Arthroplasty Today 6 (2020) 206–209

Contents lists available at ScienceDirect

Arthroplasty Today

journal homepage: http://www.arthroplastytoday.org/

Original research

Aspirin used for venous thromboembolism prophylaxis in total hip arthroplasty decreases heterotopic ossification

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ARTICLE INFO

Article history:
Received 26 November 2019
Received in revised form
6 January 2020
Accepted 21 January 2020
Available online 13 March 2020

Keywords:
Total hip arthroplasty (THA)
Heterotopic ossification (HO)
Venous thromboembolism (VTE) prophylaxis
Aspirin (ASA)

ABSTRACT

Background: Heterotopic ossification (HO) is a known complication of total hip arthroplasty (THA) that can lead to persistent pain, stiffness, nerve impingement, and instability. Aspirin (ASA) has become an increasingly popular method of venous thromboembolism (VTE) prophylaxis, given its availability, ease of use, and relative safety. Although indomethacin has been commonly used for HO prophylaxis, we wanted to determine whether ASA, given the similar mechanism of action, may be effective in reducing the risk of HO in routine unilateral, primary THA when already being used for VTE prophylaxis.

Methods: The postoperative radiographs of 222 consecutive patients undergoing unilateral, primary THA with cementless fixation were evaluated for HO formation using the Brooker classification immediately before and after surgeon protocol shifted to routine utilization of ASA as VTE prophylaxis in low-risk patients.

Results: HO was detected in 13 of 99 (13.1%) THAs prescribed ASA for VTE prophylaxis (11 grade I, 1 grade II, 1 grade III) compared with 38 of 123 (30.9%) THAs prescribed non-ASA chemoprophylaxis (26 grade I, 7 grade II, 4 grade III, 1 grade IV). Significantly more THAs in the non-ASA cohort developed HO ($P < .01$). There was no significant difference in the distribution of HO severity between cohorts ($P = .61$).

Conclusions: ASA may be effective as monotherapy for both VTE and HO reduction in low-risk patients undergoing unilateral primary arthroplasty with cementless fixation.

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Introduction

Total hip arthroplasty (THA) is a procedure that has been demonstrated to alleviate pain, increase mobility, and improve quality of life [1]. Heterotopic ossification (HO) is the growth of the bone in nonskeletal tissues including muscles, tendons, and other soft tissues [1,2]. HO after THA can result in pain, stiffness, nerve impingement, trochanteric bursitis, and instability [2]. A recent meta-analysis reported a 30% incidence of radiographic HO after THA [3], and symptomatic HO after primary THA has been reported to range from 3% to 10% [1,2]. The Brooker classification describes the radiographic severity of HO about the hip [4]. Although it seems intuitive that higher grade radiographic HO after THA, as determined by Brooker classification, would correlate with increased functional impairment, this has not been definitively shown in the literature, with some authors failing to identify a correlation, [5] whereas others have reported a positive correlation [6]. Numerous potential risk factors for developing HO after THA have been proposed and a recent meta-analysis identified the following as being most significant: male sex, cemented fixation, bilateral THA procedure, ankylosing spondylitis, hypertrophic osteoarthritis, and ankylosed hip before THA [3]. Treatment of symptomatic HO often requires surgical excision and adjunctive modalities, which are costly and often result in persistent patient morbidity [1,2]. Therefore, minimizing the risk of HO after THA, regardless of radiographic severity, is important to improve patient outcomes after THA.

Multiple interventions have been reported to reduce HO formation. Single low-dose radiation, either immediately before or after THA, has been shown to be effective prophylaxis against HO [7-9]. However, radiation can be inconvenient for the patient and surgeon, is costly, may increase risk for wound complication, and has theoretical concerns of malignant transformation, although this has not been demonstrated clinically [2]. Nonsteroidal anti-inflammatory drugs (NSAIDs) have also been demonstrated to minimize risk of HO [7,10]. NSAIDs decrease HO formation by inhibiting the cyclooxygenase (COX) enzymes, which are responsible for production of prostaglandins. Prostaglandin E_2, in particular, is central to the highly

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https://doi.org/10.1016/j.artd.2020.01.010
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orchestrated biomechanical process of endochondral bone formation, which is responsible for fracture repair, bone regeneration, and HO formation [9,11]. Indomethacin, a nonselective COX-1 and COX-2 inhibitor, [11] has been the historical NSAID used for HO prophylaxis, with a typical dosing regimen of 50 mg twice daily for at least 1 week postoperatively. Although cheaper than radiation, indomethacin has been shown to increase bleeding risk when used in concert with venous thromboembolism (VTE) prophylaxis, [12] can cause gastrointestinal disturbance [13-15], is subject to patient compliance, and is known to inhibit bone formation [16], which theoretically could limit bone ingrowth into the prosthetic components.

