Incidence of Heterotopic Ossification Without Additional Long-Term NSAID Prophylaxis After Periacetabular Osteotomy and Concomitant Hip Arthroscopy

J. Matthew Helm,* MD, Omar Stocks,* BS, Brian Crowley,* MEd, Alexis Aboulafia,* BS, Jacob Siahaan,* MS, and Alfred A. Mansour III,*† MD
Investigation performed at the Department of Orthopaedic Surgery, McGovern Medical School, University of Texas Health Science Center at Houston, Houston. Texas, USA

Background: Periacetabular osteotomy (PAO) is an established treatment for hip dysplasia and has been increasingly combined with concomitant hip arthroscopy to address additional intra-articular hip pathology. Heterotopic ossification (HO) is a complication of arthroscopic and open hip procedures. Nonsteroidal anti-inflammatory drugs (NSAIDs) have become an established form of HO prophylaxis, but their use may delay bone healing.

Purpose: To examine the incidence of HO without NSAID prophylaxis in patients after PAO with concomitant hip arthroscopy and to evaluate the impact of other variables on the development of HO in these patients.

Study Design: Case series; Level of evidence, 4.

Methods: Of 243 hips that underwent PAO with concomitant hip arthroscopy by a single surgeon over 11 years, 182 met the study inclusion criteria. No patients were discharged on NSAIDs for HO prophylaxis, although most took up to 6 weeks of aspirin 81 mg as part of the prophylaxis protocol for deep venous thrombosis. Radiographic images at 2 weeks, 6 weeks, and 3 months postoperatively were reviewed and graded for HO using the Brooker classification. Patient characteristics and surgical variables were recorded. The chi-square and *t* tests were used to determine HO incidence rates, compare groups, and identify variables associated with the presence of HO.

Results: The incidence of radiographic HO was 6.6% (12/182 hips). Nine hips were Brooker grade 1, 2 were grade 2, and 1 was grade 3. Four patients experienced clinical symptoms of HO— including pain and restricted motion. Only 1 patient required a return trip to the operating room for surgical excision. Male patients were significantly more likely to develop HO than female patients ($P = .01$). No other demographic or surgical factor influenced the development of HO. There were no cases of nonunion.

Conclusion: There was a low incidence of HO and symptomatic HO in patients who underwent PAO with concomitant hip arthroscopy without using NSAIDs for HO prophylaxis. HO was significantly more likely to develop in male patients. Given the potential risk of NSAID use on bony union, the low incidence found in this study may obviate the need for postoperative HO prophylaxis.

Keywords: heterotopic ossification; hip arthroscopy; nonsteroidal anti-inflammatory drugs prophylaxis; periacetabular osteotomy

Heterotopic ossification (HO) is a well-documented complication of both arthroscopic and open hip procedures, with reported incidence rates ranging from 0% to 44% in hips without prophylaxis.[3,5,19,30] Defined as an osteogenic response in nonskeletal soft tissue, HO can cause pain and decreased mobility/function that may necessitate operative resection and lead to poor outcomes.[3] Given its proposed mechanism of an inflammatory cascade in response to soft tissue trauma, nonsteroidal anti-inflammatory drug (NSAID) prophylaxis has become a well-established method of reducing HO formation after open and arthroscopic hip procedures. Multiple studies have demonstrated reductions in HO rates, by as much as 20%, after the use of NSAIDs.[3-5,10,18,19,25,30]

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However, the use of NSAIDs is not benign, and their use has been linked to multiple risk factors—including gastrointestinal and renal complications as well as potential adverse effects on bone healing.[1,11,13,27,29] This is particularly important in procedures that depend on bony unions, such as the periacetabular osteotomy (PAO). Originally described by Ganz et al,[12] PAO is a hip preservation procedure used to treat developmental dysplasia of the hip and femoroacetabular impingement. The procedure involves freeing the acetabulum from the pelvis through a series of osteotomies before reorienting and securing the fragment in its new position. In their initial series of 75 PAOs from 1984 to 1987, Siebenrock et al[26] noted the occurrence of HO leading to restricted hip motion in 4 hips (6%) with 2 requiring resection. While the routine use of NSAIDs for HO prophylaxis has become relatively standard in hip arthroscopy, their use remains controversial in patients with PAO because the procedure relies on bony unions. As a procedure with a documented nonunion rate ranging[24] from 1% to 17%, the potential negative impact that NSAID use can have on bony union must be considered.

