Aspirin Decreases Heterotopic Ossification After Hip Resurfacing

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Published online: 16 March 2011
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Abstract

Background Heterotopic ossification (HO) is a concern for patients undergoing hip surgery, especially surface replacement arthroplasty (SRA) who tend to be younger, more active, and anticipate good motion. It is unclear, however, whether HO occurs more frequently after SRA than traditional total hip arthroplasty (THA) and whether aspirin influences the risk.

Questions/purposes We therefore determined the incidence of HO after hip resurfacing compared with THA and determined whether aspirin influenced the incidence or severity of HO.

Methods Retrospectively we compared three patient cohorts: SRA with aspirin (176 hips; 160 patients), SRA with warfarin (60 hips; 57 patients), and THA with warfarin (240 hips; 222 patients). All patients satisfied the same selection criteria and all surgeries were performed

through the posterolateral approach using spinal anesthesia. HO was classified using the technique of Brooker et al. comparing the preoperative, immediate postoperative, and 6- to 12-month followup radiographs (minimum, 1 year; mean, 2.7 years).

Results In the SRA with aspirin group, HO was detected in four of 151 hips (2.6%; two Grade I; one Grade II; one Grade III); in the SRA with warfarin group, eight of 46 hips (17.4%) had HO with four hips (8.7%) having severe HO (Grade III). All 12 patients with HO in both SRA groups were male. The HO incidence and severity was less for the SRA patients treated with aspirin compared with those treated with warfarin. In the THA with warfarin control group, HO was detected in five of 189 hips (2.6%; two Grade I; three Grade II). The HO incidence and severity were the same between the THA with warfarin and the SRA with aspirin cohorts.

Conclusions The risk of HO is greater in SRA than in THA in patients treated with warfarin postoperatively; aspirin appears to decrease the incidence and severity of HO after hip resurfacing surgery to a similar level as total hip arthroplasty.

Level of Evidence Level III, therapeutic study. See Guidelines for Authors for a complete description of levels of evidence.

One of the authors (RLB) is a designer (royalty income) for Smith & Nephew (Memphis, TN) and receives institutional research support from Smith & Nephew. One of the authors (RMN) receives institutional research support from Smith & Nephew and is a consultant for Smith & Nephew, Wright Medical Technology (Arlington, TN), and Salient Surgical Technology (Portsmouth, NH). One of the authors (JCC) receives institutional support from Wright Medical Technology.

Each author certifies that his or her institution approved the human protocol for this investigation, that all investigations were conducted in conformity with ethical principles of research, and that informed consent for participation in the study was obtained. This work was performed at Washington University, St Louis, MO, USA.

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Introduction

Heterotopic ossification (HO) is the formation of normal bone in an abnormal, soft tissue location [16] and is a well-established complication after THA with an incidence ranging from 2% to 90% [5–7, 15, 18, 20, 23, 29, 31, 34]. A recent systematic review looked at HO formation after major hip surgery and found the overall incidence of HO

was 43% and the incidence of severe heterotopic bone formation (Grades III and IV with the classification of Brooker et al. [7]) was 9% [23].

Compared with conventional THA, surface replacement arthroplasty (SRA) reportedly is associated with a higher incidence and severity of HO because of the additional stretching and trauma incurred by the soft tissues during translocation of the femoral head to expose the acetabulum and the generation of bony debris during femoral head preparation [2]. Some authors have reported rates of HO as high as 26.5% to 58.6% after SRA [2, 4, 29]. Patients undergoing SRA also have a higher rate (12.6%) of severe HO (Grades III and IV) when compared with patients undergoing THA (2.19%) [29].

Aspirin and warfarin are commonly used for deep venous thrombosis (DVT) prophylaxis after total joint arthroplasty [14, 28]. A number of studies report moderate or high-dose aspirin can substantially decrease the prevalence and severity of HO after THA [5, 13, 17, 18, 27].

The idea for this study came when we were reviewing postoperative radiographs after SRA and observed a difference in the incidence and severity of HO in this patient population after we changed our DVT prophylaxis regimen. We decided to explore this observation in greater detail to determine if a true difference existed. It has been established that the incidence of HO is greater after SRA than THA [3, 29]. Aspirin can reduce the incidence and severity of HO after THA [5, 13, 17, 27]. It is not known whether aspirin reduces the incidence and severity of HO after SRA or whether this rate compares to that in patients undergoing THA.

