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Heterotopic ossification (HO) prophylaxis in total hip arthroplasty (THA): A systematic review of level I and level II evidence since 2000

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ABSTRACT

Introduction: Heterotopic ossification (HO) is a somewhat common occurrence after total hip arthroplasty (THA), particularly with certain approaches. This complication can be detrimental to the success of the surgical outcome. Indomethacin and radiotherapy remain common treatment modalities; however, no true gold-standard treatment is universally agreed upon. This study aims to evaluate Level I and Level II evidence for treatment practices of HO prophylaxis since 2000.

Methods: To evaluate HO prophylaxis in total hip arthroplasty, a search was conducted across MEDLINE/Pubmed, Cochrane, and Embase databases using keywords and Medical Subject Heading (MeSH) terms. Titles and abstracts were screened for eligibility for inclusion criteria. Full texts were screened and included if they met eligibility criteria.

Results: HO chemical prophylaxis was more effective than no HO prophylaxis, except for aspirin. Multiple NSAIDs showed equivalence and better side effect profiles than indomethacin. No one superior NSAID was found, and numerous modalities showed efficacy. The most effective dosages of radiation therapy and combination therapy remain unclear. Additionally, both etidronate and salmon calcitonin showed benefit in preventing HO in one study each.

Conclusion: Radiation, NSAIDs, and combination therapy all showed efficacy as HO prophylaxis modalities. HO prophylaxis treatment and modalities should be guided upon patient and surgical factors such as surgical approach, side effects and tolerability of modalities, comorbidities, and available facility resources to optimize the prevention of HO.

Level of evidence: Level IV Therapeutic.

1. Introduction

Heterotopic ossification (HO) is a process in which bone grows in the soft tissues, where it should typically not exist (Shehab et al., 2002a; Sun and Hanyu-Deutmeyer, 2023). Heterotopic ossification can require re-operation and can lead to functional limitations, mobility limitations, and peripheral nerve entrapment (Shehab et al., 2002a; Sun and Hanyu-Deutmeyer, 2023). Subsequent surgeries for HO removal can lead to additional sequelae. HO is typically more prevalent in males than in females (Sun and Hanyu-Deutmeyer, 2023; Singh et al., 2022a). It occurs in several well-known populations, including patients who undergo joint replacement surgery as well as in those sustaining trauma, brain injuries, and burns (Sun and Hanyu-Deutmeyer, 2023; Meyers et al., 2019; Huang et al., 2017; Aprato et al., 2023). HO after joint replacement surgery is a particular concern, especially in total hip arthroplasty (THA) where the incidence of HO can be well above 50 % (Di Benedetto et al., 2019; Herzberg et al., 2024).

THA is one of the most common elective orthopedic procedures in the United States (Blom et al., 2021). Many patients undergoing THA may be at high risk for HO due to pre-existing comorbidities such as diabetes and patient-related factors such as male gender and age greater than 65 (Singh et al., 2022a). HO is known to occur at higher rates in THA with certain surgical approaches, such as the direct lateral approach (Herzberg et al., 2024; Eggli and Woo, 2001). In a recent systematic review Herzberg et al. identified the incidence of HO with the modified direct lateral approach at 57.2 % (Herzberg et al., 2024).

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Surgery for HO removal can lead to further complications such as nerve injury, HO recurrence, or infection (Agarwal et al., 2017; Hunt et al., 2006).

Clear treatment guidelines are currently lacking regarding HO prophylaxis after THA. Indomethacin and radiation therapy have been preferred treatments for the prevention of HO in recent years (Geller et al., 2022; Shehab et al., 2002b). However, many additional modalities (with potentially fewer side effects) such as COX-2-specific NSAIDs and others, have recently been explored to prevent HO (Xue et al., 2011). No current gold standard treatment exists in the prevention of HO after THA.

This systematic review was performed to examine Level I and II evidence to evaluate the optimal HO prophylaxis treatments for patients undergoing THA. We hypothesize that current accepted treatments for HO prophylaxis (such as various NSAIDs and radiation therapy) will show equivalence in the prevention of HO following THA.

2. Methods

2.1. Study design

This systematic review followed the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) statement standards (Page et al., 2021).

2.2. Eligibility criteria

Studies were eligible for inclusion if they met the following criteria: 1) Evaluated a comparison of HO prophylaxis treatments after THA, 2) Studies were Level I or Level II Evidence, 3) Were conducted in human subjects, and 4) The manuscript was completed in English. Reviews, commentaries, letters to the editor, technique papers, and surveys were excluded.

2.3. Search strategy

PubMed/MEDLINE, Cochrane, and Embase databases were searched for publications from January 1, 2000 to June 18, 2024. Comprehensive

