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Efficacy of Ibuprofen after Total Hip Arthroplasty to Prevent Heterotopic Ossification: Systematic Review and Meta-Analysis*

Eficácia do ibuprofeno após artroplastia total de quadril para prevenção de ossificação heterotópica: Revisão sistemática e metanálise

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Abstract

The objective of this study was to conduct a systematic review and meta-analysis of relevant randomized control trials (RCTs) to determine the role of ibuprofen, as well as the optimum dose and duration of therapy, in preventing the incidence of heterotopic ossification (HO) after primary total hip arthroplasty (THA). A literature search was performed using the PubMed/MEDLINE and Cochrane Library databases for RCTs that compared the use of ibuprofen versus placebo as prophylaxis for HO in patients after THA. The main outcomes for this study were overall occurrence of HO, occurrence according to the Brooker classification, and gastrointestinal complications. A total of 27 potential articles were identified from the database. Eventually, four trials with 1,153 patients were included in the final analysis. When compared with placebo, the use of ibuprofen is associated with a reduction in the incidence of HO at the 3- and 12-month follow-up appointments, as well as the incidence of Brooker II and III HO ($p < 0.05$). However, there was no significant difference between the ibuprofen and placebo groups in terms of treatment discontinuation due to gastrointestinal complications or the incidence of Brooker I and IV HO ($p > 0.05$). The existing data indicates that ibuprofen is safe and efficacious in reducing the total incidence of HO along with Brooker II and III HO at follow-up. However, due to the small number of studies, the conclusions are limited; therefore, more high-quality clinical trials are required to develop guidelines for optimal dose and duration of therapy.

Keywords

- arthroplasty, replacement, hip
- ossification heterotopic
- ibuprofen
- meta-analysis

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Resumo

O objetivo deste estudo foi realizar uma revisão sistemática e metanálise de estudos clínicos randomizados (ECRs) relevantes para determinar o papel do ibuprofeno, sua dose ideal, e a duração do tratamento na prevenção de ossificação heterotópica (OH) após a artroplastia total primária do quadril (ATQ). Uma pesquisa bibliográfica foi feita nos bancos de dados PubMed/MEDLINE e Cochrane Library para a obtenção de ECRs que comparassem o uso de ibuprofeno e de placebo como profilaxia para OH em pacientes submetidos à ATQ. Os principais desfechos deste estudo foram ocorrência geral de OH, classificação de Brooker da OH, e complicações gastrintestinais. No total, 27 artigos foram identificados nos bancos de dados e 4 estudos, com 1.153 pacientes, foram incluídos na análise final. Em comparação ao placebo, o uso de ibuprofeno reduziu a incidência de OH aos 3 e 12 meses de acompanhamento e a incidência de OH Brooker II e III ($p < 0,05$). No entanto, não houve diferença significativa entre os grupos que receberam ibuprofeno e placebo em termos de interrupção do tratamento devido a complicações gastrintestinais ou da incidência de OH Brooker I e IV ($p > 0,05$). Os dados existentes indicam que o ibuprofeno é seguro e eficaz na redução da incidência total de OH e de OH Brooker II e III durante o acompanhamento. No entanto, as conclusões são limitadas devido ao pequeno número de estudos; logo, mais estudos clínicos de alta qualidade são necessários para o desenvolvimento de diretrizes em relação à dose e duração ideal da terapia.

Palavras-chave

- artroplastia de quadril
- ossificação heterotópica
- ibuprofeno
- metanálise

Introduction

Total hip arthroplasty (THA) is widely regarded as one of the most effective and successful procedures in the field of orthopedics.[1] It is a commonly performed surgery for the treatment of osteoarthritis, rheumatoid arthritis, avascular necrosis, developmental dysplasia, and a variety of other hip pathologies. Dislocation of the implant, wounds, or joint infections of the hip, intraoperative and periprosthetic fracture are all common complications after THA.[2,3] Another possible well-recognized complication after THA is heterotopic ossification (HO), which is defined as ectopic bone development in a soft-tissue structure. heterotopic ossification typically presents without clinical manifestations; however, symptomatic cases are clinically characterized by limitations in mobility due to shortened range of motion, severe pain, leg swelling, stiffness, and, in severe but rare cases, complete ankylosis, postoperatively.[4] The Brooker classification system (grades I–IV) is often utilized to evaluate and stratify the severity of HO in patients following THA.[5]