We therefore determined the incidence and severity of HO after SRA and THA and determined whether aspirin could decrease the incidence and severity of HO after SRA.

Patients and Methods

We retrospectively reviewed all 217 patients (236 hips) who underwent SRA between April 26, 2006, and January 30, 2009. All patients satisfied the same selection criteria: male younger than 65 years old and female younger than 55 years old, diagnosis of osteoarthritis, body mass index less than 35 kg/m², and no previous hip surgery. Of the 217 patients, 181 patients (197 hips) had complete radiographs for review, which included preoperative, immediate postoperative, 6-week postoperative, and 6-month to 1-year follow-up. The patients were divided into three cohorts: Group I: SRA with aspirin; Group II: SRA with warfarin; and Group III: THA with warfarin. Group I consisted of 136 patients (151 hips; 118 male, 33 female) and Group II consisted of 45 patients (46 hips; 41 male, five female) (Table 1).

Table 1. Demographic data of the patients with minimal 6-month followup in the three cohorts

Demographics	SRA with aspirin	SRA with warfarin	THA with warfarin
Hips	151	46	189
Gender			
Male	118	41	109
Female	33	5	80
Male/female ratio	3.6:1	8.2:1	1.4:1
Age (years)*	51.7 ± 7.5	48.6 ± 7.9	50.6 ± 8.7
Body mass index (kg/m ²)*	27.0 ± 3.7	28.1 ± 3.3	28.4 ± 4.1
Side			
Left	65	29	91
Right	86	17	98

* Mean ± SD; SRA = surface replacement arthroplasty.

The patients undergoing THA were selected according to the same criteria as the patients undergoing SRA during the same operative period. Most of these patients undergoing THA would have received SRA components but they were determined not to be good candidates as a result of their: (1) acetabular anatomy; (2) proximal femoral anatomy; (3) large (greater than 1 cm) femoral head degenerative cysts; (4) metal allergy; (5) symptomatic leg length inequality; (6) female of childbearing age; (7) renal impairment; (8) patient refused SRA; or (9) insurance denial of coverage for SRA. In total, all 222 patients undergoing THA (240 hips) performed during the same time period were reviewed, and in Group III, there were 177 patients (189 hips; 109 male, 80 female) with complete radiographs (Table 1).

All surgeries were performed by the two senior authors (JCC, RLB) using the posterolateral approach and spinal anesthesia. In all cases, THA and SRA, the wound was carefully irrigated after implantation of the components using pulse lavage to minimize retention of bone debris. In addition, the patients undergoing SRA had their surrounding soft tissues covered with damp lap sponges to collect bony debris during femoral head preparation. The only other unique surgical differences between the SRA and THA cohorts was the incision size, which was on average longer for the patients undergoing SRA and the gluteus maximus was routinely released and repaired only in the patients undergoing SRA.

The Birmingham hip resurfacing system (Smith & Nephew, Memphis, TN) was used on 191 hips; the Wright Conserve plus hip resurfacing system (Wright Medical Technology Inc, Arlington, TN) was used on 45 hips. Uncemented acetabular and femoral components were used in all patients undergoing THA.

In Group I, the patients received a bolus of 1000 U intravenous heparin intraoperatively just before hip

dislocation. Postoperatively, 325 mg aspirin, twice a day, was administered starting the day after surgery and was continued for 6 weeks postoperatively.

In Group II and Group III, 5 mg warfarin was administered the evening before surgery and then given daily to adjust the prothrombin time to an international normalized ratio goal of 1.8 to 2.4 and was continued for 4 weeks postoperatively.

Initially, both surgeons were using warfarin on a routine basis for DVT prophylaxis after hip surgery, but one surgeon (RLB) decided to start using aspirin for routine DVT prophylaxis in his young, active patients undergoing SRA and THA. This surgeon continued to use warfarin for patients who were: (1) on warfarin preoperatively; (2) had a history of pulmonary embolism/DVT; (3) had a known hypercoagulable state (protein C, protein S, Factor V Leiden, etc); (4) family history of thrombosis; (5) body mass index 40 kg/m² or greater; or (6) had significant heart/lung disease. After running the preliminary data on the HO data showing a decreased rate of HO in the patients treated with aspirin, the second surgeon switched to using aspirin for lower-risk patients and we continued to collect data for 1 additional year before closing the study early as a result of the overwhelming difference in the incidence and severity of HO.