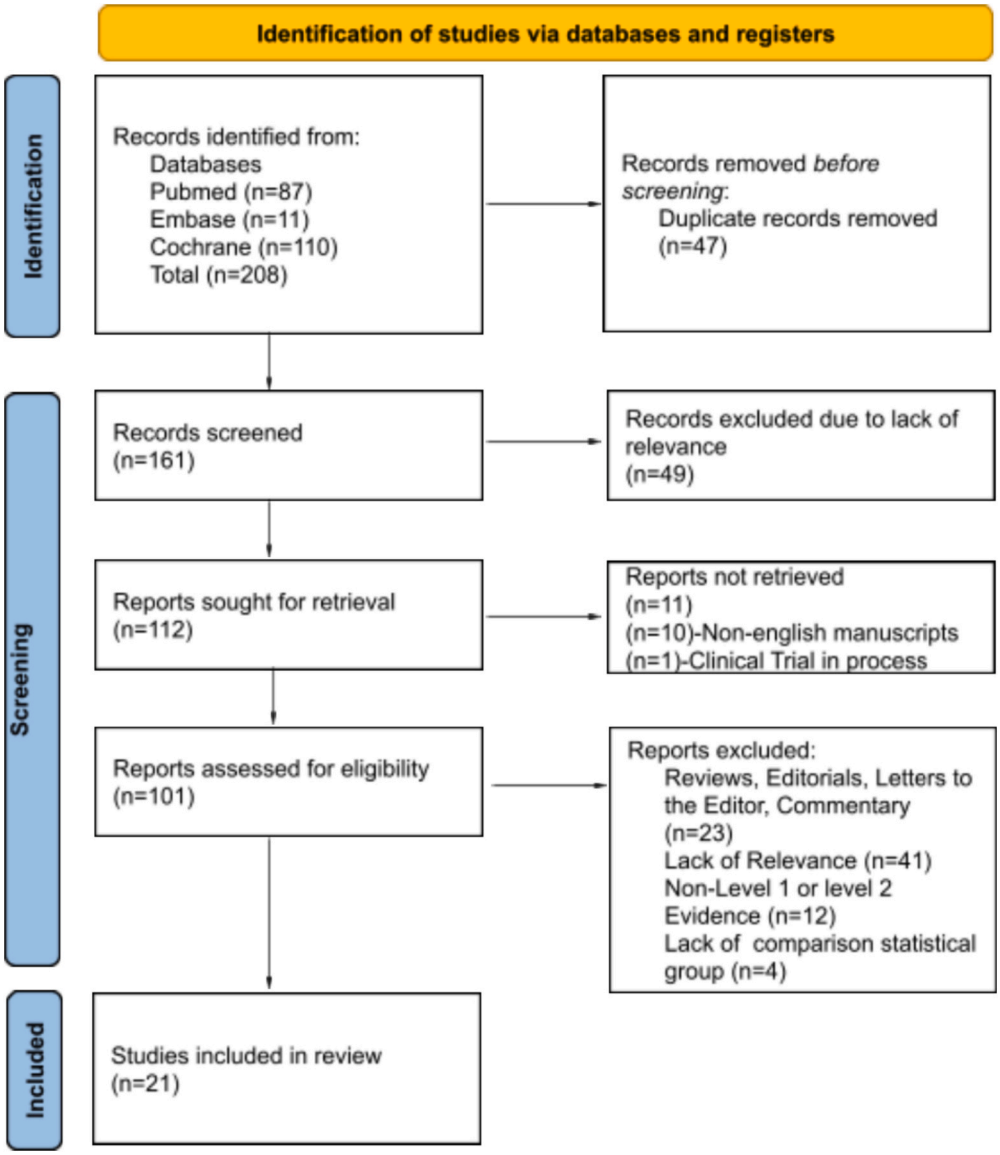

Fig. 1. PRISMA flowchart.

search strategies were developed using keywords, MeSH terms, and synonymous terms. The PubMed/Medline search (Supp. Table 1) was adapted to the Cochrane and Embase databases.

One author (T.B.P.) performed the search. Three authors (T.B.P., C.R.M., V.D.) excluded irrelevant articles and duplicates based on title and abstract. The remaining articles underwent an independent full-text review by three authors (T.B.P., C.R.M., V.M.D.) and were assessed for eligibility based on established criteria. Any conflicts were resolved by discussion among the three authors.

2.4. Data extraction

The study's demographic information, including the lead author and country of origin, study design and level of evidence, number of patients, modality used, and study follow-up length, was collected. Study results and comparisons were included in the final presentation.

2.5. Statistical analysis

Statistical analysis was not performed due to the many different trial prophylaxis modalities included.

3. Results

3.1. PRISMA flow diagram

A preliminary search of three databases provided 208 studies. 47 duplicates were removed (Fig. 1). 161 abstracts and titles were screened, and 49 were removed for lack of relevance. 112 reports were sought for retrieval. Eleven reports were not retrieved: ten of these eleven were non-English manuscripts and one is an incomplete clinical trial that is still in process without results. 101 full texts were screened. 21 studies met the final inclusion criteria and were included in this study, seven of which were Level 1 evidence studies.

3.2. Level I evidence studies

3.2.1. Study demographics

The Level I evidence studies were all randomized clinical trials that tested several treatments for HO prophylaxis including aspirin, rofecoxib, radiation therapy, celecoxib, diclofenac, and etoricoxib. These studies originated from several countries with follow-up lengths ranging from three months to one year (Table 1). All studies used the Brooker HO grading system (Fig. 2) (Brooker et al., 1973; Giardini et al., 2020). The lateral approach was the most common surgical approach used in the Level I evidence studies (Table 1).

3.2.2. Study results and comparisons

Table 2 summarizes the results of Level I studies. Aspirin showed no effect on HO versus placebo (Neal et al., 2000). Only one study showed a significant difference between HO prophylaxis modalities or dosages (celecoxib > ibuprofen) (Grohs et al., 2007; Saudan et al., 2007; Winkler et al., 2016). Liu et al., demonstrated that an increased radiation dose (700 cGy vs 400 cGy) better prevented the progression of HO (Liu et al., 2017). However, Padgett et al., showed no difference for HO when using a higher cumulative radiation dose given in divided treatments (500 cGy vs 1000 cGy) (Padgett et al., 2003).

3.3. Level II evidence studies

3.3.1. Study demographics

All Level II evidence studies were prospective comparison studies, with follow-ups ranging from six months to two years (Table 3). All studies used the Booker grading classification for HO. Studies used a variety of surgical approaches, including posterior, posterolateral, lateral, and anterolateral approaches.