Aspirin (ASA) has become increasingly popular for VTE prophylaxis after THA, given its minimal expense, wide availability, ease of administration, proven reduction in risk of significant VTE events [17,18], and lower risk of bleeding events [19,20]. ASA has also been recognized in recent clinical practice guidelines as an acceptable method for VTE prophylaxis after THA [18]. Although ASA irreversibly binds COX-1 and COX-2, similar to other NSAIDs, there are limited and contradictory data regarding the efficacy of ASA to reduce the incidence of HO after primary THA [7,10,21-25].

The purpose of our study was to determine whether ASA used for VTE prophylaxis after primary THA performed through a posterolateral approach reduced the radiographic incidence of HO compared with non-ASA VTE prophylaxis.

Material and methods

This study is a retrospective review of prospectively collected data maintained in our institutional arthroplasty database. One high-volume arthroplasty surgeon at our institution changed his protocol for VTE prophylaxis in standard-risk patients (ie, no prior history of VTE, active cancer, or other hypercoagulable state) after THA from more potent chemoprophylaxis to the routine use of ASA. Patients were not prescribed other NSAIDs during the postoperative period. The database was queried to identify all patients undergoing primary THA between January 1, 2014 and August 30, 2017. Inclusion criteria included all patients undergoing unilateral primary THA with cementless fixation who had radiographic follow-up of at least 3 months. Minimum 3-month follow-up was selected because most HO forms by this time [26,27]. Exclusion criteria included patients undergoing revision THA, conversion THA after failure of fracture fixation, simultaneous bilateral THA, and documented perioperative radiation to the hip or pelvic girdle. All patients underwent a posterolateral approach to the hip with posterior capsular repair.

One of two fellowship-trained arthroplasty surgeons reviewed preoperative and postoperative anteroposterior and lateral radiographs of the hip/pelvis for each patient and identified HO formation after the THA; this was recorded as a binary variable—present or absent. When present, HO severity was graded using the Brooker classification [4]. A random subset of 50 patients were reviewed by a second surgeon to determine whether HO had formed, and the second observer was blinded to the initial observer's determination. After radiographic review was complete, selected demographic information was obtained for all patients, including VTE prophylaxis after THA, age at surgery, body mass index, sex, laterality, and diagnosis. The radiographic review was completed before review of patient and surgical data so that reviewers were blinded to VTE prophylaxis when determining presence or absence of HO. Radiographs were reviewed in a randomized fashion so observers were blinded to the date when the radiograph was obtained.

Statistics

Given historical data demonstrating an incidence of radiographic HO of at least 30% [3], a power calculation determined that at least 60 patients were needed in each group to be appropriately powered to find a 20% reduction in risk ($P = .05$, $\beta = 0.8$). The chi-square test was used to compare HO incidence between the ASA and non-ASA cohorts, with statistical significance set at $P = .05$. Cohen's kappa coefficient was calculated to determine inter-rater agreement between for radiographic classification.

Results

The ASA cohort included 99 THAs and the non-ASA cohort included 123 THAs. The ASA cohort included 97 patients prescribed ASA alone, one received ASA and rivaroxaban, and one received ASA and clopidogrel. The ASA dosing regimen varied throughout the study period, including 325 mg twice daily, 325 mg daily, and 81 mg twice daily. ASA was typically prescribed for 4 weeks postoperatively. The non-ASA cohort included 100 patients prescribed warfarin, 8 patients prescribed warfarin and enoxaparin, 5 patients prescribed rivaroxaban, 4 patients prescribed enoxaparin, 3 patients prescribed apixaban, 2 patients treated with sequential compression devices alone, and 1 patient prescribed clopidogrel.

There was no significant difference between the ASA and non-ASA cohorts in terms of age at surgery, body mass index, sex, laterality, or diagnosis (Table 1). There was a nonsignificant trend toward the ASA cohort having a relatively higher proportion of male patients compared with the non-ASA cohort ($P = .07$). The non-ASA cohort had a significantly longer mean radiographic follow-up, which was inherent to the study design where the surgeon changed VTE protocol to ASA. Thirteen (13.1%) patients developed radiographic HO in the ASA cohort compared with 38 (30.9%) patients who developed HO in the non-ASA cohort, which was statistically significant ($P < .01$). Brooker classification for the 13 patients who developed HO in the ASA cohort was grade I in 11 patients, grade II in 1 patient, and grade III in 1 patient. Brooker classification for the 38 patients who developed HO in the non-ASA cohort was grade I in 26 patients, grade II in 7 patients, grade III in 4 patients, and grade IV in 1 patient. There was no significant difference between cohorts in terms of distribution of severity of HO as defined by Brooker classification ($P = .61$). There was substantial agreement between observers, $k = 0.747$ ($P < .001$).

