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OUTCOMES COMPARISON BETWEEN NSAID AND PLACEBO IN THE OCCURANCE OF HETEROTOPIC OSSIFICATION AFTER HIP SURGERY: A SYSTEMATIC REVIEW

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Article History	Abstract
Received on: 29-08-2023 Revised on: 22-09-2023 Accepted on: 14-10-2023	Introduction: Heterotropic Ossification (HO) is a devastating condition felt by patients and surgeons. It was caused by inflammatory response triggered by injury through various processes. NSAID is thought to have a capability to limit the process, hence preventing the condition. Materials and Methods: Various databases have been used to search for literatures included in this review. Screening and evaluation were conducted for researches. Results: Seven studies are included in this review and a table has been formed to show the comparison of HO and Control. Discussion: This study aimed to assess the occurrence of heterotopic ossification (HO) after hip arthroscopy and compare outcomes between those who received prophylactic nonsteroidal anti-inflammatory drugs (NSAIDs) and those who did not. The hypothesis was that NSAIDs could reduce postoperative HO. The significance of this trend varied in retrospective research due to differences in NSAID regimens. The usefulness of NSAID prophylaxis should be carefully weighed against potential side effects, and patient compliance should be assessed in future research, as it was inconsistently reported in the existing literature. Conclusion: NSAID lower the rate of postoperative HO, however, more studies need to be conducted to analyze certain efficacy of certain type of HO.
	Keywords: Heterotropic ossification, ectopic ossification, ossification, myositis ossificans, NSAID, radiotherapy.

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Introduction

Heterotopic ossification (HO) is a severe medical condition characterized by the development of bone tissue outside the normal skeletal structure, occurring within muscles and soft tissues. This abnormal formation of bone is a result of a faulty tissue repair process following trauma or surgical procedures and can be considered as a form of HO. The condition can be triggered by either genetic or non-genetic factors [1]. HO is believed to arise from the inflammatory response occurring at the site of tissue injury. This process encompasses angiogenesis, fibro proliferation, and endochondral ossification, culminating in the creation of anomalous bone outside its typical placement. These ectopic bone developments, termed HO, can vary in severity, and specific classification categories exist, especially crucial for assessing

periarticular HO [1, 2]. The Brooker scale classifies hip-related heterotopic ossification (HO) into four severity levels (I-IV), which are determined by measuring the distance between the ectopic bone and the hip joint. In contrast, the Hastings and Graham classification scale for elbow joint-related HO uses a three-point functional scale (I-III) to assess the clinical and radiographic seriousness of the condition. To ameliorate this concern in the hip region, it is recommended to implement postoperative administration of nonsteroidal anti-inflammatory drugs (NSAIDs) or radiation therapy, as these interventions have the potential to modulate signaling cascades, cellular constituents, and foster an environment that is less permissive to ectopic bone formation [3]. The higher frequency of NSAIDs usage could be attributed to their cost-effectiveness and convenient mode of administration, even though there are no significant differences in effectiveness between the two preventive choices. The primary objective of this investigation is to conduct a comparative analysis between the utilization of nonsteroidal anti-inflammatory drugs (NSAIDs) and their non-usage in the context of preventing heterotopic ossification (HO) among post-total hip replacement patients [4].

Materials and Method

Search Strategy

This research undertaking involved a systematic review conducted in accordance with the guidelines outlined by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). (Figure 1). A comprehensive literature search was carried out to identify fully-documented, peer-reviewed papers in English that compared the outcomes of plate and screw fixation versus pinning in metacarpal fractures. The databases searched included PubMed, Google Scholar, and Cochrane Library. The main focus of this systematic review is to compare the outcomes in patients with heterotopic ossification who were treated with NSAIDs versus those who were not. The search utilized keywords in accordance with the MeSH (Medical Subject Headings) rule, and the terms used were (("Heterotopic ossification"), AND ("Total hip ossification"), AND ("NSAID")).