3.3.2. Study results and comparisons

Modalities utilized for treatment included celecoxib, radiation, indomethacin, meloxicam, salmon calcitonin, ibuprofen, and etidronate. Three Level II studies showed that celecoxib was superior in preventing HO compared to no prophylaxis (Badi et al., 2023; Barbato et al., 2012; Lavernia et al., 2014). Five studies (Romanò et al., 2004; Legenstein et al., 2003; van der Heide et al., 2004; Schneider et al., 2023; van der Heide et al., 2007; Vasileiadis et al., 2010) demonstrated equivalence between indomethacin and other NSAIDs (celecoxib, meloxicam, ibuprofen, and rofecoxib), however, in one study indomethacin had to be discontinued more often due to side effects such as gastrointestinal side effects, excessive bleeding, and mental confusion (Romanò et al., 2004). Barthel et al., in contrast, showed indomethacin was superior to meloxicam (Barthel et al., 2002; Legenstein et al., 2003; van der Heide et al., 2004) Vasileidies et al. showed that etidronate was equivalent to indomethacin for HO prophylaxis and had a superior side effect profile (Vasileiadis et al., 2010). However, etidronate was more expensive than indomethacin. Gunal et al., showed salmon calcitonin had a statistically significant benefit in reducing HO compared with indomethacin (Günal et al., 2001). Pakos et al. showed in one study that a combination of indomethacin and radiation was superior to indomethacin alone; however, another study by the same author showed no difference in combination therapy (Pakos et al., 2009a; Pakos et al., 2009b). Pakos et al. showed that increasing radiation dosage in combination therapy did not affect the incidence of HO (Pakos et al., 2010) (Table 4).

Table 1
Study demographics of Level I evidence studies (RCT, Randomized Controlled Trial, THA, Total Hip Arthroplasty).

Author and origin	Number of patients (n)	Mean age (years)	THA Approach	Follow-up time (months)
Grohs et al., 2007 (Austria)	100	60	Anterolateral Approach	12
Liu et al., 2017 (United States)	147	61.6	Posterior and Lateral Approaches	6
Neal et al., 2000 (Australia)	2649	65	Unspecified	6
Padgett et al., 2003 (United States)	59	58.5	Posterolateral, Lateral, and Lateral Transtrochanteric (Trochanteric Osteotomy) Approaches	6
Saudan et al., 2007 (Switzerland)	250	69.5	Lateral	3
Sell et al., 2004 (Germany)	245	63	Lateral	6
Winkler et al., 2016 (Germany)	100	61	Lateral	6

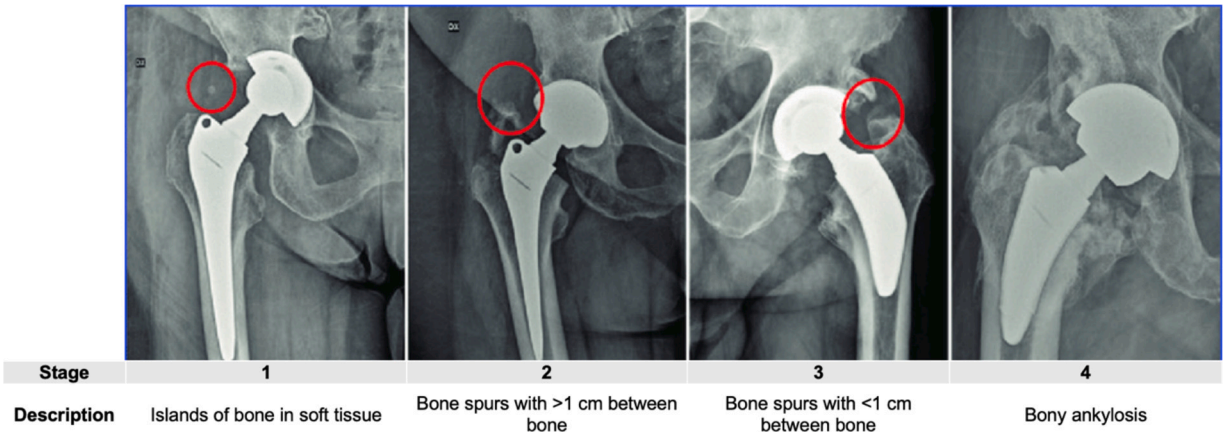

Fig. 2. Brooker heterotopic ossification classification. (*Creative Common License*: Giardini et al. (Giardini et al., 2020)).

Table 2
Study results and comparisons of Level I evidence studies. (mg, milligram; d, day).

Author and origin	Goal of treatment	Duration of treatment	Study comparison	Modality dosage	Comparison outcomes
Grohs et al., 2007	Prevention	7 days	Rofecoxib vs. indomethacin	Rofecoxib: 25 mg/day Indomethacin: 100 mg/day	No significant difference ($P > .05$)
Liu et al., 2017	Lessen progression	One time	Radiation	400 vs 700 cGy	400 cGy had significantly more HO ($P < .05$) progression compared to 700 cGy
Neal et al., 2000	Prevention	35 days	Aspirin vs. placebo	162 mg/day	No significant difference (P > .05)
Padgett et al., 2003	Prevention	2 doses of 250 cGy (500 cGy total) within 96 h 5 doses of 200 cGy (1000 cGy total) within 96 h	500 cGy vs. 1000 cGy Radiation	500 vs. 1000 cGy	No significant difference ($P > .05$)
Saudan et al., 2007	Prevention	10 days	Celecoxib vs ibuprofen	Celecoxib: 400 mg/day Ibuprofen: 1200 mg/day	Celecoxib significantly better ($P < .05$)
Sell et al., 2004	Prevention	14 days	Diclofenac	75 mg/day vs 150 mg/day	No significant difference (P > .05)
Winkler et al., 2016	Prevention	9 days	Etoricoxib vs diclofenac	Etoricoxib: 90 mg/day Diclofenac: 150 mg/day	No significant difference (P > .05)

4. Discussion

The results of this systematic review found that in multiple Level II studies, prescribing Celecoxib for HO prophylaxis is better than not prescribing any prophylaxis in preventing the formation of HO. In the only RCT comparing HO prophylaxis to a placebo, aspirin did not demonstrate any significant benefit in the prevention of HO (Neal et al., 2000; Badi et al., 2023; Barbato et al., 2012; Lavernia et al., 2014). Several NSAIDs and Etidronate proved to be equivalent to indomethacin, and one study showed celecoxib had a better overall side effect profile (Romanò et al., 2004; Schneider et al., 2023; van der Heide et al., 2007; Vasileiadis et al., 2010). Radiation may be an effective form of prophylaxis. However, the most effective levels of combination therapy or radiation dosages still need to be determined (Liu et al., 2017; Padgett et al., 2003; Pakos et al., 2009a; Pakos et al., 2009b). Ibuprofen was found inferior to Celecoxib but equivalent to indomethacin (Saudan et al., 2007; Schneider et al., 2023).

