

Incidence of Heterotopic Ossification with NSAID Prophylaxis Is Low After Open and Arthroscopic Hip Preservation Surgery



Andrew L. Schaver, B.S., Michael C. Willey, M.D., and Robert W. Westermann, M.D.

Purpose: We evaluate the incidence of heterotopic ossification (HO) development with nonsteroidal anti-inflammatory drug (NSAID) prophylaxis in patients after open and arthroscopic hip preservation surgery. **Methods:** A retrospective review identified patients who underwent hip preservation surgery at a single institution within the past 3 years. Patients who underwent hip arthroscopy with or without periacetabular osteotomy (PAO) or femoral osteotomy (FO) were included. Those who did not receive 3-month postoperative radiographs were excluded. The incidence and Brooker classification (BC) of HO in patients taking Naproxen or another NSAID (meloxicam, celecoxib, indomethacin, or aspirin alone) was assessed using AP radiographs available from 3-, 6-, and 12-month follow-up appointments. Univariate analysis was conducted to compare numerical means and categorical data (significance level $P = .05$). **Results:** A total of 328 hips (284 patients) were included. All patients received hip arthroscopy, while 71 patients (21.6%) received concurrent periacetabular osteotomy (PAO; $n = 65$) or femoral osteotomy (FO; $n = 6$). Overall, 276 hips (84.4%) received Naproxen for HO prophylaxis. In total, 5 of 328 hips (1.5%) developed HO (4, BC I; 1, BC III). The rate of HO development was significantly higher in males versus females (4 of 121 (3.31%) vs 1 of 207 (.48%), $P = .0441$). All 5 patients received arthroscopic cam resection and labral repair, and 1 patient also received PAO. Three patients in the Naproxen group (.91%) developed HO, which was not statistically different from those taking a different NSAID (.61%, $P = .1797$). **Conclusion:** The incidence of HO development was low with NSAID prophylaxis after hip preservation surgery.

Introduction

Heterotopic ossification (HO) is one of the most commonly recognized complications after hip arthroscopy, appearing in 8.3-44% of hips without

prophylaxis.^{1,2} It develops because of trauma to the surrounding soft tissues, which is believed to stimulate mesenchymal stem cells to differentiate into osteoblastic stem cells that activate in surrounding musculature.³ This can be seen radiographically on plain films as irregular opacification around the joint and can often be seen 4-6 weeks postoperatively.³ Prophylactic mechanisms target inductive signaling pathways, alter stem cells in soft tissue, and modify the environment conducive to HO formation.⁴ Nonsteroidal anti-inflammatory drugs (NSAIDs) reduce prostaglandin production and decrease stimulation of osteogenic stem cells, and they have become the recommended prophylactic treatment.⁴

Outcomes of previous studies have demonstrated that nonselective NSAIDs (cyclooxygenase 1 and 2 inhibitors), such as naproxen and indomethacin are useful to prevent HO.⁵⁻⁸ More recent research indicates that selective COX-2 NSAIDs (celecoxib, meloxicam, and etodolac) are also effective, but the most appropriate agent, dosage, and duration of treatment varies in the literature and is unknown.⁹⁻¹¹ In addition, it is currently unknown whether the incidence of symptomatic HO after hip arthroscopy increases with

Department of Orthopedics and Rehabilitation, University of Iowa Hospitals and Clinics, Iowa City, Iowa, U.S.A.

The authors report the following potential conflicts of interest, disclosures, or sources of funding: Research reported in this publication was supported by the National Center for Advancing Translational Sciences of the National Institutes of Health under Award number UL1TR002537. R. W. Westermann is on the editorial board of *Arthroscopy*, *American Journal of Sports Medicine*, and the *American Orthopedic Society for Sports*. He is a paid consultant for *Conmed Linvatec* and has received nonfinancial support from *Smith and Nephew*, outside the submitted work. M. C. Willey reports research support from *Biomet*, outside the submitted work. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. Full ICMJE author disclosure forms are available for this article online, as [supplementary material](#).