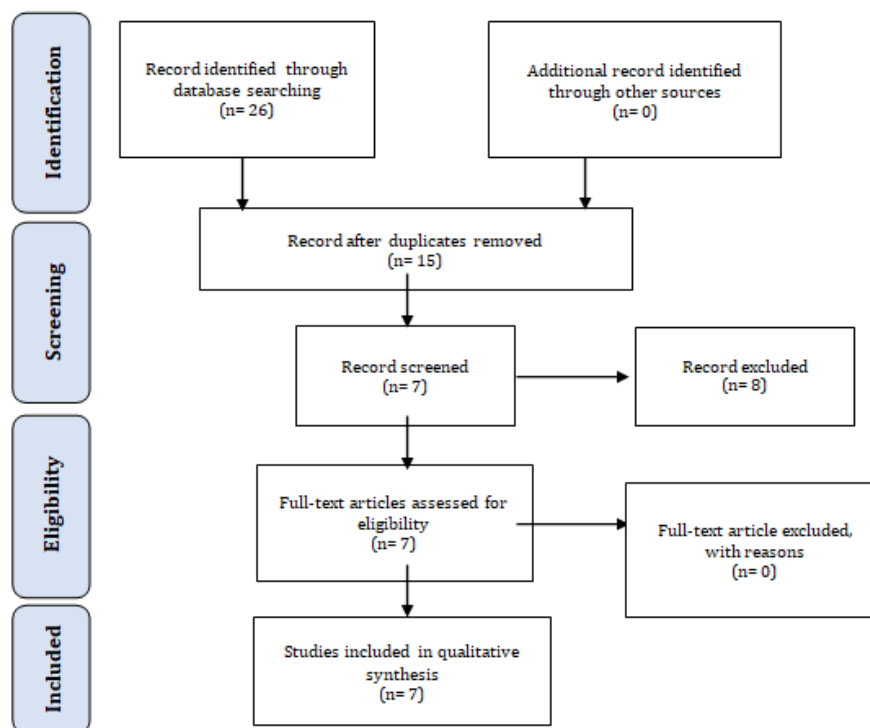


Figure1. Flow diagram describing the strategy for conducting this study based on PRISMA guideline

Inclusion Criteria

The inclusion criteria were any studies comparing between NSAID and control. The outcomes assessed includes Heterotrophic ossification. There were no restrictions based on patient demographics; however, literature written in languages other than English was excluded.

Quality Evaluation

The assessment of study quality and risk of bias was conducted using the evaluation criteria prescribed by the Oxford Center for Evidence-based Medicine. The grading of recommendations was executed in accordance with the guidelines set forth by the Grades of Recommendation Assessment, Development, and Evaluation (GRADE) Working Group. Additionally, the Agency for Healthcare Research and Quality (AHRQ) provided approval for the study procedures. The evidence was stratified into distinct categories: "class I" encompassing high-quality randomized controlled trials (RCTs), "class II" encompassing RCTs of moderate to poor quality and well-executed cohort studies, "class III" covering cohort studies and case-control studies of moderate or poor quality, and "class IV" incorporating case series data.

Results

The search strategy across PubMed, Google Scholar, Clinical Key, and Cochrane Library databases yielded a total of 26 studies. After removing duplicates and conducting title screening, 11 studies were excluded. Further exclusion occurred based on abstract reading, resulting in 9 articles for full-text review. Two of these articles were excluded during the full-text assessment, leaving a final number of 7 studies included in this systematic review (studies 5 to 9).

Tables 1 and 2 provide a comprehensive overview of the characteristics of the included studies, along with their respective levels of evidence. All studies in the review were randomized controlled trials. Males outnumbered females in all the included studies. The

average age of participants ranged from 40 to 50 years across the interventions in each study. Table 3 presents the outcomes evaluated and complications observed among 5 studies.

Table1. List of studies included

No.	Study	Journal	Study Design	Level of Evidence
1	Beckmann et al, 2014	The American Journal of Sport Medicine	Retrospective Cohort study	III
2	Beckmann et al, 2015	The Journal of Bone And Joint Surgery	A Double-Blind Randomized Placebo-Controlled Trial	I
3	Bediet al, 2012	The American Journal of Sport Medicine	Retrospective Cohort study	III
4	Nossa et al, 2014	Current Orthopaedic Practice	prospective cohort study	II
5	Randelli et al, 2010	Journal of Orthopaedic Trauma	Retrospective Study	III
6	Sagi et al, 2014	Journal of Orthopaedic Trauma	Prospective randomized double blind trial	II
7	Badi et al, 2023	Life	Restrospective Study	III

Table2. Characteristic of Patients

No.	Study	Total Sample Size	Treatment Protocol		Mean Age	Male Female Ratio
			NSAID	No NSAID		
1	Beckmann et al, 2014	357 patients	117	240	31.4	40:60
2	Beckmann et al, 2015	106 patients	52	54	35	38: 62
3	Bediet al, 2012	616 patients	616	-	30.6	55:45
4	Nossa et al, 2014	360 patients	120	240	40.4	40.6:59.4
5	Randelli et al, 2010	300 patients	285	15	37.4	180:120
6	Sagi et al, 2014	98 patients	226	67	40.75	73.25:26.75
7	Badi et al, 2023	312 patients	208	104	64.2	173:139