Several previous reviews have evaluated the efficacy of HO prophylaxis in total hip arthroplasty, however, that research does not currently contain information after 2018, therefore necessitating an updated review. Previous research has yet to clearly identify a superior treatment method for HO prophylaxis, or whether every patient should be given HO prophylaxis. Vavken et al., found no statistically or clinically significant difference in HO prophylaxis between NSAIDs or radiation (Vavken et al., 2009). Board et al., suggests that radiation therapy is more effective than indomethacin, but recommended combination therapy for recurrent HO (Board et al., 2007a). Cai et al., found that selective NSAID therapy was the safest treatment option for HO prophylaxis, with radiation therapy being the second safest (Cai et al., 2019). Several reviews also highlight that both radiation therapy and NSAID therapy, while effective, do present with shortcomings and side effects (Cai et al., 2019; Baird and Kang, 2009; Migliorini and Maffulli, 2024). The previous literature shows that many shortcomings exist within the current literature, such as exclusion of alternative treatment methods, patient specific factors, and considerations such as surgical approach (Migliorini and Maffulli, 2024). Previous studies caution the routine use of HO prophylaxis, however, recommend evaluation of the risks and benefits of treatment with HO prophylaxis therapies (Baird and Kang, 2009; Migliorini and Maffulli, 2024).

NSAIDs, primarily indomethacin, remain one of the mainstays of HO prophylaxis treatment (Pakos et al., 2009b; Łęgosz et al., 2019). Modality timeframes for NSAID therapies ranged from 7 days to 28 days. The most popular time frame used was 14 days. Multiple studies in this review showed equivalence of alternative treatments to indomethacin, and one study showed celecoxib had a better side effect profile (Romanò et al., 2004). Celecoxib therapy was used for 28 days, which was the longest use of an NSAID. Only salmon calcitonin was superior to indomethacin, and was used for the same modality time frame of 14 days (Günal et al., 2001). Future studies should consider comparing different modality timeframes in order to see if the modality timeframe has a significant impact on the prevention of HO prophylaxis. NSAIDs can be selective for COX-2 or non-selective (Shamsudin et al., 2018). COX-2

Table 3
Study demographics of Level II evidence studies.

Author and origin	Number of patients (n)	Mean age (years)	THA approach	Follow-up time (months)
Badi et al., 2023 (Canada)	312	64.2	Mini Posterior Approach	24
Barbato et al., 2012 (Italy)	480	Unspecified	Posterolateral or Direct Lateral	12
Barthel et al., 2002 (Germany)	272	63	Unspecified	6
Günal et al., 2001 (Turkey)	60	65	Lateral Approach	24
Lavernia et al., 2014 (United States)	170	66.4	Direct Lateral Approach	12
Legenstein et al., 2003 (Austria)	116	66.5	Anterolateral Approach	6
Pakos et al., 2010 (Greece)	71	63.3	Posterolateral Approach	12
Pakos et al., 2009a (Greece)	99	54.8	Posterolateral Approach	6
Pakos et al., 2009b (Greece)	146	67.3	Posterolateral Approach	6
Romanò et al., 2004 (Italy)	400	61.2	Direct lateral transgluteal approach without trochanter osteotomy	12
Schneider et al., 2023 (Germany)	1248	71	Anterolateral Approach	12
Van der Heide et al., 2007 (Netherlands)	186	Unspecified	Posterolateral Approach	12
Van der Heide et al., 2004 (Netherlands)	181	67	Posterolateral Approach	6
Vasileiadis et al., 2010 (Greece)	52	68.4	Posterolateral Approach	6

NSAIDs, such as celecoxib, have been known to have a more favorable gastrointestinal side effect profile than COX non-selective inhibitors (Davies et al., 2013). However, these COX-2 selective NSAIDs still present with notable side effects. The most notable side effect is a decline in renal perfusion, which is a commonly known side effect of NSAID therapy (Harris Jr., 2002). Patients with gastrointestinal pathology may benefit from celecoxib rather than indomethacin due to the side effect profile. Patients with renal pathology altogether would likely benefit from something other than NSAID therapy. Patient-specific factors are essential for consideration, mainly due to the side effects of NSAIDs.

Radiation therapy remains a treatment option in the perioperative period (Łęgosz et al., 2019). The ideal radiation dosage or number of doses remains unknown (Łęgosz et al., 2019). Traditionally, 700 cGy has been used for HO prophylaxis (Łęgosz et al., 2019). One study found that a single dose of 700 cGy was superior to 400 cGY (Liu et al., 2017). However, another study found that 500 cGy and 1000 cGy were equivalent in multiple divided dosages (Padgett et al., 2003). Direct comparisons of single dose 700 cGy to multiple lower dosages were not found in this review. Traditionally radiation has been given in single doses, however, Padgett et al., gave radiation doses over a 96 h period, and Pakos et al., over a 72 h period (Padgett et al., 2003; Pakos et al., 2010). The remainder of studies provided one single dose. The study results support the use and efficacy of one dose of radiation, however, more research will be needed to see if radiation over different periods influences HO prevention (Łęgosz et al., 2019). Radiation therapy, like NSAIDs, has potential side effects. Side effects include wound healing difficulties, fatigue, joint swelling, and a small risk of secondary cancer (Migliorini and Maffulli, 2024). In addition to possible side effects, radiation therapy is often expensive and requires specialized equipment and physicians to perform the treatment that may not be available at all institutions (Strauss et al., 2008). Comparisons of the effectiveness of radiation therapy and NSAIDs in previous studies have shown conflicting results (Pakos and Ioannidis, 2004; Shapira et al., 2022). There is no clear answer regarding which modality is more effective. Radiation therapy may be a great option for HO prophylaxis for patients who cannot tolerate NSAID therapy.

