RESEARCH ARTICLE

Increased Risk of Heterotopic Ossification Following Revision Hip Arthroplasty for Periprosthetic Joint Infection

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Abstract

Background: To investigate whether surgery for Periprosthetic Joint Infection (PJI) of the hip, the number of procedures and their duration contribute to risk of Heterotopic Ossification formation.

Methods: 56 patients with hip PJI undergoing one-stage (10) or two-stage (46) exchange arthroplasty were matched to 112 patients undergoing revision arthroplasty for aseptic failure based on age, gender, body mass index (BMI), surgical approach (all direct lateral) and date of surgery (2006-2013). Patients with Paget's disease and ankylosing spondylitis, or preoperative HO were excluded. Perioperative pain management included use of the anti-inflammatory medications in all patients without prophylactic radiotherapy. Six-month postoperative radiographs were reviewed based on Brooker classification.

Results: The incidence of overall HO in PJI and aseptic groups was 84% (47/56) and 11% (12/112), respectively. High grade HO (grades 3 and 4) in PJI and aseptic groups were 25% (24/56) and 4% (4/112), respectively. PJI was an independent risk factor for HO in the multivariate analysis (odds ratio of 9.3, 95% CI: 2.9-29.9, *P<0.001*).

Conclusion: Patients undergoing surgical treatment of hip PJI seem to be at increased risk of developing HO compared to aseptic failure. HO prophylaxis regimens may be recommendable in eligible patients undergoing surgical intervention for PJI of the hip.

Level of evidence: IV

Keywords: Heterotopic ossification, Hip, Periprosthetic joint infection, Revision arthroplasty

Introduction

Heterotopic Ossification (HO), namely the appearance of ectopic periarticular osseous tissue, is a common complication following total hip arthroplasty (THA) (1). HO usually affects the abductor mechanism although other muscle groups may also be involved (2). The severity of HO varies from an incidental radiological finding to bone bridging HO with considerable clinical consequences such as pain and limitation of range of motion of the hip (3). Although the incidence of asymptomatic HO following primary THA has been reported to reach 90%, the incidence of clinically significant HO varies from 1 to 18 % (3-5).

Various risk factors have been identified to increase the risk of HO formation following primary THA including patient-related factors (age, male gender, body mass

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index and underlying conditions such as ankylosing spondylitis, Paget's disease, diffuse idiopathic skeletal hyperostosis or hyperostotic osteoarthritis) and surgery-related factors such as hip resurfacing, longer duration of the procedure and surgical approach (3, 6, 7). It was our observation that patients with periprosthetic joint infection (PJI) of the hip frequently presented with moderate degree of HO that was more frequent than their counterparts undergoing revision arthroplasty for aseptic reasons. However, review of the literature did not reveal any studies that reported an association between formation of HO in the hip and an underlying diagnosis of PJI. This case-controlled study was conceived to examine whether: 1) the risk of HO formation is increased in and 2) the increased number and duration of surgical procedures as well as number of red blood cell (RBC) transfusions could contribute to the formation of HO in the hip these patients.

Materials and Methods

After Institutional Review Board approval was obtained, we queried our institutional database to identify 56 patients with PJI of the hip who underwent one or two-stage revision surgery at our institution between January 2006 and June 2013 and for whom preoperative and follow-up x-rays at six months after their last surgical intervention were available. None of these patients were considered failed PJI treatment at latest follow-up. Patients with Paget's disease, ankylosing spondylitis, and preoperative HO were excluded. Nine patients underwent one stage and 47 underwent two stage exchange.

We matched the study group in a 1:2 ratio to identify a control group of 112 patients who underwent revision hip arthroplasty for aseptic failure in the same time period. Matching criteria were age (± 5 years), gender (exact matching), BMI (± 3 Kg/m^2), surgical approach (direct lateral approach was used in all of the operations) and date of surgery (± 2 years) [Table 1]. The infecting organism in the PJI group were as follows: methicillin sensitive *Staphylococcus aureus* (24 cases), Coagulase negative *Staphylococci* (9 cases), *Streptococci* (6 cases), culture negative PJI (6 cases), Gram negative bacteria (5 cases), polymicrobial infections (4 cases) and commensal anaerobic flora (2 cases). All patients with PJI met the criteria defined by the International Consensus Meeting on PJI (8). The indications for revision surgery in the aseptic failure group consisted of loosening (34 cases), wear (31 cases), periprosthetic fracture (13 cases), instability (12 cases), implant malposition (8 cases), metallosis (5 cases), conversion of hemiarthroplasty (4 cases), mechanical failure of the implant (3 cases) and taper corrosion of the femoral neck (2 cases). Patients considered aseptic revisions had no clinical signs of infection, negative serological markers and no one had a positive intraoperative culture. The components were revised depending on the cause of revision. All aseptic revision patients had at least one component, femoral or acetabular, revised and infection had all components exchanged. Perioperative medical management was similar in all patients and included the use of non-steroidal anti-inflammatory drugs (NSAIDs) as part of the multimodal pain management. Postoperative venous thromboembolic prophylaxis was administered to all patients with either enoxaparin, warfarin or aspirin. Cases and controls were administered enoxaparin in 1.8% vs. 2.7% (1/56 vs. 3/112; *P=0.720*), aspirin in 7.1% vs. 5.9% (4/56 vs. 10/112; *P=0.693*) and warfarin in 91.1% vs.88.4% (51/56 vs. 99/112; *P=0.596*) respectively.