The average incidence of HO occurrence is reported to be at 30%, according to the results of a meta-analysis.[6] In addition to well known risk factors, such as male gender, history of hip surgery, and HO development, the risk of HO incidence is further increased when associated with certain systemic illnesses, such as diffuse idiopathic skeletal hyperostosis, Paget disease, ankylosing spondylitis, and hypertrophic osteoarthropathy.[3,7,8] Along with these factors, the incidence of HO is also dependent on the surgical approach used for THA, with direct lateral and direct anterior approach having a greater risk when compared with the posterior approach.[9,10] Currently, radiation therapy and nonsteroidal antiinflammatory drugs (NSAIDs) are the two accepted methods to prevent the incidence of HO postoperatively.[11] Radiation therapy inhibits HO formation by slowing down the rapidly dividing osteoprogenitor cells and inhibiting the differentiation of mesenchymal cells into mature osteoblasts. However, its use is restricted because it increases the cost of treatment and carries a greater risk of developing soft-tissue neoplasm.[12,13] Meanwhile, NSAIDs work by inhibiting the cyclooxygenase enzyme (COX), which limits the formation of prostaglandins particularly prostaglandin-E_2. Nonsteroidal antiinflammatory drugs have proved to be beneficial in the prevention of HO after THA, and a variety of NSAID drugs are commonly used for HO prophylaxis.[14]

Although ibuprofen, a non-selective NSAID, has been a widely used drug in the prevention of HO, there are no relevant meta-analyses on the use of ibuprofen as a prophylactic agent to prevent HO after THA. The focus of this systematic review and meta-analysis of RCTs is to evaluate the efficacy and safety of ibuprofen for the prophylaxis of HO after hip surgery, specifically primary THA.

Methods

Literature Search

Electronic databases, including the PubMed/MEDLINE and Cochrane Library databases, were searched up to April 26th, 2021, with no restriction on the language of the publications. We formulated a search strategy by combining keywords and MeSH terms using the Boolean AND/OR operator. A detailed PubMed/MEDLINE search strategy is given in (►**Table 1**). Since this article is a meta-analysis of published studies, no ethics committee or institutional review board approval was required for the research. Moreover, the reference lists of the included studies and previously published articles were searched for more relevant studies that met the eligibility

criteria. The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines were followed for this systematic review and meta-analysis.[15]

Eligibility Criteria

The eligibility criteria were determined in accordance with the Population, Intervention, Comparator, Outcomes and Study Design (PICOS) principle. 1) Population: patients undergoing primary hip arthroplasty, 2) Intervention: postoperative administration of ibuprofen (any dose and duration of therapy), 3) Comparators: placebo, 4) Outcome: incidence of HO in radiological follow-up, 5) Study Design: RCT. On the contrary, studies were excluded if they were: (1) Studies with incomplete data to perform the analysis, (2) Non-randomized control trials, comparative study, quasi-randomized trials, editorial articles, letter to editor, cohort studies, review article, meta-analyses, expert opinion, conference papers, or books (3) Animals, cadaveric, and in vitro studies (4) Duplicates or overlapping publications by same author or institution.

Data collection and Outcome Measures

Two authors were involved in the following data extraction from each of the included studies: first author's name, year of publication, country of origin of the study, patient demographics, treatment regime for each group, total sample size of the study, and radiological follow-ups. Disagreements were resolved by discussion. The outcomes of this meta-analysis are as follows: overall incidence of HO during follow-up, HO incidence according to the Brooker classification, and treatment discontinuation due to gastrointestinal complications.

Methodological Quality Assessment

Two authors examined the quality of the eligible studies, and, in case of any discrepancies, a third author was referred to. The methodological quality of the studies that met the inclusion criteria was evaluated according to Cochrane Collaboration's tool for assessing risk of bias using the Review Manager, version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, 2014).[16] For the present analysis, each study was evaluated for: allocation, randomization, blinding of participant, blinding of personnel, blinding of assessor, selective reporting, incomplete data, and unknown source of bias.

Statistical analysis

The meta-analysis was conducted using the R version 4.0.3 through RStudio Desktop version 1.4 software (R Foundation for Statistical Computing, Boston, MA, USA). The data was pooled using the DerSimonian-Laird random effects model, risk ratios (RRs) with 95% confidence intervals (CIs) were calculated.[17] Statistical heterogeneity was tested using the chi-squared (x^2) test and I^2 statistic. When $I^2 > 75\%$, it indicated high level of heterogeneity, $I^2 > 50\%$ indicated moderate level of heterogeneity, $I^2 < 50\%$ indicated low level of heterogeneity.[18] Funnel plot was used to detect the existing publication bias. Statistical significance was considered when the p-value < 0.05.