HO prophylaxis should be chosen based on patient-specific factors. Currently, HO prophylaxis is not routinely done in for total hip arthroplasty (Board et al., 2007b). However, due to the debilitating pain and functional limitations that HO can cause for patients, there may be certain populations at high risk that would benefit from HO prophylaxis (Board et al., 2007b; Singh et al., 2022b). The decision to prescribe HO prophylaxis should ultimately be determined by patient pre-existing risk factors or surgical approaches that predispose for developing HO (Board et al., 2007b; Singh et al., 2022b). Several pre-existing comorbidities such as osteoporosis, spine disease, diabetes mellitus, parathyroid disorders, and low estrogen states have been associated with an increased risk of developing HO (Singh et al., 2022b). With total hip arthroplasty, the direct lateral approach has been associated with increased rates of post-operative HO (Herzberg et al., 2024; Eggli and Woo, 2001). Herzberg et al., a recently published systematic review, found that incidence of HO with the modified direct lateral was 57.2 % and the traditional lateral was 34.6 % (Herzberg et al., 2024). The posterolateral had an incidence of HO of 12.8 % (Herzberg et al., 2024). Direct superior approaches had the lowest incidence of (1 %) (Herzberg et al., 2024). Regardless of approach, patients primarily had Brooker Class 1 or Class 2 HO (Herzberg et al., 2024). The primary approaches seen in this study were the direct lateral and posterolateral approaches. Surgeons who primarily use the direct lateral approach may be more inclined to prescribe HO prophylaxis than surgeons who use an anterior or posterolateral approach due to the significantly higher rates of HO. Surgeons can weigh the risks and consider these factors in order to determine when to prescribe HO prophylaxis.

If a patient is at high risk of developing HO and is prescribed HO prophylaxis, the patients' medical comorbidities should be considered when deciding what NSAID to prescribe or to determine whether non-NSAIDs or radiation therapy should be used. For example, if a patient has known kidney disease or has experienced previous side effects with NSAIDs, surgeons may aim to choose radiation therapy for HO prophylaxis in order to prevent morbidity from NSAID use. Convenience, cost, and compliance should also be considered when determining the appropriate treatment. For example, if patients are discharged same day or treated at a surgery center, it would be more ideal to treat with NSAIDs, rather than return to a facility or find a facility for radiation therapy. An additional consideration is that underserved populations may not be able to afford or have access to some treatment modalities such as radiation therapy. These populations may benefit from cheaper options such as NSAID therapy. Individualizing the treatment plan for HO prophylaxis for each patients' demographic factors, comorbid factors, and treatment setting should be utilized to prevent side effects and improve patient compliance.

4.1. Limitations

This study was not without limitations. The most significant limitation was the wide range of treatments that could not be directly compared to each other. Large retrospective trials that directly compare different modalities to each other and/or prospective trials comparing treatment to placebo could be conducted to find an optimal HO prophylaxis method. The second limitation of this study is the potential for

Table 4
Study results and comparisons of Level II evidence studies. (*The difference in the discontinuation and rate of side effects was statistically decreased in the celecoxib group compared to the indomethacin group($P < .05$); **Higher incidence of side effects in patients taking indomethacin compared to Etidronate).

Author and origin	Study comparison	Modality dosage	Modality timeframe	Study result
Badi et al., 2023	Celecoxib vs. no HO Prophylaxis	200 mg/day	10 days	Celecoxib had a statistically significant reduction (P < .05)
Barbato et al., 2012	Celecoxib vs. no HO prophylaxis	400 mg/day	Minimum of 14 days, maximum of 20 (Average of 17)	Celecoxib had a statistically significant reduction ($P < .05$)
Barthel et al., 2002	Indomethacin vs. meloxicam	Indomethacin (100 mg/day)	14 days	Indomethacin had a statistically significant reduction (P < .05) compared to 7.5 mg/d Meloxicam
		Meloxicam (7.5 or 15 mg/day)		No significant difference (P > .05) to 15 mg/d Meloxicam
Günal et al., 2001	Indomethacin vs. salmon calcitonin	Indomethacin (100 mg/day)	14 days	Salmon calcitonin had a statistically significant (P < .05)
		Calcitonin (3 MRC-U/kg/day)		
Lavernia et al., 2014	Celecoxib vs. no HO prophylaxis	400 mg/day	28 days	Celecoxib had a statistically significant reduction (P < .05)
Legenstein et al., 2003	Indomethacin vs. meloxicam	Indomethacin (100 mg/day)	12 days	No significant difference (P > .05)
		Meloxicam (7.5 mg/day)		
Pakos et al., 2010	Indomethacin +7 Gy radiation	Single dose 7 Gy radiation	3 days span or single dose	No significant difference ($P > .05$)
	vs. Indomethacin +10Gy radiation	5 doses of 2 Gy radiation in three-day span		
Pakos et al., 2009a	Indomethacin vs.	Indomethacin (75 mg/day)	Indomethacin: 14 days	No significant difference (P > .05)
	Combined Radiotherapy and Indomethacin	Indomethacin (75 mg/day) + 7 Gy radiation single dose	Radiation: Single dose	
Pakos et al., 2009b	Combined Radiotherapy and Indomethacin	Indomethacin (75 mg/day)	Indomethacin-15 days postoperatively	Combined radiotherapy and indomethacin showed a statistically significant reduction ($P < .05$) than indomethacin alone and historical indomethacin data
	vs. Indomethacin vs. historical Indomethacin group	Indomethacin (75 mg/day) + 7 Gy radiation single dose	Radiation-Single dose	
Romanò et al., 2004	Indomethacin vs. celecoxib	Indomethacin (100 mg/day)	20 days	No significant difference ($P > .05$)*
		Celecoxib (400 mg/day)		
Schneider et al., 2023	Ibuprofen vs. indomethacin	Ibuprofen (1200 mg/day)	21 days	No significant difference (P > .05) between indomethacin and ibuprofen
		Indomethacin (100 mg/day)		Indomethacin and ibuprofen significantly different (P < .05) than no prophylaxis.
Van der Heide et al., 2007	Rofecoxib vs. indomethacin	Rofecoxib (50 mg/day)	7 days	No significant difference ($P > .05$)
		Indomethacin (150 mg/day)		
Van der Heide et al., 2004	Indomethacin vs. Meloxicam	Indomethacin (50 mg/day)	7 days	No significant difference ($P > .05$)
		Meloxicam (15 mg/day)		
Vasileiadis et al., 2010	Etidronate vs. indomethacin	Etidronate (20 mg/kg/day)	Etidronate: 84 days	No significant difference (P > .05)**
		Indomethacin (75 mg/day)	Indomethacin: 14 days	