In addition, with the high prevalence of intraarticular pathology in hip preservation patients, the addition of concomitant hip arthroscopy to the PAO has been recently popularized. Although multiple studies have demonstrated adjunctive hip arthroscopy to be safe and efficacious, the incidence of HO in these patients is not well documented, especially in those not receiving NSAID prophylaxis. Rates of HO have been documented in the hip arthroscopy and PAO literature, but little is known about the impact the combination of these procedures has on the development of HO. Furthermore, the addition of concomitant hip arthroscopy to the PAO complicates the decision of whether to prescribe NSAIDs to these patients by emphasizing the need to further evaluate the risk-benefit ratio with respect to the dual impact these drugs may have on HO development and bony union.

This study aimed to determine the incidence of HO in patients undergoing PAO with concomitant hip arthroscopy who did not receive formal NSAID prophylaxis, as well as to evaluate the surgical and clinical factors associated with the development of HO in this population. We hypothesized that the incidence of HO would be low, potentially obviating the need for NSAID prophylaxis in a population where bony union is imperative. We hope the findings of this study will help guide clinical decision-making regarding HO prophylaxis in patients undergoing hip preservation surgery to maximize patient benefit while minimizing undue risk.

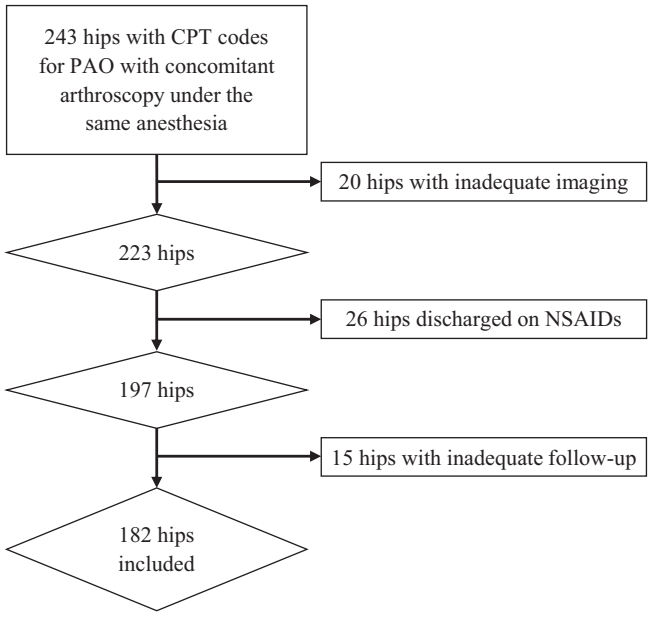

Figure 1. A flow chart of the winnowing procedure using the study inclusion and exclusion criteria. CPT, Current Procedural Terminology; NSAID, nonsteroidal anti-inflammatory drugs; PAO, periacetabular osteotomy.

METHODS

This study protocol was approved by our institutional review board. Billing codes were reviewed by a single, high-volume hip preservation surgeon (A.A.M.) at a single institution. Medical records were retrospectively reviewed for 243 hips undergoing PAO with concomitant hip arthroscopy from January 2012 to December 2022, and patients were included if they had Current Procedural Terminology codes for PAO (S2115, 27146) and concurrent hip arthroscopy (29914, 29915, 29916) under the same anesthesia and were not discharged on NSAID prophylaxis for HO. Patients were excluded if they were discharged on postoperative NSAIDs for HO prophylaxis, lacked adequate follow-up, or lacked adequate imaging for any designated time point. After applying the exclusion criteria, 182 hips were included in the final analysis (Figure 1).

Many patients received short-term (1- to 3-day) courses/doses of NSAIDs in the immediate perioperative window before discharge as part of multimodal pain control, which also included tramadol, oxycodone, and pregabalin; these patients were only included in the analysis if they were

†Address correspondence to Alfred A. Mansour III, MD, Department of Orthopaedic Surgery, McGovern Medical School, University of Texas Health Science Center at Houston, 5420 West Loop South, Suite 2300, Houston, TX 77401, USA (email: alfred.a.mansour@uth.tmc.edu).