Discussion

One of the principals aims of this study was to evaluate the occurrence rate of heterotopic ossification (HO) subsequent to hip arthroscopy, comparing outcomes between cases with and without prophylactic utilization of nonsteroidal anti-inflammatory drugs (NSAIDs). It was hypothesized that the use of NSAIDs could potentially decrease the occurrence of postoperative HO. The results demonstrated that the incidence of heterotopic ossification (HO) among patients who did not receive any prophylactic nonsteroidal anti-inflammatory drugs (NSAIDs) was determined to be 13.4%. However, when NSAIDs were employed in the postoperative period, this rate significantly decreased by more than fourfold [10]. Although the statistically significant pooled odds ratios of prospective studies confirm this, given the considerable variability in retrospective research, we cannot be certain of the importance of the trend detected. This disparity in retrospective trials could be due to the use of different NSAID regimens [7, 10].

Beckmann et al.'s study exhibited a notable increase in the prevalence of femoral osteoplasty. These findings underscore the necessity for additional well-structured trials to establish the efficacy of prophylactic nonsteroidal anti-inflammatory drugs (NSAIDs) following hip arthroscopy [5]. Although the results indicate a potential decrease in the radiographic

occurrence of heterotopic ossification (HO) with NSAID prophylaxis, the clinical significance of this reduction in relation to symptomatic HO remains uncertain. Remarkably, a substantial number of patients with heterotopic ossification (HO) appear to be asymptomatic in both the NSAID-prophylaxis group (70%) and the no-prophylaxis group (75%), as highlighted in this review [11]. This information is of paramount importance for hip arthroscopists contemplating the use of NSAID prophylaxis, as it can be crucial in reducing the rate of radiographic complications.

Sagi et al. (2014) observed different duration of indomethacin with the incidence of HO and its side effects of nonunion in hip surgery. The study found that one week of indomethacin prophylaxis is the optimal duration to prevent heterotopic ossification without disturbing the union process of the bone. Another important part of the study was the measurement of mean volume of HO where, 1 week indomethacin prophylaxis shows the smallest volume (6300mm³) compared to other duration of the treatment. However, compared with other included studies in this review, the sample size of the trial in considerably small and the author mentioned the potential of sampling error of the study.

The popularity of selective COX-2 inhibitor has been rising lately. Its popularity is based on minimal COX-1 inhibition side effects that cause various problems on patients. The latest research by Badi et al. tried to evaluate its effect on HO. He found that a low dose of celecoxib significantly reduce the likelihood of HO occurrence on hip surgery [12]. Due to indomethacin side effect on gastrointestinal tract, the use of it should be monitored tightly; hence COX-2 selective inhibitor is more appealing.

If heterotopic ossification (HO) is unlikely to cause symptoms or be clinically significant, the usefulness of NSAID prophylaxis might be limited. In such cases, the benefits of using NSAIDs for prevention need to be carefully weighed against potential drug-related issues and side effects. Additionally, preliminary results from the randomized controlled trial conducted by Beckmann et al. indicate that NSAID prophylaxis may not offer any functional advantage [5, 6]. In this systematic review, the investigation also delved into the influence of various NSAID regimens. Despite a greater proportion of patients receiving nonselective NSAIDs, the study revealed that all forms of NSAID prophylaxis were linked to a reduced risk of postoperative heterotopic ossification (HO). In a separate systematic review and meta-analysis centered on hip arthroplasty, there was no statistically significant difference found between the application of selective cyclooxygenase-2 (COX-2) inhibitors and nonselective NSAIDs. Nevertheless, selective COX-2 inhibitors were recommended due to their comparatively milder adverse-effect profile [10].

In the present study, it was observed that the reporting of NSAID medication side effects in the existing hip arthroscopy literature is inconsistent. Given the ongoing concerns regarding these side effects, it is imperative for future research to also assess patient compliance as an additional outcome. However, in the current review, it was noted that the majority of the included trials did not document the level of compliance, which could potentially impact the outcomes of the patient groups under study.

Conclusion

The administration of NSAIDs has been shown to reduce the incidence of postoperative HO. However, in order to thoroughly assess the effectiveness of specific medications in the context of hip arthroscopy, larger prospective trials are necessary.

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Conflict of Interest

All authors declare no conflict of interest.

Informed Consent

Written informed consent was obtained from the patient.

Ethical Statement

The patient provided written informed consent for this case to be published.

Author Contribution

PTA, IGNSA, AS, DD, and FL designed the study. PTA, IGNSA, AS, DD, and FL retrieved the data. PTA, IGNSA, AS, DD, and FL reading, reviewing, and sorting the journals. PTA, IGNSA, AS, DD, and FL wrote the manuscript. All author approved the final version of the manuscript

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