INTRODUCTION

Review question / Objective: Patients undergoing orthopedic surgery usually suffer considerably from peri-operative pain and intrathecal morphine (ITM) has recent been used as an effective analgesia method. The intrathecal morphine dose achieving optimal analgesia for orthopedic surgery while minimizing side effects has not yet been determined. There is currently a lack of literature synthesis in the safety and effects of low-dose ITM on orthopedic surgery.

Condition being studied: Low-dose intrathecal morphine on orthopedic surgery.

Information sources: We will search the following electronic databases, registries and websites on January 11th 2022, unrestricted by date. Grey literature and non-English studies will not be excluded. English Databases: PubMed, Cochrane library and Web of science. Chinese database: Cnki.net Trial registries: ClinicalTrials.gov.

INPLASY registration number: This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 11 February 2022 and was last updated on 11 February 2022 (registration number INPLASY202220029).
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**Condition being studied:** Low-dose intrathecal morphine on orthopedic surgery.

**METHODS**

**Participant or population:** Patients who underwent orthopedic surgeries, including spinal surgery, joint surgery, bone fracture surgery or surgery for bone tumors.

**Intervention:** Low dose ITM was implemented (≤ 100 µg of morphine).

**Comparator:** Comparison group that used morphine administered via other approaches (e.g., intravenous, subcutaneous, or oral) or comparison group of unclear contrast.

**Study designs to be included:** Only randomized controlled trials.

**Eligibility criteria:** Inclusion: Patients who underwent orthopedic surgeries, including spinal surgery, joint surgery, bone fracture surgery or surgery for bone tumors; Low dose ITM was implemented (≤ 100 µg of morphine). We will exclude studies that included participants with: Comparison group that used morphine administered via other approaches (e.g., intravenous, subcutaneous, or oral) or comparison group of unclear contrast; Participants who underwent non-orthopedic surgeries.

**Information sources:** We will search the following electronic databases, registries and websites on January 11th 2022, unrestricted by date. Grey literature and non-English studies will not be excluded. English Databases: PubMed, Cochrane library and Web of science. Chinese database: Cnki.net. Trial registries: ClinicalTrials.gov.

**Main outcome(s):** 1. Pain intensity at the first 12-24 h after surgery. 2. Incidence of postoperative nausea and vomiting, the most common opioid-related side-effect.

**Additional outcome(s):** 1. Cumulative dose of analgesics at 24 h postoperatively (converted to morphine equivalent according to Opioid Equivalence Chart by NHS[10]). 2. Pain intensity at the first 12-24 h after surgery. 3. Time to first analgesic requirement after the operation. 4. The proportion of patients required rescue analgesics post-operatively. 5. Incidence of other opioid-related adverse events. 6. Blood loss of the surgery.

**Quality assessment / Risk of bias analysis:** The risk of bias for each included RCTs will be assessed by two reviewers (Y. L. and M. G. Z.) independently using the Cochrane risk of bias tool, and the overall quality of each included trial will be assessed by Jadad score. Any disagreement will be resolved by the consensus of the whole group. The graphical presentation of the assessment of risk of bias will be generated by RevMan 5.3. We will also apply the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach to evaluate the overall quality of the evidence-based on five domains: limitations of design, inconsistency of results, indirectness, imprecision, and other factors (e.g., publication bias). GRADE approach evaluates the quality of evidence as ‘high’, ‘moderate’, ‘low’, or ‘very low’ by the outcomes.

**Strategy of data synthesis:** The results from finally screened studies will be combined to estimate as effective results in standardized mean differences (SMD) and 95% CI for continuous outcomes. As to dichotomous outcomes, pooled risk ratio (RR) and 95% CI will be estimated. The synthesis will be done by generating a forest plot of the study estimates. We will evaluate the heterogeneity of the included studies with I2 test. Heterogeneity will be examined by I2 value as low, moderate or high (I2 value of 25%, 50% and 75% respectively). Statistical significance will be set at P<0.05 in this review.

**Subgroup analysis:** Subgroup analysis will be performed on the pooled estimates of at least 10 trials.
Sensitivity analysis: To confirm the robustness of our findings, a sensitivity analysis will be conducted by omitting the data from the trial one by one from the pooled analysis.

Language: English.

Country(ies) involved: China.

Keywords: Orthopedic surgery; intrathecal morphine; analgesics.

Contributions of each author:
Author 1 - Lei Yue - Y.L. conceived the research questions, designed the search strategy and prepared the manuscript draft. Y.L. will independently screen the potential studies, extract data and assess the risk of bias from included studies. Y.L. revised the search strategy and the manuscript.
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