*Department of Orthopaedic Surgery, McGovern Medical School, University of Texas Health Science Center at Houston, Houston, Texas, USA.

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Ethical approval for this study was obtained from the University of Texas Health Science Center at Houston (reference No. HSC-MS-22-1116).

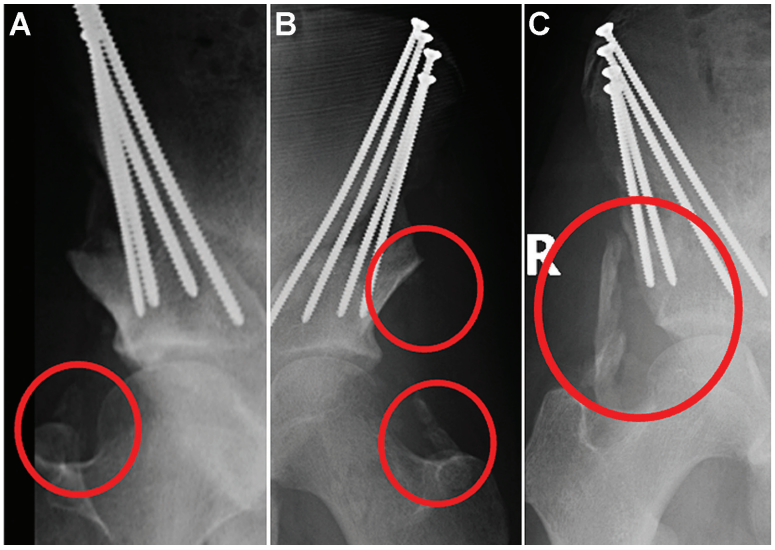

Figure 2. Examples of Brooker grades (A) 1, (B) 2, and (C) 3 for heterotopic ossification.

not discharged on NSAIDs for HO prophylaxis. The type of NSAID received was recorded and included in subanalyses. Most patients who met the inclusion criteria for this study were prescribed low-dose (81 mg) aspirin for up to 6 weeks immediately after surgery as part of the protocol for deep venous thrombosis (DVT) prophylaxis. Patients were substratified based on the method of DVT prophylaxis to account for aspirin exposure (aspirin for 6 weeks, aspirin for <6 weeks, or enoxaparin); nonetheless, aspirin was not considered as an exclusion criterion or a form of HO prophylaxis because of its low dosage.

Radiographic Assessment of HO

Radiographs of all patients were assessed by 3 independent observers (J.M.H., O.S., and B.C.) for HO development at 2 weeks, 6 weeks, and 3 months postoperatively. This timeline was used based on previous literature, which demonstrates that HO after hip arthroscopy almost always manifests radiographically by 75 days[4] and that a minimum follow-up of 9 weeks is needed.[19] Radiographs were compared with preoperative images, and HO development was assessed using the Brooker classification,[26] in which grade 1 is described as small islands of bone within the soft tissue, grade 2 is bone islands between the pelvis and femur with >1 cm of space remaining between the bony surfaces, grade 3 is bone islands large enough to reduce the space between the pelvis and femur to <1 cm, and grade 4 is complete ankylosis[3,26] (Figure 2).

Any disagreement between the observers was reviewed concurrently until a consensus classification was reached. If patients had radiographic signs of HO at 2 weeks or 6 weeks that resolved by 3 months, they were not placed in the HO cohort and instead were deemed not to have HO. Interobserver reliability calculations were not performed.

Data Collection and Statistical Analysis

Patient characteristics and surgical/clinical variables—such as concomitant hip pathology, surgical procedures performed, revision status, symptoms, DVT prophylaxis, and in-house NSAID use—were recorded. Concomitant procedures included labral repair, femoroplasty, and microfracture. The type of arthroscopic capsulotomy was recorded as "T-capsulotomy," "interportal," or "other."

Continuous variables were calculated and reported as means with standard deviations. Means were compared with the Mann-Whitney *U* test. Categorical variables were expressed as frequencies and percentages, and Fisher exact tests were utilized to compare categorical variables between patient groups. All analyses were performed with an alpha level of .05, indicating statistical significance as <.05, in STATA Version 17 (StataCorp).