Results

Search Results and Study Characteristics

A summary of the study selection process is presented in (►**Fig. 1**). We identified a total of 27 studies from the initial search of the databases. Following the removal of duplicate studies, an initial screening of articles was conducted based on title and abstract. Eleven articles with full text were selected to be evaluated using the inclusion criteria. Finally, four RCTs were included in the meta-analysis.[19–22]

Study Characteristics

The 4 trials published between 1985 and 2006, represent a total of 1,153 patients with sample sizes ranging from 50 to 902. Three studies were conducted in Sweden, while one was conducted in Australia and New Zealand. The age of

Table 1 Search strategy for PubMed

Search#	Query
#1	heterotopic ossification [MeSH Terms]
#2	heterotopic ossification* [TIAB] OR heterotopic ossify* [TIAB] OR periarticular ossification* [TIAB] OR periarticular ossify* [TIAB] OR ectopic ossification* [TIAB] OR ectopic ossify* [TIAB] OR pathological ossification* [TIAB] OR pathological ossify* [TIAB]
#3	Arthroplasty [MeSH Terms] OR hip arthroplasty [MeSH Terms] hip prosthesis [MeSH Terms] OR hip replacement [MeSH Terms]
#4	hip arthroplasty [TIAB] OR hip replacement*[TIAB] OR hip prosthesis [TIAB] OR hip prosthetic* [TIAB]
#5	Ibuprofen [MeSH Terms]
#6	Ibuprofen [TIAB] OR Advil [ALL] OR Ibutab [ALL] OR Motrin [ALL] OR Brufen [ALL] OR Motrin [ALL]
#7	#1 OR #2
#8	#3 OR #4
#9	#5 OR #6
#10	#7 AND #8 AND #9

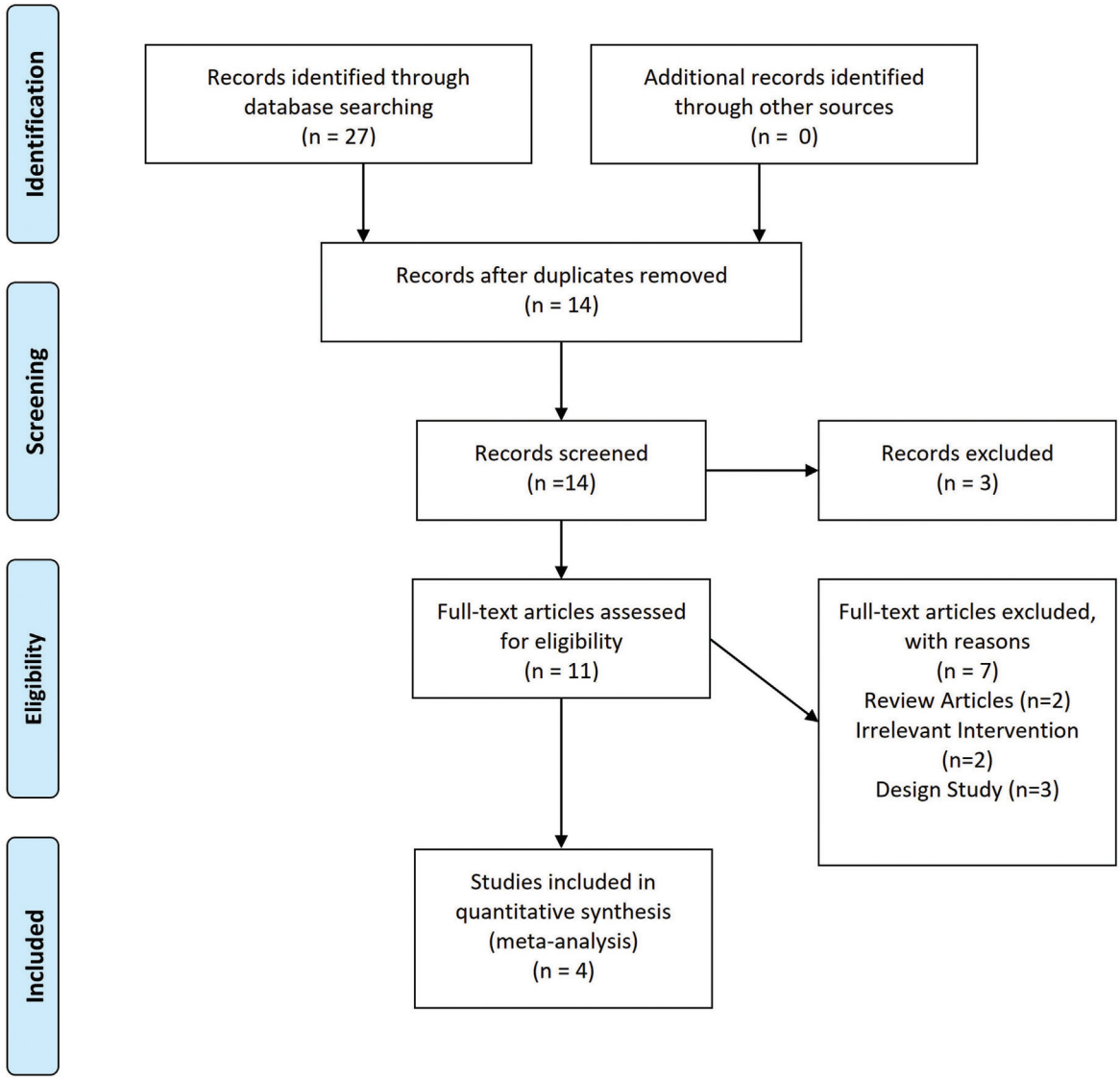

Fig. 1 PRISMA (Preferred Reporting Items for Systematic Reviews) flow diagram summarizing of the process of selecting relevant clinical studies.

participants of these trials ranged from 66 to 70 years. The daily dose of ibuprofen administered in these trials varied from 1,200 mg to 1,500 mg for a postoperative period of 7 to 92 days. The general characteristics of the included studies are presented in (►**Table 2**).