Table 1
Patient demographics, surgical details, and heterotopic ossification status for patients undergoing total hip arthroplasty via posterolateral approach.

Variables	ASA	Non-ASA	*P* value
THAs	99	123	
Age [years]	64.8 ± 12.7	66.1 ± 11.4	.4
BMI [Kg/m^2]	27.6 ± 4.3	27.2 ± 5.7	.65
Follow-up [years]	1.3 ± 0.8	2.1 ± 1.6	<.001
Sex			.07
Male	53	51	
Female	46	72	
Laterality			.94
Right	52	64	
Left	47	59	
Diagnosis			.76
OA	90	113	
AVN	4	4	
RA	2	0	
Dysplasia	3	6	
Heterotopic ossification			<.01
Present	13 (13.1%)	38 (30.9%)	
Brooker classification			.61
Grade 1	11	26	
Grade 2	1	7	
Grade 3	1	4	
Grade 4	0	1	

BMI, body mass index; AVN, avascular necrosis; RA, rheumatoid arthritis.
Data are reported as mean ± standard deviation.

Discussion

HO is a common complication after primary THA that may result in pain and dysfunction [5]. Patients considered to have a higher risk to develop HO after THA may be offered prophylaxis, which is typically achieved with a single dose of radiation and/or postoperative NSAIDs, historically with indomethacin. Using ASA for both HO prophylaxis and VTE prophylaxis is an attractive option, given ASA's attractive risk profile, low cost, availability, and ease of administration. Previous authors have investigated the potential for ASA to reduce HO formation after THA, but the results have been contradictory.

A large, randomized trial demonstrated no effect of low-dose ASA to prevent HO [10]. Patients were randomized to either ASA 162 mg/day for 35 days or to placebo. The ASA group included 1039 patients; Brooker classification was grade 0 in 727 (70%), grade I in 220 (21%), grade II in 60 (6%), grade III in 22 (2%), and grade IV in 10 (1%) [10]. The placebo group included 1009 patients, Brooker classification was grade 0 in 694 (69%), grade I in 202 (20%), grade II in 69 (7%), grade III in 32 (3%), and grade IV in 12 (1%) [10]. Results of this study are limited by concomitant use of NSAIDs outside the study, which occurred in 44% of patients in the ASA group and 42% of patients in the placebo group [10]. Use of other NSAIDs might washout any effect of ASA.

A retrospective review of 687 THAs (641 patients) evaluated HO formation in context of a multimodal analgesia protocol [21]. THAs were performed by 2 different surgeons using the posterior approach. ASA 325 mg BID was routinely used for VTE prophylaxis, and warfarin was used for patients considered high risk. Patients received ketorolac for 3 doses and then celecoxib for 10 days. 158 patients did not receive ASA for VTE prophylaxis, and 43 (27.2%) patients developed HO compared with 50 (9.5%) patients who received ASA, which was statistically significant ($P < .01$). The authors did not specify the duration of postoperative ASA therapy for VTE prophylaxis. The non-ASA group was selected by the authors as being at high risk for VTE, which may or may not place the group at higher risk for HO. The multimodal analgesia protocol included the use of celecoxib. Despite the possible washout effect with routine NSAID use postoperatively, ASA demonstrated a nearly three-fold reduction in HO. The results of this study contradict those reported by Neal et al [10].

A prospective, randomized study compared different HO prophylaxis strategies after THA [7]. The authors compared HO formation in various treatment groups to their historical control group (n = 100) who underwent THA without HO prophylaxis with a 65% rate of HO. Results demonstrated HO formation in treatment groups as follows: 36.6% ASA (75 mg, TID, 14 days, n = 99), 12.2% indomethacin (50 mg, BID, 14 days, n = 94), 15.9% indomethacin (50 mg, BID, 7 days, n = 118), 5.0% irradiation (3 Gy over 4 doses, n = 102), 11.6% irradiation (7 Gy single dose, n = 95), and 30.1% (irradiation 5 Gy single dose, n = 93) [7]. The 65% rate of HO among control group patients is considerably higher than most contemporary studies, including the 30.9% reported in our control group. The authors included revisions and THAs on previously operated hips and their cohorts included a large number of THAs using cemented fixation, both of which may partially explain the higher rate of HO. The authors also did not describe their surgical approach.