missed literature. While our search was comprehensive and searched three major literature databases, pertinent literature in a language other than English or a different database may exist. Future studies are needed to help physicians determine the most effective form of HO prophylaxis.

5. Conclusions

Prescribing prophylaxis for the prevention of HO is more effective than not prescribing any prophylaxis. Radiation, NSAIDs, and combination therapy all showed efficacy as HO prophylaxis modalities. HO prophylaxis treatment and modalities should be guided upon patient and surgical factors such as surgical approach, side effects and tolerability of modalities, comorbidities, and available facility resources to optimize the prevention of HO.

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CRediT authorship contribution statement

Troy B. Puga: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **McKenna W. Box:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Vincent M. Dieu:** Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Resources, Investigation, Formal analysis, Data curation. **Charles R. Marchese:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Software, Resources, Investigation, Formal analysis, Data curation. **John T. Riehl:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Ethical approval

This research activity was determined to be exempt or excluded (reference number 2024-905) from the HCA Healthcare Graduate Medical Education Institutional Review Board oversight in accordance with current regulations and institutional policy,

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Declaration of competing interest

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Data availability

Data will be made available on request.

References

Agarwal, S., Loder, S., Cholok, D., et al., 2017. Surgical excision of heterotopic ossification leads to re-emergence of mesenchymal stem cell populations responsible for recurrence. Stem Cells Transl. Med. 6 (3), 799–806. https://doi.org/10.5966/sctm.2015-0365.

Aprato, A., Cambursano, S., Artiaco, S., Bevilacqua, S., Catalani, P., Massè, A., 2023. Heterotopic ossification in primary total hip arthroplasty: risk factor analysis. Eur J Orthop Surg Traumatol. 33 (4), 1037–1041. https://doi.org/10.1007/s00590-022-03244-9.

Badi, H.A., Tanzer, M., Nooh, A., Hall, B., Hart, A., 2023. A short course of celecoxib prevents heterotopic ossification following Cementless Total hip arthroplasty. Life (Basel). 13(4):944. https://doi.org/10.3390/life13040944. Published 2023 Apr 4.

Baird, E.O., Kang, Q.K., 2009. Prophylaxis of heterotopic ossification - an updated review. J. Orthop. Surg. Res. 4, 12. Published 2009 Apr 20. https://doi.org/10.1186/1749-799X-4-12.

Barbato, M., D'Angelo, E., Di Loreto, G., et al., 2012. Adherence to routine use of pharmacological prophylaxis of heterotopic ossification after total hip arthroplasty: results from an Italian multicenter, prospective, observational survey. J. Orthop. Traumatol. 13 (2), 63–67. https://doi.org/10.1007/s10195-012-0180-4.

Barthel, Thomas, Baumann, Bernd, Nöth, Ulrich, Eulert, Jochen, 2002. Prophylaxis of heterotopic ossification after total hip arthroplasty. Acta Orthop. Scand. 73 (6), 611–614. https://doi.org/10.3109/17453670209178023.

Blom AW, Donovan RL, Beswick AD, Whitehouse MR, Kunutsor SK. Common elective orthopaedic procedures and their clinical effectiveness: umbrella review of level 1 evidence. BMJ. 2021;374:n1511. Published 2021 Jul 7. https://doi.org/10.1136/bmj.n1511.

Board, T.N., Karva, A., Board, R.E., Gambhir, A.K., Porter, M.L., 2007a. The prophylaxis and treatment of heterotopic ossification following lower limb arthroplasty. J. Bone Joint Surg. Br. 89 (4), 434–440. https://doi.org/10.1302/0301-620X.89B4.18845.

Board, T.N., Karva, A., Board, R.E., Gambhir, A.K., Porter, M.L., 2007b. The prophylaxis and treatment of heterotopic ossification following lower limb arthroplasty. J. Bone Joint Surg. Br. 89 (4), 434–440. https://doi.org/10.1302/0301-620X.89B4.18845.

Brooker, A.F., Bowerman, J.W., Robinson, R.A., Riley Jr., L.H., 1973. Ectopic ossification following total hip replacement. Incidence and a method of classification. J. Bone Joint Surg. Am. 55 (8), 1629–1632.

Cai, L., Wang, Z., Luo, X., She, W., Zhang, H., 2019. Optimal strategies for the prevention of heterotopic ossification after total hip arthroplasty: a network meta-analysis. Int. J. Surg. 62, 74–85. https://doi.org/10.1016/j.ijsu.2018.12.011.

Davies, N.M., Smith, G.D., Windmeijer, F., Martin, R.M., 2013. COX-2 selective nonsteroidal anti-inflammatory drugs and risk of gastrointestinal tract complications and myocardial infarction: an instrumental variable analysis. Epidemiology 24 (3), 352–362. https://doi.org/10.1097/EDE.0b013e318289e024.

Di Benedetto P, Zangari A, Magnanelli S, et al. Heterotopic Ossification in Primary Total Hip Arthroplasty: which is the role of drainage?. Acta Biomed. 2019;90(1-S):92–97. Published 2019 Jan 10. 10.23750/abm.v90i1-S.8077.