Results of Meta-Analysis

The Incidence of HO at 3 Months Follow-up

Two studies with 194 participants reported data on the incidence of HO at 3 months follow-up.[20,22]

The reported rate of incidence of HO at 3 months was 13.67% in the ibuprofen group and 43.10% in the control group. The pooled results indicate that the use of ibuprofen was associated with significant reduction in occurrence of HO 3 months after surgery. (RR = 0.33 [95% CI, 0.20–0.54]; $p < 0.01$; $I^2 = 0.0\%$) (►**Fig. 2A**).

The Incidence of HO at 12 Months Follow-up

All studies with 1,153 patients reported data on the incidence of HO at 12 months follow-up.[19–22]

The reported rate of incidence of HO at 12 months was 27.89% in ibuprofen group and 45.85% in control group. There was moderate heterogeneity observed between the included studies ($I^2 = 66\%$). Therefore, a subgroup analysis was performed with respect to daily dose of Ibuprofen administered. According to the results, daily administration of 1,200 mg/day of ibuprofen significantly reduced occurrence of HO at 12 months post-operatively. (RR = 0.53 [95% CI, 0.39–0.74]; $p < 0.01$) (►**Fig. 2B**).

Treatment Discontinuation Due to Gastrointestinal Complications

All four studies with 1,153 patients reported data on treatment discontinuation due to GI complications.[19–22] The

Table 2 The general characteristic of the included studies

Author	Year	Country	Treatment				Patients			
			Study design	Intervention daily dose (mg)	Control	Duration (days)	Radiological follow-up (months)	Male (%)	Mean age (years)	Sample	Dropouts
Elmstedt	1985	Sweden	RCT	Ibuprofen 1,200	Placebo	92	1.4, 3, 6, 12	53	70/70	50	7
Ahrengat	1994	Sweden	RCT	Ibuprofen 1,500	Placebo	10	2, 12	47	70/70	57	10
Persson	1998	Sweden	RCT	Ibuprofen 1,200	Placebo	21[(A)], 7[(B)]	3, 12	N/S	N/S	144	15
Fransen	2006	Australia, New Zealand	RCT	Ibuprofen 1,200	Placebo	14	12	54	66/67	902	49

Abbreviations: RCT, randomized control trial; N/S, not stated.
[A]Ibuprofen for 21 days.
[B]Ibuprofen for 8 days, then 2 weeks of placebo.

reported incidence of treatment discontinuation in ibuprofen group was 11.71% and 7.85% in control group. No statistically significant difference was observed between the two groups (RR = 1.40 [95% CI, 0.97–2.01]; $p = 0.07$; $I^2 = 0\%$) (►**Fig. 2C**).

The Incidence of Brooker I HO

Three studies with 1,103 patients reported data on incidence of Brooker I HO.[19–21] The reported incidence of Brooker I HO in the ibuprofen group was 19.9% and 25.6% in the control group. There was no statistically significant difference observed between the 2 groups in the incidence of Brooker I HO (RR = 0.86 [95% CI, 0.54–1.37]; $p = 0.52$; $I^2 = 49\%$) (►**Fig. 3A**)

The Incidence of Brooker II HO

Three studies with 1,103 patients reported data on the frequency of Booker II HO.[19–21] The reported rate of incidence was 6.71% in the ibuprofen group and 10.7% in the control group. The results suggest there was a statistically significant difference between the 2 treatment groups. The use of ibuprofen was associated with a 36% reduction in the incidence of Brooker II HO (RR = 0.64 [95% CI, 0.43–0.97]; $p = 0.04$; $I^2 = 0\%$) (►**Fig. 3B**).

The Incidence of Brooker III HO

Three studies with 1,103 patients reported data on the incidence of Brooker III HO.[19–21] The reported rate of incidence was 2.37% in the ibuprofen group and 6.69% in the control group. Our analysis of the result indicates that ibuprofen had a statistically significant impact in preventing the development of Brooker III HO postoperatively (RR = 0.38 [95% CI, 0.20–0.73]; $p = < 0.01$; $I^2 = 0$) (►**Fig. 3C**).