Received December 29, 2020; accepted June 7, 2021.

Address correspondence to Robert W. Westermann, M.D., University of Iowa, Department of Orthopaedics and Rehabilitation, 2701 Prairie Meadow Dr., Iowa City, IA 52246, U.S.A. E-mail: robert-westermann@uiowa.edu

© 2021 Published by Elsevier on behalf of the Arthroscopy Association of North America. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

2666-061X/202078

<https://doi.org/10.1016/j.asmr.2021.06.001>

concurrent periacetabular osteotomy or femoral osteotomy. The purpose of this study was to evaluate the incidence of HO development with NSAID prophylaxis in patients after open and arthroscopic hip preservation surgery. We hypothesize that the incidence of HO development with NSAID prophylaxis will be low in the setting of hip arthroscopy with and without concurrent osteotomy procedures.

Methods

This study was approved by the Institutional Review Board at the University of Iowa. A retrospective review of patients who underwent hip preservation surgery at a single institution over the past 3 years was completed. Patients who underwent hip arthroscopy (HA) with or without periacetabular osteotomy (PAO) or femoral osteotomy (FO) were identified. Patients who did not receive at least 3-month postoperative radiographs were excluded. Any patients with preoperative heterotopic ossification were also excluded. Baseline patient demographics, procedure variables, and any intraoperative complications were recorded. Surgical indications, procedures, and operative times were also recorded. All procedures, including primary and revisions, were included in the analysis.

Postoperatively, patients returned to the hip preservation surgery clinic for 3-week, 3-month, 6-month, and 1-year follow-up appointments. Follow-up radiographs were obtained for all patients at 3-month visits and repeated for those who returned for their 1-year follow-up appointment. Radiographs were read by the treating orthopedic surgeons (M.C.W. and R.W.W.) and a musculoskeletal radiologist independent from the study. All patients were managed with a standard postoperative rehabilitation program. Those who underwent hip arthroscopy alone used a standard hip

brace and were toe-touch weight-bearing with crutches for 4-6 weeks after surgery. Patients started formal physical therapy soon after surgery. Those who underwent concurrent PAO or FO were toe-touch weight bearing with crutches for 6 weeks and started formal physical therapy 3 weeks after surgery.

Nonsteroidal anti-inflammatory drugs (NSAIDs) were routinely used for postoperative HO prophylaxis. The majority of patients were prescribed 500 mg Naproxen and were instructed to take one tablet twice per day for 21 days. On the basis of previous evidence,¹ a combination of 75 mg indomethacin for 1 week plus Naproxen for the following 2 weeks was used for patients deemed to be at greater risk of developing HO (i.e., revision procedures). In addition, patients with contraindications to Naproxen (e.g., allergies and prior adverse reaction) were given a different NSAID agent, including either 15 mg meloxicam (1 tablet daily for 14 days), 200 mg celecoxib (2 tablets daily for 14 days), or 325 mg aspirin alone. Aspirin (325 mg) was prescribed for 14 days for blood clot prevention in all patients, except for those with contraindications ($n = 37$, 11%). Any side effects, including gastrointestinal issues experienced by patients attributable to their NSAID regimen, were recorded. Patients were grouped according to the medicines they received, with the aim of comparing the rate of HO development in patients taking Naproxen versus another NSAID agent.