Freiberg et al. [22] used 650 mg ASA BID for 14 days for VTE prophylaxis after cemented primary THA. The authors studied HO formation in a cohort of 177 THAs (131 patients) performed via the anterolateral or lateral approach with trochanteric osteotomy. HO was absent in 74 (41.8%) hips, grade I in 95 (53.7%) hips, grade II in 6 (3.4%) hips, grade III in 2 (1.1%) hips, and grade IV in 0 hips [22]. The authors also noted that 8 patients were not started on ASA for VTE prophylaxis because of "known, active, peptic ulcer disease," and HO developed in each of the 8 patients (grade II in 5 and grade III in 3) [22]. Despite the author's conclusion that ASA limits HO formation, the 58.2% of patients developing HO while receiving ASA is much higher than reported in our study. In addition, given the extremely small group of 8 patients not receiving ASA for gastrointestinal contraindication, it is difficult to compare the 100% incidence of HO in the no-ASA group to the 58.2% incidence in the ASA group.

Cohn et al. performed a controlled, retrospective study evaluating the efficacy of ASA to reduce HO incidence when used for VTE prophylaxis in primary THA [23]. Results demonstrated reduced risk of HO with ASA (11.4%) compared with warfarin (34.2%) [23]. This series was smaller, included bilateral THAs and cemented femoral fixation, used ASA dosing of 325 mg BID for 6 weeks, and patients in the warfarin group were significantly older compared with those in the ASA group [23]. Bek et al [24] demonstrated reduced risk of HO when ASA was used for VTE prophylaxis compared with warfarin, but this was in the setting of simultaneous bilateral THA via a posterior approach. Results are subject to bias with one surgeon contributing most ASA patients and a second surgeon contributing most warfarin patients. In addition, the warfarin group had significantly higher rate of cemented femoral fixation, a known risk factor for HO. Nunley et al [25] also demonstrated reduced risk of HO in the setting of hip resurfacing with ASA (2.4%) compared with warfarin (17.4%).

Our study demonstrates that ASA used for VTE chemoprophylaxis after primary THA is protective against HO. Our incidence was comparable with those previously reported. Strengths of our study include utilization of a control group, use of a single surgeon with a consistent surgical approach, and a large, appropriately powered series when compared with previous studies. Our study is the first to demonstrate risk reduction for HO formation with ASA used for VTE prophylaxis in primary, unilateral, cementless THA.

Our study has several weaknesses that readers should contemplate when interpreting the results. First, the retrospective design is subject to bias; however, there were no changes other than VTE prophylaxis to the perioperative care pathway or surgical technique used between the 2 cohorts. Second, although patients were not prescribed NSAIDs after THA, our design precluded determining whether patients took over-the-counter NSAIDs on their own accord postoperatively. However, a systematic difference in incidence of over-the-counter NSAID self-medication between the ASA and non-ASA cohorts would be unlikely. Third, we could not verify patient compliance with VTE prophylaxis, and patients may have taken their prescribed agent differently than prescribed or not at all.

Given that ASA irreversibly binds COX compared with reversible binding by indomethacin, [11] it is questionable whether concurrent use of ASA and indomethacin would offer significant benefit in HO prophylaxis over one of the agents alone, although to the best of our knowledge, this has not been evaluated in any published studies to date. Use of indomethacin with non-ASA VTE chemoprophylaxis has been shown to increase the risk of bleeding complications [12], making utilization of radiation a safer alternative in this group of patients despite the theoretical risks of radiation that have not been borne out in clinical studies. ASA may also have a synergistic effect in high-risk patients who undergo preoperative prophylactic radiation when used as VTE prophylaxis postoperatively.

Conclusions

Our study demonstrates that ASA reduces the risk of HO after primary, uncemented unilateral THA. Given the proven efficacy of ASA for VTE prophylaxis and attractive safety profile, our data suggest that ASA might be considered for routine use as

monotherapy for both VTE and HO prophylaxis in low-risk patients after primary THA.

Conflict of interest

William D. Bugbee, MD, Paid consultant for Arthrex, DePuy, Insight Medical, JRF Ortho, Orthalign, Smith & Nephew Stock for Insight Medical, Orthalign Medical/Orthopaedic publications editorial/governing board for Cartilage.

All other authors declare no potential conflicts of interest.

For full disclosure statements refer to https://doi.org/10.1016/j.artd.2020.01.010

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