Eggli, S., Woo, A., 2001. Risk factors for heterotopic ossification in total hip arthroplasty. Arch. Orthop. Trauma Surg. 121 (9), 531–535. https://doi.org/10.1007/s004020100287.

Geller, J.S., Allegra, P.R., Seldon, C.S., et al., 2022. Prophylactic radiotherapy for prevention of heterotopic ossification after Periacetabular fractures: a review of efficacy and associated conditions. J. Surg. Orthop. Adv. 31 (2), 113–118.

Giardini P, Christodoulidis A, Pagliari, et al. Impact of a fast track protocol on the development of heterotopic ossification following hip arthroplasty. Lo Scalpello Journal. 2020;34(3). doi:10.36149/0390-5276-190.

Grohs, J.G., Schmidt, M., Wanivenhaus, A., 2007. Selective COX-2 inhibitor versus indomethacin for the prevention of heterotopic ossification after hip replacement: a double-blind randomized trial of 100 patients with 1-year follow-up. Acta Orthop. 78 (1), 95–98. https://doi.org/10.1080/17453670610013484.

Günal, I., Hazer, B., Seber, S., Göktürk, E., Turgut, A., Köse, N., 2001. Prevention of heterotopic ossification after total hip replacement: a prospective comparison of indomethacin and salmon calcitonin in 60 patients. Acta Orthop. Scand. 72 (5), 467–469. https://doi.org/10.1080/000164701753532781.

Harris Jr., R.C., 2002. Cyclooxygenase-2 inhibition and renal physiology. Am. J. Cardiol. 89 (6A), 10D–17D. https://doi.org/10.1016/s0002-9149(02)02232-4.

Herzberg, R., Tracey, O.C., Tahvilian, S., Baksh, N., Zikria, B., Naziri, Q., 2024. Incidence of heterotopic ossification following total hip arthroplasty by approach: a systematic review. Eur. J. Orthop. Surg. Traumatol. 34 (4), 2089–2098. https://doi.org/10.1007/s00590-024-03896-9.

Huang, H., Cheng, W.X., Hu, Y.P., Chen, J.H., Zheng, Z.T., Zhang, P., 2017. Relationship between heterotopic ossification and traumatic brain injury: why severe traumatic brain injury increases the risk of heterotopic ossification. J Orthop Translat. 12, 16–25. Published 2017 Nov 14. https://doi.org/10.1016/j.jot.2017.10.002.

Hunt, J.L., Arnoldo, B.D., Kowalske, K., Helm, P., Purdue, G.F., 2006. Heterotopic ossification revisited: a 21-year surgical experience. J. Burn Care Res. 27 (4), 535–540. https://doi.org/10.1097/01.BCR.0000226023.58438.14.

Lavernia, C.J., Contreras, J.S., Villa, J.M., Rossi, M.D., 2014. Celecoxib and heterotopic bone formation after total hip arthroplasty. J. Arthroplasty 29 (2), 390–392. https://doi.org/10.1016/j.arth.2013.06.039.

Legenstein, R., Bösch, P., Ungersböck, A., 2003. Indomethacin versus meloxicam for prevention of heterotopic ossification after total hip arthroplasty. Arch. Orthop. Trauma Surg. 123 (2–3), 91–94. https://doi.org/10.1007/s00402-003-0487-y.

Łęgosz, P., Otworowski, M., Sibilska, A., et al., 2019. Heterotopic ossification: a challenging complication of Total hip arthroplasty: risk factors, diagnosis, prophylaxis, and treatment. Biomed. Res. Int. 2019, 3860142. Published 2019 Apr 16. https://doi.org/10.1155/2019/3860142.

Liu, J.Z., Frisch, N.B., Barden, R.M., Rosenberg, A.G., Silverton, C.D., Galante, J.O., 2017. Heterotopic ossification prophylaxis after Total hip arthroplasty: randomized trial of 400 vs 700 cGy. J. Arthroplasty 32 (4), 1328–1334. https://doi.org/10.1016/j.arth.2016.10.030.

Meyers, C., Lisiecki, J., Miller, S., et al., 2019. Heterotopic ossification: a comprehensive review. JBMR Plus. 3 (4), e10172. Published 2019 Feb 27. https://doi.org/10.1002/jbm4.10172.

Migliorini, F., Maffulli, N., 2024. Prevention of heterotopic ossification in primary total hip arthroplasty: a bone in the dark. Eur J Orthop Surg Traumatol. 34 (8), 3805–3807. https://doi.org/10.1007/s00590-024-04087-2.

Neal, B.C., Rodgers, A., Gray, H., et al., 2000. No effect of low-dose aspirin for the prevention of heterotopic bone formation after total hip replacement: a randomized trial of 2,649 patients. Acta Orthop. Scand. 71 (2), 129–134. https://doi.org/10.1080/000164700317413085.

Padgett, D.E., Holley, K.G., Cummings, M., et al., 2003. The efficacy of 500 CentiGray radiation in the prevention of heterotopic ossification after total hip arthroplasty: a prospective, randomized, pilot study. J. Arthroplasty 18 (6), 677–686. https://doi.org/10.1016/s0883-5403(03)00265-1.

Page, M.J., McKenzie, J.E., Bossuyt, P.M., et al., 2021. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 372, n71. . Published 2021 Mar 29. https://doi.org/10.1136/bmj.n71.

Pakos, E.E., Ioannidis, J.P., 2004. Radiotherapy vs. nonsteroidal anti-inflammatory drugs for the prevention of heterotopic ossification after major hip procedures: a meta-analysis of randomized trials. Int. J. Radiat. Oncol. Biol. Phys. 60 (3), 888–895. https://doi.org/10.1016/j.ijrobp.2003.11.015.

Pakos, E.E., Stafilas, K.S., Politis, A.N., Tsekeris, P.G., Mitsionis, G., Xenakis, T.A., 2009a. Heterotopic ossification after total hip arthroplasty (THA) in congenital hip disease:

comparison of two different prophylactic protocols. Clin. Transl. Oncol. 11 (2), 103–108. https://doi.org/10.1007/s12094-009-0322-1.