The Incidence of Brooker IV HO

Three studies with 1,103 patients reported data on the incidence of Brooker IV HO.[19–21] The reported rate of incidence was 0.39% in the ibuprofen group and 1.72% in the control group. The pooled result indicates that the use of ibuprofen had no significant impact in preventing the development of Brooker IV HO compared with placebo (RR = 0.36 [95% CI, 0.11–1.22]; $p = 0.10$; $I^2 = 0$) (►**Fig. 3D**).

Methodological Quality and Publication Bias Assessment

The methodological quality and risk of bias assessment of the included trials is summarized in (►**Fig. 4A**). All the four included studies were described as RCTs. Three studies reported appropriate methods of randomization, and only one study clearly described the process of allocation concealment. Blinding of participants and personnel was performed in all four studies. The blinding of outcome assessment was not reported clearly in three studies. All the included articles displayed a low risk of bias for the blinding of participants, personnel, incomplete outcome data and selective outcome reporting. Three studies were with unclear risk of bias for other biases. On visual inspection, asymmetry was observed in the funnel plot assessing publication (►**Fig. 4B**). Generally, when the number of studies included a meta-analysis is less than 10 the funnel plot

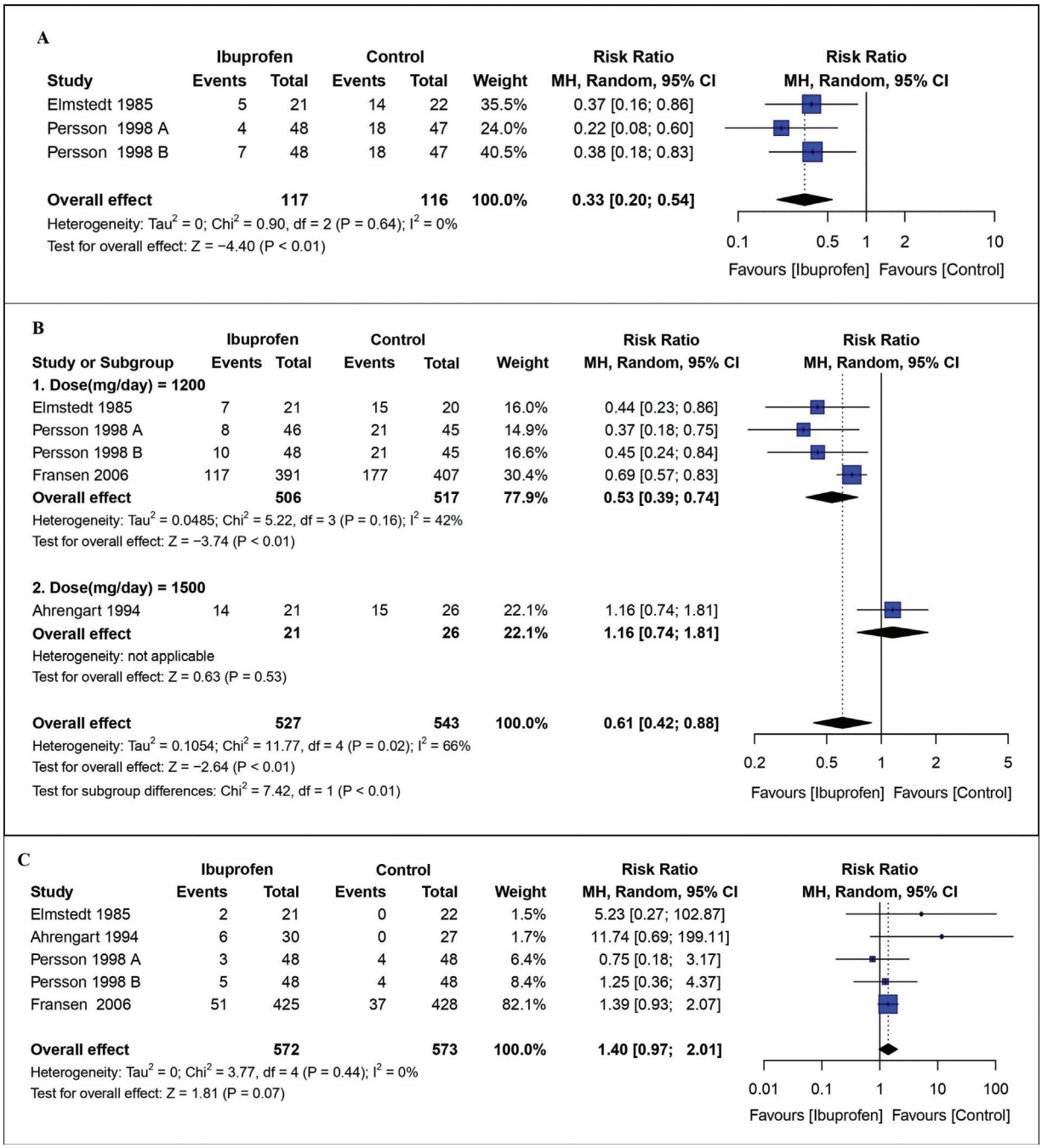

Fig. 2 (A) Forest Plot at 3 months follow-up comparing occurrence of HO between the two groups. (B) Forest Plot at 12 months follow-up comparing occurrence of HO between the two groups. (C) Forest Plot comparing Discontinuation Due to GI side effects between the two groups.

asymmetry is considered non-significant.[23] Since only four studies were included in this meta-analysis, we did not perform the Egger regression test to statistically test for asymmetry.