Statistical Analysis

Descriptive statistics were performed. Continuous data were presented as means and standard deviations. Patient demographics, including age, gender, and body mass index (BMI) were compared between groups. Further comparison of specific procedures, operative times, and the incidence of HO was reported for each

Table 1. Demographic Information for all Included Hips

	All Hips ($n = 328$)	Naproxen ($n = 276$)	Other NSAIDs* ($n = 52$)	<i>P</i> Value
Female [†]	207 (63.1)	169 (61.2)	38 (73.1)	.1044
Male [†]	121 (36.9)	107 (38.8)	14 (26.9)	
Age (years) [‡]	28.22 ± 8.87	28.5 ± 8.95	26.90 ± 8.44	.2254
BMI (kg/m ²) [‡]	26.64 ± 5.19	26.66 ± 5.16	26.58 ± 5.37	.9216
Race (n , %)				
Caucasian	311 (94.8)	260 (94.2)	51 (98.1)	.2477
African American/Black	7	6	1	
Other	10	10	0	
Smokers (n , %)	45 (13.7)	39 (14.1)	6 (11.5)	.6182
Indication				
FAI ± labral tear	218 (66.5)	189 (68.5)	29 (55.8)	.0749
FAI with hip dysplasia	61	49	12	.3655
FAI + other [§]	49	38	11	.1705

BMI, body mass index; FAI, femoroacetabular impingement; NSAIDS, nonsteroidal anti-inflammatory drugs.

*Includes meloxicam, celecoxib, indomethacin, and aspirin.

[†]Shown as n (%), with % = $n/\text{total hips} \times 100$.

[‡]Data are given as means ± SD.

[§]Other includes loose bodies, os acetabuli, and femoral version abnormalities.

Table 2. Completed Procedures and Operative Times

	Naproxen (<i>n</i> = 276)	Other (<i>n</i> = 52)	<i>P</i> Value
Procedures			
OCP + LR*	97 (35.1)	11 (21.2)	.0489
OCP, AP, LR	25 (9.06)	5 (9.62)	.8982
+AIIS†	98 (35.5)	21 (40.4)	.5022
+PAO	51 (18.5)	14 (26.9)	.1611
+FO	5 (1.81)	1 (1.92)	1.000
Operative Time (h:mm)			
OCP + LR*	1:33 ± 0:19	1:47 ± 0:13	.0090
OCP, AP, LR	2:00 ± 0:49	1:43 ± 0:15	.1227
+AIIS†	1:50 ± 0:48	2:02 ± 0:15	.5307
+PAO	3:56 ± 0:38	4:03 ± 0:49	.9327
+FO	4:13 ± 0:28	4:38 (1 case)	

NOTE. Bolded values indicate significant difference.

AIIS, anterior inferior iliac spine decompression; AP, acetabuloplasty; FO, femoral osteotomy; LR, labral repair; OCP, osteochondroplasty of femoral head-neck; PAO, peri-acetabular osteotomy.

*Loose body removal (*n* = 10) and capsular plication included.

†Includes HA + PAO cases (*n* = 15).

medication. An unpaired, two-tailed Student's *t*-test was used to compare numerical means, and χ^2 and Fisher exact tests were used to compare categorical variables (significance level: *P* = .05). Statistical analysis was performed using Excel v.16.43 (Microsoft, Inc., Redmond, WA).

Results

Demographics

Medical records from 353 hip preservation procedures (309 patients) were reviewed. After excluding those without adequate follow-up or postoperative radiographs (*n* = 25), there were 328 hips (284 patients) included in the analysis. The overall mean ± SD age was 28.22 ± 8.87 years (range: 18-50). The average BMI was 26.64 ± 5.19 kg/m² (range: 17.75-47.35 kg/m²) (Table 1).

Procedure Results

All patients in our review underwent hip arthroscopy (HA). Overall, 71 patients (22.0%) received concurrent periacetabular osteotomy (PAO; *n* = 65) or femur osteotomy (FO; *n* = 6). The majority of patients received arthroscopic osteochondroplasty (OCP) of the femoral head-neck with labral repair (LR) (Table 2).

Heterotopic Ossification Prophylaxis

All patients received NSAIDs for postoperative HO prophylaxis. The majority received 500 mg naproxen (*n* = 276; 84.4%), compared with another agent (meloxicam, celecoxib, indomethacin, or aspirin alone; *n* = 52; 15.5%). The specific agents and dosages are listed in Table 3. There were two patients who had side effects attributed to NSAIDs. One patient reported stomach pain while taking naproxen, and another

patient experienced nausea while taking celecoxib. Both patients self-discontinued these medications. Neither developed HO after surgery.

