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### ADMINISTRATIVE INFORMATION

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**Review Stage at time of this submission** - Formal screening of search results against eligibility criteria.

**Conflicts of interest** - None declared.

**INPLASY registration number:** INPLASY202470130

**Amendments** - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 31 July 2024 and was last updated on 31 July 2024.

### INTRODUCTION

**Review question / Objective** Review Question: What is the efficacy and safety of indomethacin in preventing the development of heterotopic ossification following orthopedic surgeries?

**Objective:** To systematically evaluate and summarize the available evidence on the effectiveness of indomethacin in reducing the incidence and severity of heterotopic ossification (HO) post-operatively, with an emphasis on its efficacy in high-risk surgical procedures, such as hip replacement and acetabular fracture repair surgeries. Additionally, the objective is to assess the safety profile of indomethacin use for this purpose, including potential adverse effects and drug interactions.

**PICO Breakdown:**

**Population (P):** Patients undergoing orthopedic surgeries with a high risk of developing heterotopic

ossification, such as hip arthroplasty and acetabular fracture repair surgeries.

**Intervention (I):** Administration of indomethacin, either prophylactically or therapeutically, post-operatively.

**Comparison (C):** No indomethacin administration or alternative prophylactic/therapeutic strategies for preventing heterotopic ossification.

**Outcome (O):**

**Primary Outcomes:** Incidence and severity of heterotopic ossification post-operatively, as measured by radiological assessment (e.g., Brooker classification).

**Secondary Outcomes:** Safety of indomethacin use, including adverse effects (e.g., gastrointestinal complications, renal dysfunction), drug interactions, and impact on patient-reported outcomes (e.g., pain, functional status).

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**Condition being studied** Effectiveness of Indomethacin in Preventing Heterotopic Ossification.

## METHODS

**Participant or population** Patients undergoing orthopedic surgeries with a high risk of developing heterotopic ossification, such as hip arthroplasty, acetabular and elbow fracture repair surgeries.

**Intervention** Administration of indomethacin, either prophylactically or therapeutically, post-operatively.

**Comparator** No indomethacin administration or alternative prophylactic/therapeutic strategies for preventing heterotopic ossification.

**Study designs to be included** Randomized controlled trials.

**Eligibility criteria** Criteria encompassed non-English articles, retrospective studies, case reports, conference proceedings, and systematic reviews.

**Information sources** Electronic databases, contact with authors and trial registers.

**Main outcome(s)** Incidence and severity of heterotopic ossification post-operatively, as measured by radiological assessment (e.g., Brooker classification).

**Additional outcome(s)** Safety of indomethacin use, including adverse effects (e.g., gastrointestinal complications, renal dysfunction), drug interactions, and impact on patient-reported outcomes (e.g., pain, functional status).

**Quality assessment / Risk of bias analysis** Cochrane risk-of-bias tool for randomized trials.

**Strategy of data synthesis** Statistical analyses were performed with Review Manager 5.4 (Cochrane Collaboration, Oxford, UK) and STATA 16.0 (StataCorp LP, College Station, Texas). Odds ratio (OR) with 95% confidence interval (CI) were used to compare binary variables. The weighted mean difference (WMD) and 95% CI were calculated for continuous outcomes. Based on the method described by Wan et al, the medians and interquartile ranges of continuous data were converted to means and standard deviations. For all meta-analyses the Cochrane Qpvalue and I<sup>2</sup> statistic were applied to check heterogeneity. When p value > 0.05, there was no significant

heterogeneity, a random-effect model was used to merge the results. Otherwise, a fixed-effect model was used. A p value less than 0.05 was considered statistically significant. We performed Egger's test to assess publication bias (only for outcomes including ten or more studies).

**Subgroup analysis** It is planned to conduct a subgroup analysis of patients with acetabular fractures and those who have undergone hip surgery.

**Sensitivity analysis** This involves re-analyzing the data under varying assumptions or conditions to assess how changes in these factors impact the overall findings. By systematically altering variables such as study inclusion criteria, exclusion of low-quality studies, changing analytical models (e.g., from fixed-effects to random-effects), or adjusting for potential biases, we can determine the sensitivity of the results to these modifications. If the conclusions remain consistent across various sensitivity analyses, it suggests a higher level of confidence in the robustness of the meta-analysis. Conversely, substantial variations in results may indicate instability and require further investigation.

**Country(ies) involved** China.

**Keywords** Heterotopic Ossification, Indomethacin, Meta-Analysis.

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