As part of our routine pain control regimen, every patient received a dose of 400 mg Celebrex (celecoxib; Pfizer Inc., New York, NY) the day before and the day of surgery as well as 200 mg twice a day for 1 week postoperatively.

The radiographs were independently evaluated by one researcher (JZ) who was not involved with the clinical care of these patients and was blinded to their DVT prophylaxis treatment for the presence of HO at a minimum of 6 months followup for all patients. HO was classified according to the classification of Brooker et al. [7]: Grade I, islands of bone within the soft tissues about the hip; Grade II, bone spurs from the pelvis or proximal end of the femur, leaving at least 1 cm between opposing bone surfaces; Grade III, bone spurs from the pelvis or proximal end of the femur, reducing the space between opposing bone surfaces to less than 1 cm; and Grade IV, apparent bone ankylosis of the hip. The grading of HO using the Brooker et al. [7] classification is reportedly reliable [29, 33]. Immediate preoperative and postoperative radiographs were also reviewed to confirm that the HO represented new bone formation (Fig. 1A–D) and not bone islands that were present on preoperative images or residual bone debris generated at the time of surgery, which did not change over time, and serial radiographs.

The chi square test was used for categorical variables analysis. The analysis was performed with SPSS software (SPSS, Inc, Chicago, IL).

Results

In Group I, SRA with aspirin, HO occurred in four of 151 hips (2.6%). One of 151 hips (0.7%) had severe HO (Grade III) (Table 2). In Group II, SRA with warfarin, HO was detected in eight of 46 hips (17.4%). Four of 46 hips (8.7%) had severe HO (Grade III) (Table 2). The odds ratio comparing SRA with aspirin with SRA with warfarin is 7.7 and the number needed to treat is 6.8. Overall, there were 12 patients with HO in both SRA groups, and all were male. The HO incidence and severity was less ($p < 0.01$) in the SRA with aspirin group when compared with the SRA with warfarin group.

In Group III, THA and warfarin, HO occurred in five of 189 hips (2.6%), including three male and two female. No hip had severe HO (Table 2). The incidence of HO was less ($p < 0.01$) when comparing Group II with Group III with Group II having a higher ($p < 0.001$) incidence of severe HO than Group III. There was no difference between Group I (SRA and aspirin) and Group III (THA with aspirin).

Seventeen hips with HO occurred in these three groups, of which 15 of 17 hips were in male patients and two of 17 hips were in female patients. No female patient had severe HO (Table 3). There were no cases of symptomatic DVT or pulmonary embolism in any of the groups.

Overall, five hips had Grade III and none with Grade IV HO. Clinically, two of these five patients had some limitation associated with the HO. One patient had occasional sharp pain in the groin region when placing the hip in certain positions of flexion and internal rotation. The pain did not limit him from activities and at 2 years postoperatively, no additional treatments or surgery had been performed. The other patient had moderately diminished hip ROM in flexion and internal/external rotation compared with preoperatively but no associated pain or reported limitations.

Discussion

HO is a known complication after THA and hip resurfacing surgery. We determined the incidence of HO after SRA compared with a matched cohort of patients undergoing THA at the same institution and the effect of different options for DVT prophylaxis, aspirin and warfarin, on the incidence and severity of HO after SRA.

Limitations of the study include the following. First, we had a relatively small number of patients. Second, the patients were not randomized between the three groups. This could introduce selection bias. Third, patient selection and demographics differ between SRA and THA with SRA favoring younger males with predominantly osteoarthritis

Fig. 1A–D Hip radiographs showing preoperative (A) end-stage hip degeneration and the interval development of heterotopic ossification (HO) after hip resurfacing between the immediate postoperative image (B) and the 6-week followup (C); by 6 months (D), the HO has matured.