RESULTS

The mean age of the 167 study patients (182 hips) was 25.5 ± 8 years, the mean body mass index (BMI) was 24.4 ± 4.5 kg/m^2, and 8.2% of the patients were men. Of the 182 hips analyzed, 12 hips developed radiographically significant HO, with a total incidence rate of 6.6%. Nine of these hips were classified as Brooker grade 1, 2 hips as Brooker grade 2, and 1 hip as Brooker grade 3 at 3 months postoperatively. Of these 12 patients with HO, 4 (33%) were symptomatic, which equates to 2.2% of the entire cohort. Symptoms ranged from pain with hip flexion and internal rotation to restricted hip motion. Of the 182 patients, only 1 patient (0.5%) required a return trip to the operating room for resection because of restricted hip motion; the procedure led to a complete resolution of her symptoms.

TABLE 1
Comparison of Patient Characteristics According to Presence of HO[a]

Variable	HO Absent (n = 170 Hips)	HO Present (n = 12 Hips)	*P*
Age, y	25.5 ± 8	24.3 ± 9.9	.57
Sex			.01
Female	159 (95.5)	8 (66.7)	
Male	11 (6.5)	4 (33.3)	
Ethnicity			.14
Non-White	37 (21.8)	0 (0)	
White	132 (77.6)	12 (100)	
N/A	1 (0.6)		
BMI, kg/m^2	24.4 ± 4.5	24.2 ± 3.8	≥.99
Previous hip arthroscopy			.50
No	154 (93.9)	11 (91.7)	
Yes	10 (6.1)	1 (6.3)	

[a]Data are reported as mean ± SD or n (%). BMI, body mass index; HO, heterotopic ossification.

TABLE 2
Comparison of Perioperative Characteristics According to the Presence of HO[a]

Variable	HO Absent (n = 170 Hips)	HO Present (n = 12 Hips))	*P*
Postop CPM[b]			≥.99
No	43 (25.3)	3 (25)	
Yes	125 (73.5)	9 (75)	
DVT prophylaxis[c]			.32
Aspirin 6 wk	153 (90)	10 (83.3)	
Aspirin <6 wk	11 (6.5)	2 (16.7)	
Enoxaparin	2 (1.2)	0 (0)	
None	2 (1.2)	0 (0)	
Inpatient NSAID use			.09
No	34 (20)	0 (0)	
Yes	136 (80)	12 (100)	

[a]Data are reported as n (%). CPM, continuous passive motion; DVT, deep venous thrombosis; HO, heterotopic ossification; NSAID, nonsteroidal anti-inflammatory drugs; Postop, postoperative.
[b]Data unavailable for 2 patients.
[c]Data unavailable for 2 patients.

The patient characteristics according to the presence of HO can be viewed in Table 1. Male patients were significantly more likely than female patients to develop HO (27% vs 4.8%, respectively; $P = .01$). No significant difference was observed in HO incidence based on age, BMI, or race. The perioperative characteristics according to HO presence can be seen in Table 2. All but 2 patients received DVT prophylaxis, with the majority (90%) receiving aspirin for 6 weeks. Thirteen patients received aspirin for <6 weeks because of noncompliance, and 2 patients received enoxaparin. While 15.4% of patients receiving DVT prophylaxis of aspirin for <6 weeks developed HO, as opposed to 6% of patients who received aspirin for the full 6 weeks, this difference was underpowered and lacked statistical significance ($P = .32$) (Table 2).

TABLE 3
Comparison of Surgical Variables According to Presence of HO[a]

Variable	HO Absent (n = 170 Hips)	HO Present (n = 12 Hips)	*P*
Labral repair			.20
No	51 (30)	1 (8.3)	
Yes	119 (70)	11 (91.7)	
Femoroplasty			.73
No	38 (22.4)	3 (25)	
Yes	132 (77.6)	9 (75)	
Microfracture			
No	167 (98.2)	12 (100)	≥.99
Yes	3 (1.8)	0 (0)	
Capsulotomy			.30
Interportal	43 (25.3)	1 (98.3)	
T-capsulotomy	127 (74.7)	11 (91.7)	

[a]Data are reported as n (%). HO, heterotopic ossification.