Overall, there were 5 cases of postoperative HO development (5/328 hips; 1.5%). (Table 4) Three hips developed HO in the naproxen group (3/328; .91%), compared to 2 patients (affecting two hips) taking other medications (2/328 [.61%], *P* = .1797). The odds of developing HO in the naproxen group versus a different NSAID was not statistically significant (OR 3.64, 95% CI .59-22.3, *P* = .1628). The rate of HO development was significantly higher in males versus females (4 of 121 [3.31%] vs 1 of 207 [.48%], *P* = .0441). Among those who underwent PAO, there were two cases of symptomatic superior pubic ramus nonunion (2/65 hips; 3.08%). One of these patients took naproxen for HO prophylaxis, while the other took aspirin alone.

The median age of those who developed HO was 27 years old (range: 21-36 years), and the median BMI was 36 kg/m² (range: 25-40 kg/m²). Four patients were male, and all had a BMI of 25 kg/m² or more. Among the 5 cases of HO, all patients received hip arthroscopy with femoroplasty/osteochondroplasty of the head-neck and labral repair. One patient received concurrent anterior inferior iliac spine decompression (AIIS) decompression, and another received PAO. One case was a revision procedure. No patient in our series who developed postoperative HO required surgical reoperation as treatment.

Discussion

The results of our study show the overall incidence of HO development with NSAID prophylaxis after hip preservation surgery was low (1.5%, 5/328 patients), which affirms our hypothesis. Overall, three patients developed HO while taking naproxen, whereas two patients developed HO, while taking another NSAID regimen (meloxicam, and aspirin alone). In addition, the rate of HO development after hip preservation surgery was proportionally higher in males versus females (3.21% vs .48%; *P* = .0441). Each patient had a

Table 3. NSAIDs Used for Heterotopic Ossification Prophylaxis

Medications (mg)	No. of Hips (<i>n</i> = 328)
Naproxen 500	276 (84.4%)
Other NSAIDs	52 (15.5%)
Meloxicam 15	14
Aspirin 325 only	20
Celecoxib 200	8
Indomethacin 75†	10

NSAID, nonsteroidal anti-inflammatory drug.

*Dose (mg).

†Indomethacin, 75 mg for first 7 days, and then naproxen 500 mg for the following 14 days (*n* = 7).

Table 4. Cases of Heterotopic Ossification

Patient*	Presentation of HO	Brooker Grade of HO	Medication	Procedures
36 M BMI 40	12 months	Type I	Naproxen only	OCP, LR, AIIS, CP
35 M BMI 40	3 months	Type 3	Naproxen and aspirin	OCP, AP, LR, LOA [†]
21 M BMI 28	3 months	Type I	Naproxen and aspirin	OCP, LR
27 M BMI 25	3 months	Type I	Meloxicam and Aspirin	OCP, LR
26 FM BMI 36	3 months	Type I	Aspirin only	OCP, LR, PAO

AIIS, anterior inferior iliac spine decompression; AP, acetabuloplasty; BMI, body mass index; CP, capsular plication; F, female; FO, femoral osteotomy; HO, heterotopic ossification; LR, labral repair; M, male; OCP, osteochondroplasty of femoral head-neck; PAO, peri-acetabular osteotomy; LOA, lysis of adhesions.

*Age, sex, and BMI.

[†]This was a revision procedure.

BMI greater than 25 kg/m². One case was Brooker grade III; this patient developed HO after undergoing revision hip arthroscopy for residual cam-type femoroacetabular impingement (FAI). This patient also received an iliopsoas tenotomy for a chronic hip contracture and later developed HO at the tenotomy site. The patient presented with postoperative pain and underwent corticosteroid injection as treatment. The remaining cases of HO were incidental radiographic findings; no patient presented with symptoms. None of the patients required reoperation as treatment.

