

Prostaglandin is the main factor that causes pain, fever and inflammation. Nonsteroidal Anti-Inflammatory Drugs (NSAIDs), can relieve the pain by inhibiting the synthesis of prostaglandins in the endoperoxide pathway. A 20% to 50% reduction in opioid consumption, sometimes with improved quality of analgesia, has been reported using different NSAIDs following various types of surgery\(^4\). Diclofenac as a nonspecific NSAIDs, is used to relieve acute pain in children\(^5\), for acute postoperative pain in adults\(^6\)-\(^8\) by oral administration. Some RCTs on diclofenac and cesarean delivery were conducted and there’s no systematic review of its effectiveness and safety based on these studies.

OBJECTIVES
To evaluate the effectiveness and safety of diclofenac for the pain management after cesarean.

METHODS
Criteria for considering studies for this review
Types of studies
We will consider randomized controlled trials (RCTs).

Types of participants
Patients undergoing both elective and emergency lower segment cesarean section.

Types of interventions
Compared diclofenac monotherapy with other NSAIDs, Opioids, placebo or blank control after cesarean.

Types of outcome measures
Primary outcomes
The main outcome is patient-reported effectiveness of pain control on perceived pain using validated scales, e.g. visual analogue.

Secondary outcomes
1. Side effects, 2. Interacting with infant, 3. Breastfeeding etc.
Search methods for identification of studies

Electronic searches
We will search PubMed; EMBASE, Cochrane Central Register of Controlled Trials(CENTRAL), Chinese BioMedical Literature Database(CBM), Wanfang Data, China National Knowledge Infrastructure (CNKI) and WHO International Clinical Trails Registry Platform from up to Apr 2014. and the details of the search strategy are in the annex 1.

Data collection and analysis
Each review team will follow the same methods to assess study eligibility, extract data from trial reports and to carry out analyses.

Selection of studies
Two review authors (XX and XX) will independently screen the titles and abstracts of all the potential studies for inclusion. We identify a result of the search and code them as “retrieval” (eligible or potentially eligible or unclear) or “do not retrieve”. We will retrieve the full-text study reports and two review authors (XX and XX) will independently screen the full text and identify studies for inclusion; and record reasons for exclusion of the ineligible studies. We will resolve any disagreement through discussion or, if required, we will consult a third author (XX). We will identify and exclude duplicates and 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 record the selection process in sufficient detail to complete a PRISMA flow diagram.

Data extraction and management
For eligible studies, at least two review authors will extract the data using an agreed form and will enter data into Review Manager Software checking for accuracy. When information regarding any of the above is unclear, review authors will attempt to contact authors of the original reports to provide further details.

Assessment of risk of bias in included studies
Two review authors (XX and XX) will independently assess risk of bias for each study using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions. We will resolve any disagreements by discussion or by involving another author (XX). We will assess the risk of bias according to the following domains.

1. Random sequence generation.
2. Attrition bias.
3. Allocation concealment.
4. Blinding of participants and personnel.
5. Blinding of outcome assessment.
6. Incomplete outcome data.
7. Selective outcome reporting.
8. Other bias.

We will grade each potential source of bias as high, low, or unclear and provide a quote from the study report together with a justification for our judgment in the “Risk of bias” table. We will summaries the risk of bias judgements across different studies for every domain listed. We will consider blinding separately for different key outcomes, where necessary. Where information on risk of bias relates to unpublished data or correspondence with a trialist, we will note this in the “Risk of bias” table. When considering treatment effects, we will take into account the risk of bias for the studies that contribute to the outcome.
Assessment of bias in conducting the systematic review
We will conduct the review according to this published protocol and report any deviations from it in the ‘Differences between protocol and review’ section of the systematic review.

Measures of treatment effect
We will analyse dichotomous data as odds ratios and continuous data as mean difference or standardised mean difference. We will enter presented data as a scale with a consistent direction of effect. We will undertake meta-analysis only where this is meaningful, that is, if the treatments, participants, and the underlying clinical question are similar enough (homogeneous) for pooling to make sense.

We will describe skewed data reported as medians and interquartile ranges.
Where multiple trial arms are reported in a single trial, we will include only the relevant arms.

Unit of analysis issues
Studies with similar units of analysis will be grouped together for the purposes of analysis. Studies with different units of analysis will not be pooled for analysis.

Dealing with missing data
We will contact investigators or study sponsors in order to verify key study characteristics and obtain missing numerical outcome data, where possible (for example when a study is identified as abstract only). Where this is not possible and the missing data are thought to introduce serious bias, we will explore the impact of including such studies in the overall assessment of results by a sensitivity analysis.

Assessment of reporting biases
If we are able to pool more than 10 trials, we will create and examine a funnel plot to explore possible small study biases.

Data synthesis
All eligible studies will be summarised in RevMan. The authors will extract the data and enter all data into RevMan, and all the entries will be rechecked by the authors. Disagreements will be resolved by discussion. We will use a fixed-effect model and perform a sensitivity analysis with the random effects model.

Summary of findings table
The main results of the review, with the quality of evidence with GRADE system, will be presented in a 'Summary of findings table'.

Subgroup analysis and investigation of heterogeneity
Possible sources of heterogeneity in this review will include comorbidity, age and follow-up. We plan to carry out the following subgroup analyses:
1. Compared diclofenac with different kinds of anaesthetic,
2. Compared rectal medication with oral or intramuscular medication.

We will use the following outcomes in subgroup analyses.
1) Patient-reported effectiveness of pain control on perceived pain.
2) Kinds and volumes of other anesthetic used.
3) Adverse effects.

We will use the formal test for subgroup interactions in Review Manager (RevMan) 5.

Sensitivity analysis
If the number of studies and data available allow for sensitivity analysis, we shall perform a sensitivity analysis by using one or all of the following strategies.
1. Removing studies with high risk of bias to see if there is any effect on the results of the meta-analysis.
2. Studies with missing data may be re-analysed using a reasonable range of missing values.
3. Data may be re-analysed using different statistical approaches.

**Reaching conclusions**

We will base our conclusions only on findings from the quantitative or narrative synthesis of included studies for this review. We will avoid making recommendations for practice and our implications for research will suggest priorities for future research and outline what the remaining uncertainties are in the area.

**ACKNOWLEDGEMENTS**

**Annex 1:**

**Additional references**

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<th>Database</th>
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【参考文献】