Surgical variables can be seen in Table 3. Of the 3 patients who underwent microfracture, none developed HO. While 91.7% of patients who developed HO had a labral repair and 75% had a femoroplasty, these values were not statistically significant ($P = .2$ and $P = .73$, respectively). No association was found between HO and revision status, continuous passive motion, or type of arthroscopic capsulotomy (Tables 2 and 3).

Overall, 145 (80%) patients received short-term courses of NSAIDs—including celecoxib, toradol, and naproxen—in the immediate perioperative period before discharge. The duration of these doses ranged from 1 to 3 days and varied based on the overall length of stay at the hospital. None of these patients were discharged home with NSAID prescriptions. There was no statistically significant association between HO incidence and short-term in-house NSAID use (8.3% of patients who received in-house NSAIDs developed HO versus 0% in patients who did not; $P = .09$), type of NSAID received (8% of patients receiving in-house celecoxib developed HO versus 8.16% of patients receiving an NSAID other than celecoxib; $P \geq .99$), or amount of different NSAIDs received (7.1% of patients receiving 2 in-house NSAIDs developed HO versus 8.3% of patients who received 1 in-house NSAID; $P \geq .99$) (Table 2).

DISCUSSION

Given the rise in popularity of hip arthroscopy and the growing field of hip preservation, there is a large amount of literature regarding the topic of HO and a subsequently extensive variation of reported HO rates.[2] Multiple studies have examined the rates of HO in hip arthroscopy and PAO, however, few have specifically studied this in patients undergoing these procedures concurrently,

especially in those not receiving NSAID prophylaxis. It is unknown whether the addition of concomitant hip arthroscopy to PAO affects the development of HO and its subsequent clinical relevance.[23] In this study, we found a relatively low 6.6% incidence of radiographically significant HO development in the setting of PAO with concomitant hip arthroscopy in patients not receiving formal, long-term NSAID prophylaxis. Only 2.2% of patients developed symptomatic HO and even fewer (0.5%) required operative resection. In addition, HO development after PAO with concomitant hip arthroscopy was found to be higher in men versus women (27% vs 4.8%; $P = .01$). Our study found no other significant clinical or surgical association with HO development in this population.

Numerous previous studies have examined the incidence of HO after hip arthroscopy. In 2010, Randelli et al[18] demonstrated a 33% rate of radiographic HO in 15 patients undergoing hip arthroscopy who did not receive NSAID prophylaxis, as opposed to 0% in 285 patients who did. While their incidence rate is substantially higher than ours, their small sample size of patients not receiving prophylaxis makes it difficult to draw comparisons or meaningful conclusions. In 2016, Yeung et al[30] systematically reviewed 5 studies regarding HO after hip arthroscopy. They reported a pooled HO incidence of 13% in patients who did not receive prophylaxis contrasted with 3.3% in those who did (a 4-fold decrease). Of those who did not receive prophylaxis, 7.7% experienced symptomatic HO, and only 3.7% required revision surgery. Given the low rate of symptomatic HO and revision procedures, the authors questioned the clinical significance of NSAID prophylaxis when weighed against the possible complications and side effects of the medications.

In 2014, Beckmann et al[3] demonstrated a 25% incidence of HO in 92 hip arthroscopy patients not receiving prophylaxis compared with a 5.6% rate in 196 cases receiving prophylaxis (naproxen 500 mg twice daily for 3 weeks). Patients not receiving prophylaxis were 13.6 times more likely to develop HO. Nine of the 34 patients with HO were symptomatic and required operative resection. While the incidence of HO in patients not receiving prophylaxis was 18.4% higher than the rate reported in this study, their cohort was half the size, and their rate of symptomatic HO was similar. In their subsequent double-blinded placebo-controlled trial, Beckmann et al[4] further demonstrated a 42% decrease in the rate of HO development in those receiving postoperative naproxen and only 2 patients required operative resection.