A strength of the present study is that it further demonstrates the efficacy of NSAIDs for HO prophylaxis after hip arthroscopy. Four cases were Brooker grade I incidental radiographic findings, which has previously been considered not a true complication after hip arthroscopy.¹²⁻¹⁴ The low incidence of HO in our study is comparable to others reported in the current literature.^{1,2,5,6} In their series, Bedi et al.¹ had an

overall incidence of 4.7% (29 of 616) after hip arthroscopy, and they similarly found that males who underwent osteoplasty with capsulotomy represented the majority of cases of heterotopic ossification. They also found that starting HO prophylaxis with indomethacin for postoperative days 1-4 followed by 30 days of naproxen significantly reduced the rate of HO compared to 30 days of naproxen alone (1.8% [6/339] and 8.3% [23/277], $P < .05$).¹ Additionally, recent systematic review by Yeung et al.⁹ found a 4-fold decrease in the incidence of HO with NSAID prophylaxis compared to no HO prophylaxis after hip arthroscopy alone. Previous studies of HO development after hip arthroscopy for FAI have also found that the majority of cases occur in male patients who undergo femoral osteochondroplasty and/or acetabuloplasty with a capsular incision.^{1,6} Because of comparably higher bone mass in male patients, the potential amount of bone resection can be substantial, which



Fig 1. Radiograph of the left hip with development of heterotopic ossification after osteochondroplasty of femoral head-neck.

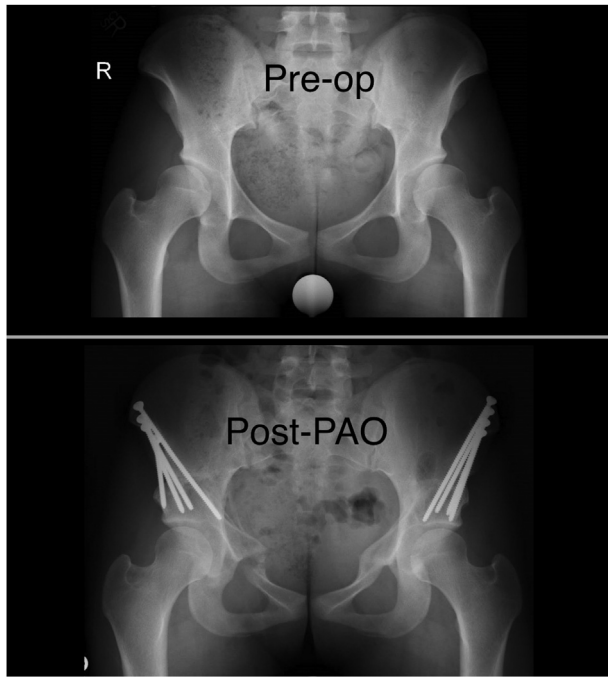


Fig 2. Anteroposterior pelvis radiograph demonstrating postoperative healing after periacetabular osteotomy.

theoretically may increase risk of HO development around the hip joint (Fig 1).

Our study broadens the scope to include additional hip preservation surgery procedures, including AIIS decompression, periacetabular osteotomy (PAO), and femoral osteotomy (FO) (Fig 2). While there are multiple reports of the incidence of HO with and without NSAID prophylaxis after hip arthroscopy,^{6,9} it is still unknown whether these concurrent procedures increase the rate of clinically relevant HO after hip arthroscopy.¹²⁻¹⁴ Two patients in our series developed grade I HO after PAO and AIIS decompression, but both did not require additional treatment. There was also a sizable difference in the number of patients who received AIIS decompression or an open osteotomy procedure versus arthroscopic procedures alone, but the rate of HO observed in patients who underwent an osteotomy was not increased in comparison hip arthroscopy alone. Another consideration in these patients is the postoperative nonunion rate with NSAID HO prophylaxis. Multiple studies have examined how NSAIDs affect bone remodeling and fracture-healing, and some have demonstrated that the administration of NSAIDs can result in delayed healing and weaker bone after fractures have healed.^{15,16} Studies of HO prophylaxis with indomethacin after acetabular fractures have found greater risk of nonunion compared to placebo.^{17,18} In our study, there were two cases of symptomatic superior pubic ramus nonunion (2/65 hips, 3.08%). One of these patients was in the naproxen group, while the other patient took aspirin alone.