Discussion

To our knowledge, this is the only meta-analysis performed to date that assesses the effectiveness of ibuprofen versus placebo in preventing HO after primary hip arthroplasty. The main findings indicate ibuprofen was successful in reducing the incidence of HO at the 3 and 12-month follow-ups. Furthermore, no difference was observed in the incidence of treatment discontinuation due to gastrointestinal complications between the two groups. The most common etiology of HO can be due to acquired or non-genetic reasons such as complications of surgery, like arthroplasty, fracture repair, and neurogenic and musculoskeletal trauma; however, rare genetic causes exist as well.[24,25] Similar to fracture healing, HO development occurs by a combination of intramembranous and endochondral ossification, and the pathogenesis of HO is considered to be dependent on these three

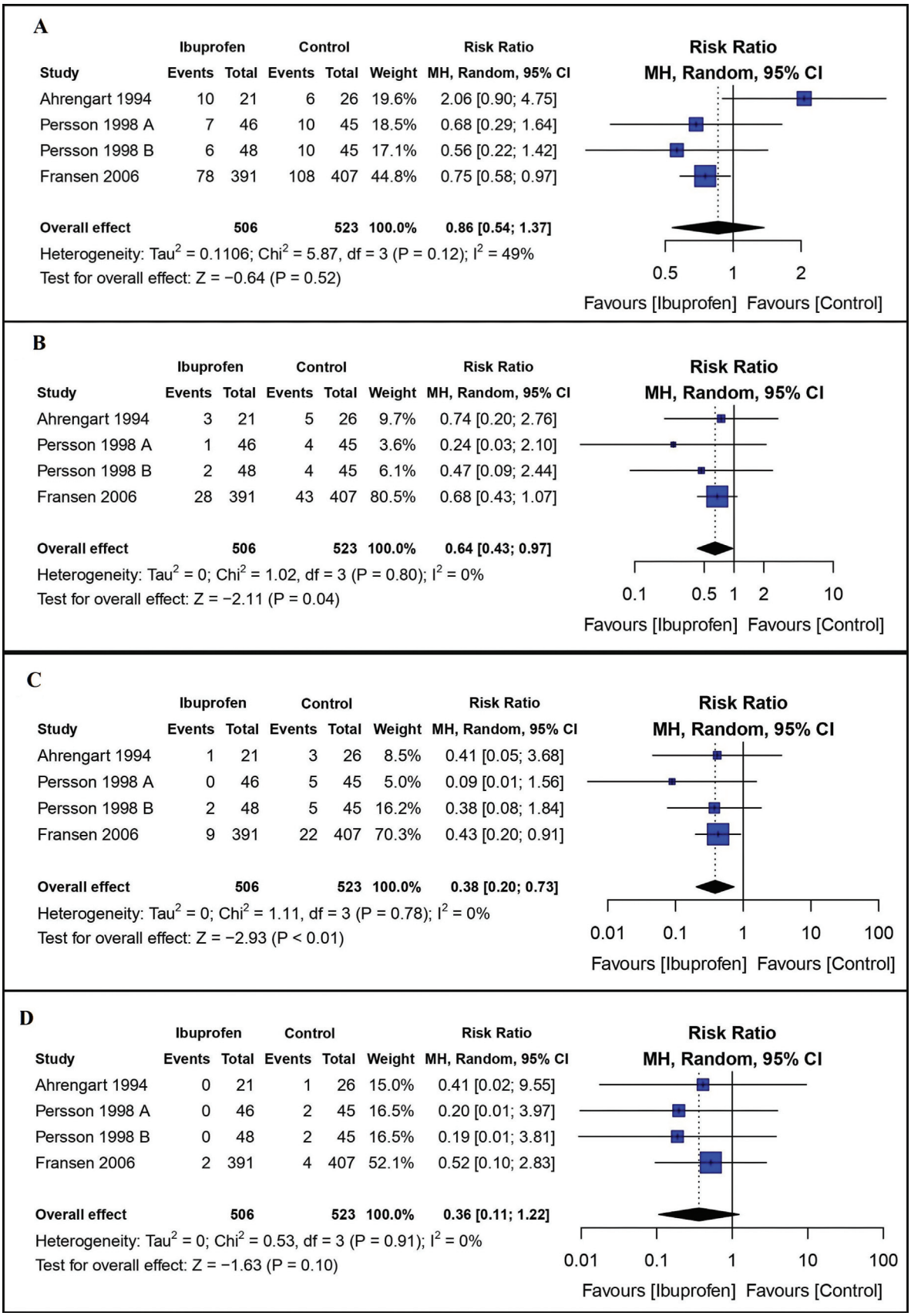

Fig. 3 (**A**) Forest Plot for Incidence of Brooker I HO after surgery between the two groups. (**B**) Forest Plot for Incidence of Brooker II HO after surgery between the two groups. (**C**) Forest Plot for Incidence of Brooker III HO after surgery between the two groups. (**D**) Forest plot for incidence of Brooker IV HO after surgery between the two groups.

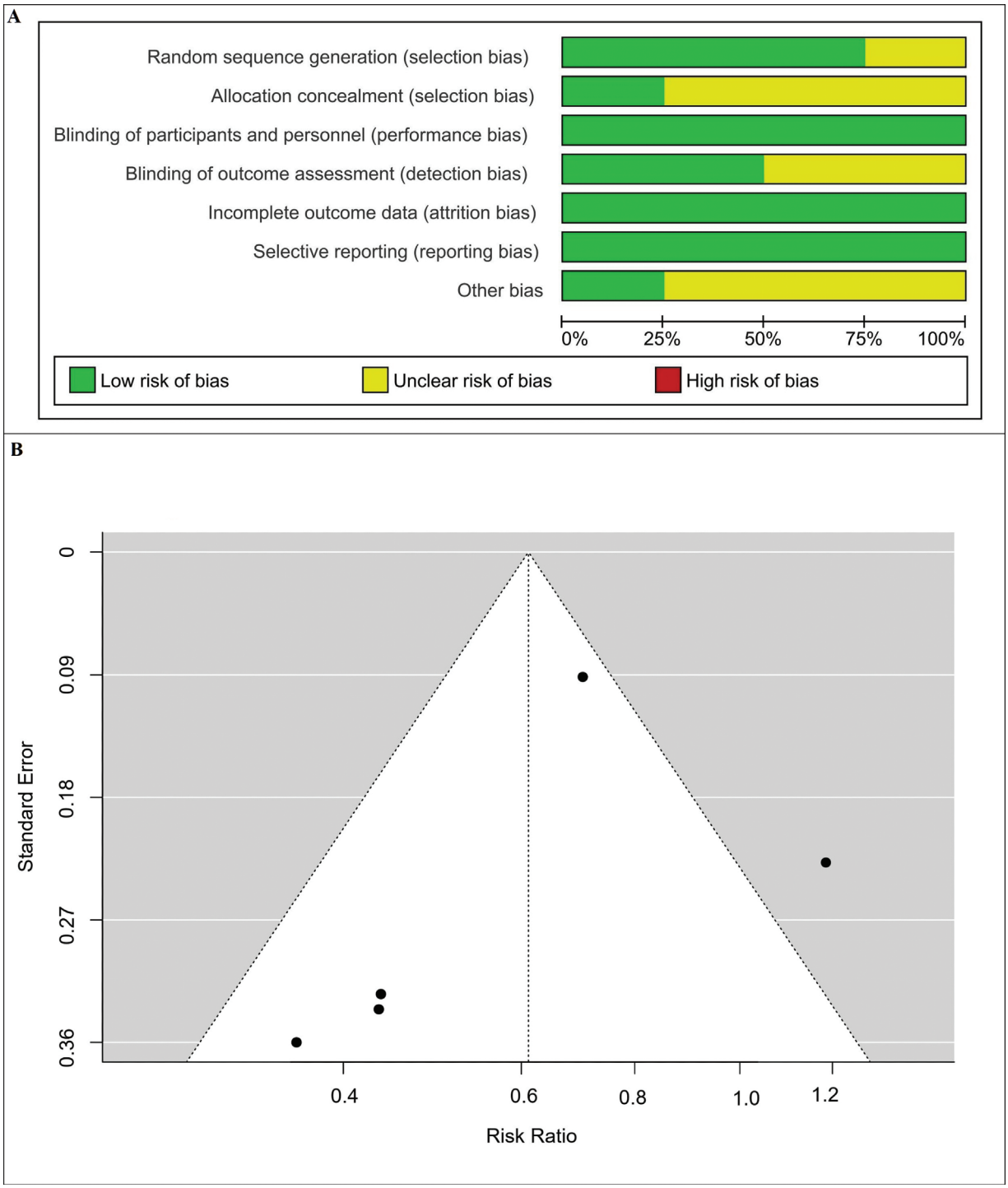

Fig. 4 (**A**) Risk of bias graph: review authors judgements about each risk of bias item presented as percentages across all included studies. (**B**) Funnel plot illustrating publication bias assessment.