When Siebenrock et al[26] initially described the PAO procedure in 1984, they demonstrated an incidence rate of HO of 6% in 75 patients, with 2 requiring resection due to restricted hip motion. In a subsequent series[15] of >500 PAOs, revision for resection of HO was necessary in <1%. The authors stated that modified surgical exposures with careful soft tissue dissection and retractor placement can be employed to limit soft tissue damage and the subsequent damage to the acetabular blood supply, thus decreasing the risk of HO. In 2009, Clohisy et al[7] performed a systematic review of the PAO that included 13 studies with a minimum follow-up of 2 years. The authors reported symptomatic HO as one of the most common major complications, with rates of asymptomatic HO ranging from 4% to 31%, while rates of symptomatic HO were much lower, ranging from 2% to 8%. HO excision rates were <5% across all studies, ranging from 1% to 4%.

While NSAIDs have been proven to suppress the development of HO, the clinical significance of this remains debatable. Rath et al[19] examined 50 patients who underwent hip arthroscopy and did not receive NSAID prophylaxis, demonstrating radiographic signs of HO in 22 (44%) patients. None of the patients with HO required a subsequent operation, and the presence of HO had no impact on functional outcome scores (modified Harris Hip Score and Hip Outcome Score at 1 year postoperative). In a subsequent study, Rath et al[20] reported a 36% incidence rate of radiographically significant HO in 100 patients after hip arthroscopy not receiving NSAID prophylaxis compared with 0% in 63 patients receiving prophylaxis. Again, no patients required operative resection and only 4% were classified as Brooker grade 3. In 2020, Dow et al[10] demonstrated a 2.4-fold reduction in the incidence of HO in patients treated with 400 mg of celecoxib once daily for 6 weeks; nonetheless, this did not influence clinical outcome scores (12-item International Hip Outcome Tool) between patients who developed HO and those who did not. They concluded that most radiographically significant HO is asymptomatic and therefore the clinical benefits must outweigh the risks of NSAID prophylactic treatment to warrant their routine use.

Most recently, in 2022, Arshad et al[2] performed a systematic review of HO after hip arthroscopy. Of the 45 studies included, 14 (31%) reported an HO incidence of <1%, 30 (67%) an incidence of <5%, and 36 (80%) an incidence of <10%—all comparable to that of our study. Of the 19 studies that recorded a Brooker classification, all but 2 classified the majority as Brooker grade 1. Sixteen studies (34.8%) prescribed HO prophylaxis (naproxen, celecoxib, indomethacin, or aspirin, typically for a minimum of 3 weeks). Only 6 studies (13%) examined placebo groups not receiving prophylaxis (mean HO incidence, 29.5% [range, 1.3%-45.8%]), 5 of which documented statistically reduced rates of HO in patients receiving NSAID prophylaxis. Reoperation rates varied broadly from 9.8% to 37.5% of the patients developing HO. Overall, the authors similarly concluded that the incidence of HO in hip arthroscopy is low, and most cases are not symptomatic and do not require further intervention. This point is further supported in a commentary and perspective written by Løken[16] on the trial performed by Beckmann et al,[4] in which the author states that clinically relevant HO is uncommon, and it is thus important to be mindful of the risk-benefit ratio of routine NSAID prophylaxis.

Since the addition of adjunctive hip arthroscopy to the PAO, multiple series have examined the associated operative findings and complications, but few have studied HO development specifically. In 2 series that reviewed 95 and 248 hips respectively, Gosey et al[14] and Sabbag et al[21] each reported only 1 case of HO requiring excision. Schaver et al[23] reported an HO incidence of 3% in 65 patients who underwent PAO and hip arthroscopy; however, all patients received NSAID prophylaxis—most

commonly, naproxen 500 mg for 14 days. Our study demonstrated a similarly low incidence rate of HO to these studies, suggesting that the incidence of radiographic and symptomatic HO in the setting of PAO with concomitant hip arthroscopy continues to be low even in patients who do not receive NSAID prophylaxis.