Pakos, E.E., Stafilas, K.S., Tsekeris, P.G., Politis, A.N., Mitsionis, G., Xenakis, T.A., 2009b. Combined radiotherapy and indomethacin for the prevention of heterotopic ossification after total hip arthroplasty. Strahlenther. Onkol. 185 (8), 500–505. https://doi.org/10.1007/s00066-009-1954-3.

Pakos, E.E., Tsekeris, P.G., Paschos, N.K., Pitouli, E.J., Motsis, E.K., Xenakis, T.A., 2010. The role of radiation dose in a combined therapeutic protocol for the prevention of heterotopic ossification after total hip replacement. J. B.U.ON. 15 (1), 74–78.

Romanò, C.L., Duci, D., Romanò, D., Mazza, M., Meani, E., 2004. Celecoxib versus indomethacin in the prevention of heterotopic ossification after total hip arthroplasty. J. Arthroplasty 19 (1), 14–18. https://doi.org/10.1016/s0883-5403(03)00279-1.

Saudan, M., Saudan, P., Perneger, T., Riand, N., Keller, A., Hoffmeyer, P., 2007. Celecoxib versus ibuprofen in the prevention of heterotopic ossification following total hip replacement: a prospective randomised trial. J. Bone Joint Surg. Br. 89 (2), 155–159. https://doi.org/10.1302/0301-620X.89B2.17747.

Schneider, J., Maffulli, N., Eschweiler, J., et al., 2023. Efficacy of ibuprofen and indomethacin as prophylaxis of heterotopic ossification: a comparative study. Sci. Rep. 13, 20210. https://doi.org/10.1038/s41598-023-47508-8.

Sell, S., Phillips, O., Handel, M., 2004. No difference between two doses of diclofenac in prophylaxis of heterotopic ossifications after total hip arthroplasty. Acta Orthop. Scand. 75 (1), 45–49. https://doi.org/10.1080/00016470410001708080.

Shamsudin, Y., Gutiérrez-de-Terán, H., Åqvist, J., 2018. Molecular mechanisms in the selectivity of nonsteroidal anti-inflammatory drugs. Biochemistry 57 (7), 1236–1248. https://doi.org/10.1021/acs.biochem.7b01019.

Shapira, J., Yelton, M.J., Chen, J.W., et al., 2022. Efficacy of NSAIDs versus radiotherapy for heterotopic ossification prophylaxis following total hip arthroplasty in high-risk patients: a systematic review and meta-analysis. Hip Int. 32 (5), 576–590. https://doi.org/10.1177/1120700021991115.

Shehab, D., Elgazzar, A.H., Collier, B.D., 2002a. Heterotopic ossification. J. Nucl. Med. 43 (3), 346–353.

Shehab, D., Elgazzar, A.H., Collier, B.D., 2002b. Heterotopic ossification. J. Nucl. Med. 43 (3), 346–353.

Singh, S., Morshed, S., Motamedi, D., et al., 2022a. Identification of risk factors in the development of heterotopic ossification after primary Total hip arthroplasty. J. Clin. Endocrinol. Metab. 107 (9), e3944–e3952. https://doi.org/10.1210/clinem/dgac249.

Singh, S., Morshed, S., Motamedi, D., et al., 2022b. Identification of risk factors in the development of heterotopic ossification after primary Total hip arthroplasty. J. Clin. Endocrinol. Metab. 107 (9), e3944–e3952. https://doi.org/10.1210/clinem/dgac249.

Strauss, J.B., Chen, S.S., Shah, A.P., Coon, A.B., Dickler, A., 2008. Cost of radiotherapy versus NSAID administration for prevention of heterotopic ossification after total hip arthroplasty. Int. J. Radiat. Oncol. Biol. Phys. 71 (5), 1460–1464. https://doi.org/10.1016/j.ijrobp.2007.12.006.

Sun, E., Hanyu-Deutmeyer, A.A., July 31, 2023. Heterotopic ossification. In: StatPearls. Treasure Island (FL). StatPearls Publishing.

van der Heide, H.J., Spruit, M., Slappendel, R., Klooster, N., van Limbeek, J., 2004. Prophylaxis for heterotopic ossification after primary total hip arthroplasty. A cohort study between indomethacin and meloxicam. Acta Orthop. Belg. 70 (3), 240–246.

van der Heide, H.J., Rijnberg, W.J., Van Sorge, A., Van Kampen, A., Schreurs, B.W., 2007. Similar effects of rofecoxib and indomethacin on the incidence of heterotopic ossification after hip arthroplasty. Acta Orthop. 78 (1), 90–94. https://doi.org/10.1080/17453670610013475.

Vasileiadis, G.I., Sakellariou, V.I., Kelekis, A., et al., 2010. Prevention of heterotopic ossification in cases of hypertrophic osteoarthritis submitted to total hip arthroplasty. Etidronate or indomethacin? J. Musculoskelet. Neuronal Interact. 10 (2), 159–165.

Vavken, P., Castellani, L., Sculco, T.P., 2009. Prophylaxis of heterotopic ossification of the hip: systematic review and meta-analysis. Clin. Orthop. Relat. Res. 467 (12), 3283–3289. https://doi.org/10.1007/s11999-009-0924-5.

Winkler, S., Springorum, H.R., Vaitl, T., et al., 2016. Comparative clinical study of the prophylaxis of heterotopic ossifications after total hip arthroplasty using etoricoxib or diclofenac. Int. Orthop. 40 (4), 673–680. https://doi.org/10.1007/s00264-015-3077-z.

Xue, D., Zheng, Q., Li, H., Qian, S., Zhang, B., Pan, Z., 2011. Selective COX-2 inhibitor versus nonselective COX-1 and COX-2 inhibitor in the prevention of heterotopic ossification after total hip arthroplasty: a meta-analysis of randomised trials. Int. Orthop. 35 (1), 3–8. https://doi.org/10.1007/s00264-009-0886-y.