factors: inciting stimuli, a conductive environment, and osteogenic precursor cells.[24–26]

Both non-selective NSAIDs (e.g. ibuprofen, indomethacin, diclofenac, naproxen) and selective NSAIDS (e.g. Celecoxib, meloxicam, rofecoxib) are routinely used as prophylaxis for HO post hip surgery.[27–30] A recent meta-analysis by Shapira et al.[11] reported that both non-selective and selective NSAIDs are equally effective in the prevention of HO. In our review, the study by Persson et al.[20] indicates that an ibuprofen course for either 7 days or 21 days postoperatively was equally effective in reducing the incidence of HO. A similar study was conducted on the use of indomethacin prophylaxis for either 3 days, 7 days, or 42 days to prevent HO formation and reported the use indomethacin for a longer period, that is, 42 days, had no positive outcomes but rather increased the incidence of complications, whereas a 7-day treatment had the most beneficial outcomes.[31] Therefore, further investigation is recommended to determine the effectiveness of

shorter course of prophylaxis treatment, which may be helpful in avoiding the undesirable effects of ibuprofen. The use of non-selective NSAIDs have been accompanied by GI symptoms due to blockage of cyclooxygenase-I (COX-I) along with of cyclooxygenase-II (COX-II) enzyme, while selective COX-II inhibitor NSAID have been attributed to decreased gastrointestinal side effects.[32] However, the possible positive outcomes associated with COX-II NSAIDs still warrant caution due to risk of cardiovascular complications as noted by Macfarlane et al.[33] Studies have pointed out that selective NSAID etoricoxib is identified with a tendency to cause blood pressure instability, while rofecoxib has been withdrawn from the market.[34,35] The Cross Trial Safety group performed a meta-analysis on cardiovascular risk of celecoxib and found evidence of dose related risk for cardiovascular events.[36] The decision of whether to administer selective or non-selective NSAID prophylaxis should vary by patient based on preexisting risk factors and the potential for adverse effects.

The Brooker classification is the most common and widely used classification of HO based on anteroposterior (AP) X-Ray of the pelvis.[37] This classification was also used in the studies we examined, except for the study by Elmstedt et al.,[22] which utilized the Rosendahl classification. The Brooker classification assigns four grades to the severity of HO formation following THA. Grade 1 is categorized as small distinct bony regions in the soft tissues surrounding the hip, grade 2 consists of bone exophytes that originate from the pelvis or proximal end of the femur with 1 cm between opposing bone surfaces, while in grade 3, the bone exophytes decrease the separation between opposing bone surfaces to less than 1 cm, and grade 4 is described as bone ankylosis between the pelvis and proximal femur.[37,38] Our analysis indicates that the use ibuprofen had significant reduction in the events of Brooker II and III HO at the final follow-up. Patients with severe HO, such as those with the radiological diagnosis of Brooker III and IV, are of great clinical relevance due to immense pain, limited mobility, and functionality. But there was limited evidence in the included studies to quantify these symptoms using the patient-reported outcome measures such as Harris hip score (HHS), and hip disability and osteoarthritis outcome score (HOOS),[39] making it hard to ascertain the impact of the two treatment groups on functional outcome. Therefore, it is difficult to report if the use of ibuprofen correlates with any improvement in clinical outcomes.

This analysis has the following potential strengths: First, we used a comprehensive methodology in identifying articles from PubMed, Cochrane Library. Second, the study design of the included studies was limited to RCTs, which provides reliable findings. Third, we used subgroup analysis to improve the robustness of our findings. The limitations of this meta-analysis are as follows. First, there were only a few related studies discovered during the literature search. Despite the number of studies found, a significant number of patients were compiled through these studies, with 1,153 patients analyzed in this review. Second, the included RCTs had some potential methodological weaknesses. Third, because the number of included studies was lower than 10, we could not perform the Egger regression test for statistical assessment of funnel plot asymmetry. Finally, no newer studies were discovered during the literature search, the most recent related clinical trial was published in 2006.

Future trials in this area should focus on the methodological design; they need to be double-blinded trials and should clearly report on allocation concealment and method of randomization. Since different doses of ibuprofen ranging from 1,200 mg to 1,500 mg were administered daily over a variety of treatment duration, further studies are needed to investigate for the best dosage and duration of ibuprofen treatment. Additionally, future trials need to comprehensively assess the clinical relevance of HO in patients by utilizing self-reported outcome measures regarding hip function and symptoms.

Conclusion

In conclusion, ibuprofen may be used to prevent HO after THA owing to its significant effect in preventing HO with no increased risk of gastrointestinal complication when compared with placebo.

However, we propose more research is needed to determine the ideal dose and treatment duration for the use of ibuprofen as a prophylactic agent after THA for the prevention of HO.

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Conflict of interests
The authors declare they have no conflict of interests.

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