Table 2. The incidence and severity of heterotopic ossification in the three cohorts

Brooker grade/group	Mild HO		Severe HO		Total (%)
	I (%)	II (%)	III (%)	IV (%)	
SRA with aspirin (151 hips)	2 (1.3%)	1 (0.7%)	1 (0.7%)	0	2.7%
SRA with warfarin (46 hips)	3 (6.5%)	1 (2.2%)	4 (8.7%)	0	17.4%
THA with warfarin (189 hips)	2 (1.1%)	3 (1.6%)	0	0	2.7%

HO = heterotopic ossification; SRA = surface replacement arthroplasty.

and who are more active and muscular. Thus, we had a disproportionate number of male patients in the two SRA groups compared with the THA group and this introduces selection bias because it is known that gender is a risk factor for HO, but this shift is in the right direction for this study. Therefore, these confounding factors originally made it challenging to determine from a nonrandomized study whether the observed differences in the incidence of HO between the patients undergoing SRA and those undergoing THA was the result of the surgical procedure or one of the cofounding variables. It was not until the

preliminary data for this study were being analyzed that we recognized that the patients undergoing SRA treated with aspirin had a lower incidence of HO compared with patients undergoing SRA treated with warfarin. This finding caused us to abandon using warfarin in patients undergoing SRA altogether and change our DVT prophylaxis protocol for all future patients undergoing SRA to include aspirin, unless contraindicated. However, because all the SRA and THA cases were performed by the same two senior surgeons at the same institution, using the posterior approach to the hip, the same postoperative pain

Table 3. The gender distribution of heterotopic ossification in the three cohorts

Brooker grade/gender	Group	Mild HO Grade I and II	Severe HO Grade III and IV	Total (%)
Male (hips)	Group I (118 hips)	3	1	15/268 (5.6%)
	Group II (41 hips)	4	4	
	Group III (109 hips)	3	0	
	Total (%)	10/268 (3.7%)	5/268 (1.9%)	
Female (hips)	Group I (33 hips)	0	0	2/118 (1.7%)
	Group II (5 hips)	0	0	
	Group III (80 hips)	2	0	
	Total (%)	2/118 (1.7%)	0	

HO = heterotopic ossification.

management, and rehabilitation protocols in all patients, we believed this reduced some of the confounding variables and offsets the selection bias. Fourth is the possible impact of Celebrex on the incidence and severity of HO. Our overall incidence of HO in both groups, SRA and THA, is on the low side and it is likely this can be attributed, in part, to the use of Celebrex. Because all patients in this study received Celebrex as part of our standard perioperative pain protocol, this is a nondifferential bias between the three groups, but aspirin and Celebrex are both cyclo-oxygenase II inhibitors and possibly had synergistic effects in Group I, which contributed to lowering the incidence of HO.

Although there were two different hip resurfacing implant systems used in this study, all surgeries were performed using the same surgical technique and therefore we do not believe it is likely during this short observational period that the type of hip resurfacing implant would influence the rate of HO formation in the SRA groups, especially because the decision for the type of DVT prophylaxis was independent from the type of SRA implant used.

The majority of data regarding HO after hip arthroplasty in the literature deals with either THA or SRA (Table 4) [1–4, 7–10, 12, 19, 21, 22, 24, 29, 30, 32]. There are only two studies comparing the incidence of HO between SRA and THA [3, 29]. Amstutz et al. [3] reported on an earlier generation SRA (n = 135) compared with THA (n = 150) in a consecutive series of patients with primary osteoarthritis over a 6-year period, but the patients were not matched or randomized and the authors did not report their DVT prophylaxis. They determined the rate of severe HO was higher in the SRA cohort than the THA cohort (16% versus 9%). A more recent study by Rama et al. [29], using a randomized clinical study comparing the incidence and severity of HO in patients with either SRA (n = 103) or THA (n = 97), observed a similar overall incidence of HO: 43.7% for SRA and 30.9% for THA but found the

incidence of severe HO (Grade 3–4) was higher in the SRA group (12.6% versus 2.1%). The authors did not, however, note whether the patients had any DVT prophylaxis post-operatively. The overall incidence of HO in our study was higher in the combined SRA groups (6.1%) compared with the THA group (2.7%), and we only found severe HO (Grade 3–4) in the patients undergoing SRA and none in the patients undergoing THA, which compares favorably to the literature.

The extent of soft tissue trauma is an important factor leading to the development of HO [1, 11]. Muscular male patients with stiff hips present a substantial challenge when performing SRA as a result of the need for a more extensive surgical approach and soft tissue dissection. When using the posterior approach for SRA, extreme maneuvering of the leg into nonphysiological positions is required to release the anterior capsule and coupled with excessive retraction to translate the femoral head anteriorly during the exposure and preparation of the acetabulum may cause more soft tissue necrosis and injury to the gluteal muscles when compared with THA. In addition, excessive bony debris generated during the preparation of the femoral head, which gets deposited onto the already traumatized soft tissue structures, may induce these transplanted osteoprogenitor cells to produce ectopic bone [11]. Similar to other studies, we found male gender was a risk factor for a higher incidence and severity of HO. Minimizing soft tissue injury and necrosis can be improved through better patient selection, more extensile surgical exposure, improved instrumentation, meticulous collection of bony debris, and surgeon experience, which may reduce the potential for developing HO [25, 26].

