INPLASY PROTOCOL

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Intrathecal Morphine versus Intrathecal Hydromorphone for Analgesia after Cesarean Delivery: A protocol for systematic review and dose-response meta-analysis

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Review question / Objective: **P: patients after cesarean delivery; I and C: intrathecal morphine or intrathecal hydromorphone for post-cesarean analgesia; O: outcomes related to the effectiveness of analgesia and adverse events.; S: non-randomized or randomized treatment allocation.**
Condition being studied: **The analgesic effectiveness and opioid-related side effects of ITM and ITH after cesarean delivery lack comprehensive systematic reviews.**
Information sources: **Two independent reviewers are planned to participate in the screening process. Inclusion criteria are as follows: (1) randomized or non-randomized treatment allocation; (2) comparison of ITH with ITM; (3) adult patients after cesarean; (4) trials reporting on perioperative outcomes and/or drug adverse events. Exclusion criteria: (1) patients having additional analgesia techniques; (2) patients undergoing surgeries other than cesarean; (3) women with chronic pain or frequent opioid use.**

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 07 December 2020 and was last updated on 07 December 2020 (registration number INPLASY2020120038).

INTRODUCTION

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delivery lack comprehensive systematic reviews.

METHODS

Search strategy: We will search extensively in Embase, PubMed, the Cochrane Library, the China National Knowledge Infrastructure, Wanfang Database and Chinese Science and Technology Periodical Database. The query of our primary search would be "(((Cesarean Section[MeSH Terms]) OR (Cesarean Section[Title/Abstract])) OR (Cesarean[Title/Abstract])) AND ((Intrathecal Morphine[Title/Abstract]) AND (Intrathecal Hydromorphone[Title/Abstract]))". The last electronic search will be performed in December 2020. Additional references would be searched in the bibliographies of retrieved articles. There is no restriction on language or publication time but incomplete papers such as posters would be excluded.

Participant or population: Women after cesarean delivery.

Intervention: Intrathecal morphine.

Comparator: Intrathecal hydromorphone.

Study designs to be included: Non-randomized or randomized treatment allocation.

Eligibility criteria: Two independent reviewers are planned to participate in the screening process. Inclusion criteria are as follows: (1) randomized or non-randomized treatment allocation; (2) comparison of ITH with ITM; (3) adult patients after cesarean; (4) trials reporting on perioperative outcomes and/or drug adverse events. Exclusion criteria: (1) patients having additional analgesia techniques; (2) patients undergoing surgeries other than cesarean; (3) women with chronic pain or frequent opioid use.

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Main outcome(s): The time of postoperative analgesia, opioids consumption (mg) in 24h, times of patients asking for opioids postoperatively, analgesic adverse events.

Quality assessment / Risk of bias analysis: Quality of data reporting will be assessed independently by two authors and a third author would be consulted for any dispute. For the randomized trials, we would use the risk of bias assessment (ROBIS) tool which includes the following criteria: sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias) and others. For non-randomized trials, we will use the Newcastle-Ottawa scale (NOS). The criteria are sample selection (S), comparability (C), and outcome assessment (O). The higher scores represent a better quality of studies. The study was considered with good quality if it was scored more than 7 points.

Strategy of data synthesis: Firstly, we evaluated the distribution of potential effect modifiers (publication year, mean age, sample size, BMI, follow-up time) across studies. Secondly, we summarized the study results used to risk ratios with 95% confidence intervals (CIs) for dichotomous data and standardized mean differences (SMD) with 95% CIs for continuous variables. A random-effects model was chosen over the fixed-effects model to estimate the average treatment effect based on the assumption of differences in the treatment effect and/or sampling variability between studies. This assumption would be tested with Cochran's Q-test (p-value < 0.1), I2 statistic and $\tau 2$ statistic for heterogeneity

expressed as a percentage. Secondly, we used the influence analyses to detect studies that influence the overall estimate of our meta-analysis the most and showed relative plots as measured by I2 ordered by heterogeneity (low to high) as previously described (1). Also, we selected funnel-plot-based methods to resolve publication bias, which can affect the validity and generalization of conclusions in meta-analysis(2). In the end, we estimate the dose-dependency for the outcomes. With the American Pain Society opioid conversions guideline, the total dose of opioids will be calculated by converting all opioids to oral morphine equivalents (OME), reported in mg. The meta-analysis of incremental odds ratios (ORs) per unit of drug exposure would be performed following the procedure described in. For exploring which dose-response model fits the data best, linear or quadratic would be tested.

Subgroup analysis: No subgroup analysis would be conducted.

Sensibility analysis: We used the influence analyses to detect studies that influence the overall estimate of our meta-analysis the most and showed relative plots as measured by I2 ordered by heterogeneity (low to high) as previously described.

Language: No limitation on the language.

Country(ies) involved: China.

Keywords: post-cesarean delivery analgesia, protocol, systematic review, hydromorphone, morphine.

Contributions of each author:

Author 1 - Hengxin Cui - The author took part in Conceptualization Protocol/Project development Investigation Software execution Manuscript writing & review & editing.
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