When discussing adjunctive hip arthroscopy to PAO, it is also important to note that postoperative nonunion is a consideration. The prevalence of nonunion after PAO has a reported[24] range of 1% to 17%. Furthermore, multiple studies have demonstrated the negative impact of NSAIDs on bone remodeling and delayed fracture healing,[1,11,13,23,27,29] with some studies further demonstrating greater rates of nonunion and delayed fracture healing in patients with acetabular fractures receiving indomethacin for HO prophylaxis.[6,22] Sagi et al[22] demonstrated higher rates of nonunion after 6 weeks of indomethacin in patients undergoing acetabular fracture surgery but also showed that shortened prophylactic doses of indomethacin for as low as 1 week significantly decreased the incidence of HO without increasing the incidence of nonunion. Schaver et al[23] reported 2 cases of nonunion (incidence of 3%), 1 of which occurred in a patient who received HO prophylaxis with naproxen. These results suggest that NSAID use may have an impact on nonunion after PAO, but that shorter/lower doses may still mitigate the risk of HO development without increasing the risk of nonunion. While a large number of patients in the present study received 6 weeks of aspirin for DVT prophylaxis and short-term, low-dose exposure to NSAIDs before discharge, these time frames (1-3 days) were significantly shorter than even the 1-week time frame reported by Sagi et al.[22] To our knowledge, no studies have reported protective effects of NSAIDs on HO development in time frames as short as 1 to 3 days. Experimental studies have also demonstrated soft tissue healing to the bone to be impaired by NSAIDs,[9] which Løken[16] points out may affect the healing of sutured labrum or capsule in hip arthroscopy. Like the conclusions of Beckmann et al,[3,4] the ideal therapy would be the lowest dose and shortest duration that protects against HO formation while minimizing the risk of nonunion and impaired soft tissue healing. Larger, prospective studies are needed to determine the true impact the use of postoperative NSAIDs has on nonunion rates in the setting of PAO.

Limitations

Our study has several limitations, the first of which was its retrospective nature. This presents innate limitations regarding patients lost to follow-up and/or incomplete medical records, accurate determination of the etiology of symptoms in patients with HO, as well as the inability to know whether patients were specifically counseled to avoid NSAIDs during the postoperative period. In addition, specific outcome measures were not collected before or after the procedure. This precluded any quantitative analysis of symptoms or outcome scores from being performed, which also affected our reported incidence rate of symptomatic HO. Furthermore, symptoms from HO can be confounded by symptoms from the procedure itself, making it difficult to determine the exact incidence of symptomatic HO.

The timetable of our radiographic follow-up may also be considered a limitation and affect our overall incidence of HO. The time points chosen were consistent with previous literature demonstrating that HO is radiographically evident by 6 weeks and that ossification does not typically progress beyond 3 months.[3,4,19,20] However, Dow et al,[10] recently reported the progression of HO and new cases of radiographic HO as far as 1 to 2 years out from surgery. Therefore, it is possible that our radiographic timeline did not capture all patients who developed HO.

This study did not consider the use of aspirin for DVT prophylaxis as a form of HO prophylaxis. While this is largely consistent with previous literature, it may still be considered a limitation due to possible confounding effects. In a randomized trial of 2649 hip arthroplasty patients, Neal et al[17] demonstrated no detectable effect of low-dose aspirin on the risk of HO formation. While there are limited studies within the arthroplasty literature that have made connections between aspirin use and lower rates of HO formation, these results are inconsistent and have not translated into hip arthroscopy.[28] In a recent systematic review of chemoprophylactic modalities for HO in hip arthroscopy, aspirin was considered a potential prophylactic agent in only 1 of the 15 included studies.[8] Our patient population differed from the studies these authors considered, as our patients received aspirin for 6 weeks, whereas most studies they considered studied aspirin use <3 weeks. Furthermore, our subgroup analysis of DVT prophylaxis showed no significant association between aspirin use and rates of HO.

CONCLUSION

Overall, this study demonstrated a low incidence (6.6%) of radiographic HO in the setting of PAO with concomitant hip arthroscopy in the absence of formal NSAID for HO prophylaxis. We further demonstrated an even lower incidence of clinically significant HO that causes symptoms and/or requires further intervention or operative resection. When considering the risk NSAID use poses to the bony union in the setting of PAO with concomitant hip arthroscopy, the study findings suggest that the use of routine postoperative NSAIDs for HO prophylaxis may not be necessary.

ORCID iDs

Omar Stocks https://orcid.org/0009-0007-0824-8528
Alexis Aboulafia https://orcid.org/0009-0002-4428-487X
Alfred A. Mansour III https://orcid.org/0000-0001-5073-246X

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