Although patient-related factors are important in the development of HO after THA and SRA, comparable information regarding the incidence of HO and the type of DVT prophylaxis is lacking in the literature. Most series in the literature have focused on the incidence of HO in either patients undergoing SRA or those undergoing THA

Table 4. The incidence and severity of heterotopic ossification in the literature

Author	THA or SRA	Total number of hips (male/female)	Incidence HO (Brooker I–IV)	Severe HO (Brooker III–IV)	Comments/DVT prophylaxis
Charnley (1972) [8]	THA	379 (1 male to 2.5 females)	5%		Dindevan for DVT prophylaxis
DeLee et al. (1976) [10]	THA	2173 (674/1499)	14.6%	4.5%	DVT prophylaxis not reported
Matos et al. (1975) [21]	THA	221	41%	13%	DVT prophylaxis not reported
Nollen and Slooff (1973) [24]	THA	THA = 200 (31/124)	52.5%	7%	Pharmacologic DVT prophylaxis started POD 1
Riegler and Harris (1976) [30]	THA	102 (38/64)	50%	8.8%	DVT prophylaxis not reported
Langan and Weiss (1980) [19]	THA	4 (4/0)	100%	25%	DVT prophylaxis not reported
Errico et al. (1984) [12]	THA	100	58%	17%	DVT prophylaxis not reported
Sodemann et al. (1988) [32]	THA	150 (88/62)	67%	23%	DVT prophylaxis not reported
Ahrengart et al. (1987) [1]	THA	31 (17/14)	77%	30%	DVT prophylaxis not reported
Brooker et al. (1973) [7]	THA	100	21%	9%	DVT prophylaxis not reported
De Smet et al. (2002) [9]	SRA	200	1%		Only reported Brooker grade 1
McMinn et al. (1996) [22]	SRA	235 (125/110)	14%	1.5%	Low dose warfarin during inpatient stay
Amstutz et al. (2004) [2]	SRA	SRA = 400 (259/96)	26.5%	7.0%	Adjusted low-dose warfarin for 3 weeks
Back et al. (2007) [4]	SRA	SRA = 220 (142/78)	58.6%	8.2%	Warfarin for 179 cases, 300 mg aspirin for 41 cases for 6 weeks postoperatively
Amstutz et al. (1984) [3]	THA/SRA	THA = 150 (35/115) SRA = 135 (60/75)	Not Noted	Total = 12.3% THA = 8.7% SRA = 16.3%	TED Hose for 2 months; warfarin for 2–3 weeks w/PTT 1.5x normal Older generation SRA, patients' DVT prophylaxis not reported
Rama et al. (2009) [29]	THA/SRA	THA = 97 (66/31) SRA = 103 (63/38)	Total = 37% THA = 30.9% SRA = 43.7%	Total = 7.5% THA = 2.1% SRA = 12.6%	DVT prophylaxis not reported Celecoxib morning of the operation and 200 mg twice a day during hospitalization for pain
Nunley et al. (current study)	THA/SRA	THA = 189 SRA = 197	Total = 4.4% THA = 2.6% SRA = 6.1%	Total = 1.3% THA = 0% SRA = 2.6%	In SRA, 325 mg aspirin 2x daily for 6 weeks postoperatively or warfarin with INR 1.8–2.4 for 4 weeks postoperatively; in THA, warfarin with INR 1.8–2.4 for 4 weeks postoperatively Celecoxib started night before surgery and continued a total of 10 days

SRA = surface replacement arthroplasty; HO = heterotopic ossification; DVT = deep vein thrombosis; POD = postoperative day; PTT = partial thromboplastin time; INR = international normalized ratio.

although none have compared patients undergoing SRA and those undergoing THA using different regimens for DVT prophylaxis. We found aspirin, when compared with warfarin for routine DVT prophylaxis, reduced the incidence and severity of HO development in patients undergoing SRA to a level similar to THA and as a result has changed our clinical management of these patients.

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