The patient taking naproxen experienced pain at the site of the superior ramus nonunion and was treated with open reduction and internal fixation with bone grafting. The patient also underwent total hip arthroplasty for the development of osteoarthritis.

More recent studies have examined using more selective NSAIDs, such as celecoxib as HO prophylaxis after hip arthroscopy alone.^{10,19} Selective cyclooxygenase 2 (COX-2) inhibitors have been shown to reduce gastrointestinal side effects and reduce HO after total hip arthroplasty.^{20,21} However, COX-2 is important for fracture healing, and the effect of selective COX-2 inhibitors on nonunion rates is mixed and has yet to be fully determined.^{22,23} Similar to our comparison of hip preservation procedures, there was a substantial difference in the number of patients who received an NSAID other than naproxen. Larger prospective studies are needed to determine the rate of symptomatic HO development after concurrent hip arthroscopy with PAO or FO, as well as prophylaxis with selective NSAIDs. Future studies should attempt to include a larger series of hip preservation procedures and standardize NSAID prophylaxis groups to compare the incidence of postoperative heterotopic ossification and/or nonunion.

Limitations

The present study has several limitations. First, the small sample of patients who received osteotomy procedures and an NSAID agent other than naproxen limits the strength of these comparisons. These limitations also restricted our ability to evaluate for any significant factors related to HO development after hip preservation surgery due to the likelihood of type II or β -error for these outcomes. In addition, variation in procedure types (primary vs revision) and HO prophylaxis regimen between patients may represent confounding variables. The present study also evaluated for the presence of radiographic HO without patient-reported outcomes to correlate for any clinically significant differences in symptoms. Finally, the study's retrospective nature limits the ability to standardize postoperative follow-up and medication compliance among patients.

Conclusion

The incidence of HO development was low with NSAID prophylaxis after hip preservation surgery.

References

1. Bedi A, Zbeda RM, Bueno VF, Downie B, Dolan M, Kelly BT. The incidence of heterotopic ossification after hip arthroscopy. *Am J Sports Med* 2012;40:854-863.
2. Rath E, Sherman H, Sampson TG, Ben Tov T, Maman E, Amar E. The incidence of heterotopic ossification in hip arthroscopy. *Arthroscopy* 2013;29:427-433.

3. Balboni TA, Gobeze R, Mamon HJ. Heterotopic ossification: Pathophysiology, clinical features, and the role of radiotherapy for prophylaxis. *Int J Radiat Oncol Biol Phys* 2006;65:1289-1299.
4. Kaplan FS, Glaser DL, Hebela N, Shore EM. Heterotopic ossification. *J Am Acad Orthop Surg* 2004;12:116-125.
5. Beckmann JT, Wylie JD, Potter MQ, Maak TG, Greene TH, Aoki SK. Effect of naproxen prophylaxis on heterotopic ossification following hip arthroscopy: A double-blind randomized placebo-controlled trial. *J Bone Joint Surg Am* 2015;97:2032-2037.
6. Beckmann JT, Wylie JD, Kapron AL, Hanson JA, Maak TG, Aoki SK. The effect of NSAID prophylaxis and operative variables on heterotopic ossification after hip arthroscopy. *Am J Sports Med* 2014;42:1359-1364.
7. Zhang AH, Chen X, Zhao QX, Wang KL. A systematic review and meta-analysis of naproxen for prevention heterotopic ossification after hip surgery. *Medicine (Baltimore)* 2019;98:e14607.
8. Ma R, Chen GH, Zhao LJ, Zhai XC. Efficacy of naproxen prophylaxis for the prevention of heterotopic ossification after hip surgery: a meta-analysis. *J Orthop Surg Res* 2018;13:48.
9. Yeung M, Jamshidi S, Horner N, Simunovic N, Karlsson J, Ayeni OR. Efficacy of nonsteroidal anti-inflammatory drug prophylaxis for heterotrophic ossification in hip arthroscopy: A systematic review. *Arthroscopy* 2016;32:519-525.
10. Rath E, Warschawski Y, Maman E, et al. Selective COX-2 inhibitors significantly reduce the occurrence of heterotopic ossification after hip arthroscopic surgery. *Am J Sports Med* 2016;44:677-681.
11. Xue D, Zheng Q, Li H, Qian S, Zhang B, Pan Z. 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* 2011;35:3-8.
12. Sabbag CM, Nepple JJ, Pascual-Garrido C, Lalchandani GR, Clohisy JC, Sierra RJ. The addition of hip arthroscopy to periacetabular osteotomy does not increase complication rates: A prospective case series. *Am J Sports Med* 2019;47:543-551.
13. Zaltz I, Baca G, Kim YJ, et al. Complications associated with the periacetabular osteotomy: a prospective multicenter study. *J Bone Joint Surg Am* 2014;96:1967-1974.
14. Edelstein AI, Duncan ST, Akers S, Pashos G, Schoenecker PL, Clohisy JC. Complications associated with combined surgical hip dislocation and periacetabular osteotomy for complex hip deformities. *J Hip Preserv Surg* 2019;6:117-123.
15. Altman RD, Latta LL, Keer R, Renfree K, Hornicek FJ, Banovac K. Effect of nonsteroidal antiinflammatory drugs on fracture healing: a laboratory study in rats. *J Orthop Trauma* 1995;9:392-400.
16. Giannoudis PV, MacDonald DA, Matthews SJ, Smith RM, Furlong AJ, De Boer P. Nonunion of the femoral diaphysis. The influence of reaming and non-steroidal anti-inflammatory drugs. *J Bone Joint Surg Br* 2000;82:655-658.
17. Sagi HC, Jordan CJ, Barei DP, Serrano-Riera R, Steverson B. Indomethacin prophylaxis for heterotopic ossification after acetabular fracture surgery increases the risk for nonunion of the posterior wall. *J Orthop Trauma* 2014;28:377-383.
18. Burd TA, Hughes MS, Anglen JO. Heterotopic ossification prophylaxis with indomethacin increases the risk of long-bone nonunion. *J Bone Joint Surg Br* 2003;85:700-705.
19. Dow T, King JP, Wong IH. The reduction of heterotopic ossification incidence after hip arthroscopy in patients treated with selective cyclooxygenase 2 inhibitor (celecoxib). *Arthroscopy* 2020;36:453-461.
20. Patrono C, Baigent C. Coxibs, Traditional NSAIDs, and cardiovascular safety post-PRECISION: What we thought we knew then and what we think we know now. *Clin Pharmacol Ther* 2017;102:238-245.
21. Zhu XT, Chen L, Lin JH. Selective COX-2 inhibitor versus non-selective COX-2 inhibitor for the prevention of heterotopic ossification after total hip arthroplasty: A meta-analysis. *Medicine (Baltimore)* 2018;97:e11649.
22. George MD, Baker JF, Leonard CE, Mehta S, Miano TA, Hennessy S. Risk of nonunion with nonselective NSAIDs, COX-2 inhibitors, and opioids. *J Bone Joint Surg Am* 2020;102:1230-1238.
23. Wang Z, Bhattacharyya T. Trends of non-union and prescriptions for non-steroidal anti-inflammatory drugs in the United States, 1993-2012. *Acta Orthop* 2015;86:632-637.