The study population had a mean age of 65.1 years (range 43.7-86.0) and was composed of 26 males and 30 females. The average BMI for this group was 29.2 kg/m^2 (range 20.2-49.1). The control group had a mean age of 66 years (range 44-88), with 60 females and 52 males. The average BMI for the controls was 28.7 kg/m^2 (range 17.9-43.2). All patients had a minimum of 1 year follow-up (1-13 years). There were no differences between the groups with regards to age (65.2 vs. 66; *P=0.730*), gender (53.6% female vs. 53.6% female; *P=1.000*), or BMI (29.2 kg/m^2 vs 28.7 kg/m^2; *P<0.219*. The demographic characteristics of all patients are shown in Table 1. None of the patients received prophylactic radiotherapy for HO. The severity of HO was graded based on the Brooker's classification (9). Medical records were reviewed to obtain demographic data and details related to the surgical procedure (operative time, transfusion). Two investigators evaluated preoperative and postoperative digital radiographs to observe and grade HO and in cases of disagreement consensus was reached with the use of a third observer.

Statistical analysis was performed using the R software (version 3.11, R Foundation for Statistical Computing, Vienna, Austria). Fisher's exact test was used for comparison of categorical variables. Backward step-wise logistic regression was done to analyze the potential confounding influence of number of surgical procedures and transfusion. Spearman's rho was calculated to for the assessment of linear correlation. *P values* of less than 0.05 were regarded as statistically significant.

Table 1. Characteristics of patients in PJI and aseptic groups. * Numbers represent mean with range in parentheses

	PJI patients (56)	Aseptic patients (112)	*P value*
Age (years)*	65.1 (43.7-86.0)	66 (44-88)	0.730
Gender (female/male)	30/26	60/52	1.000
BMI (kg/m^2)*	29.2 (20.2-49.1)	28.7(17.9-43.2)	0.219

Results

The incidence of any type of HO was significantly higher in the PJI group compared with the aseptic group being 84% (47/56) versus 11% (12/112), respectively, with *P<0.001* and odds ratio of 25.6 (95% Confidence Interval: 8.8-74.6) [Figure 1]. Similarly, the incidence of high grade HO (grades 3 and 4) was higher in patients with PJI compared with the aseptic group (14/56=25% versus 4/112=4%, respectively, *P<0.001*). When evaluating one- versus two-stage revision for PJI, patients did not have any difference in the incidence of high grade HO (2/9=22.2% versus 10/47=21.3%, respectively, *P=0.949*).

The number of surgical procedures was significantly higher in the PJI group compared with the aseptic group (2.4 versus 1.2, *P=0.001*) [Figure 2]. The total surgical time and the number of blood transfusions

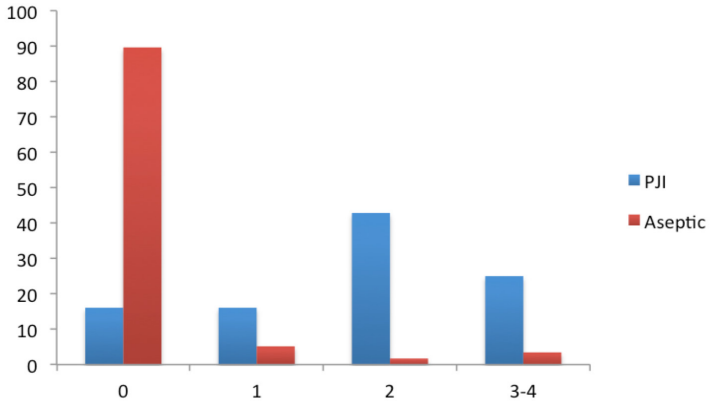

Figure 1. Comparative distribution of different grades of Heterotopic Ossification (HO) demonstrates increased incidence of high grade HO in periprosthetic infection joint patients compared with aseptic group.

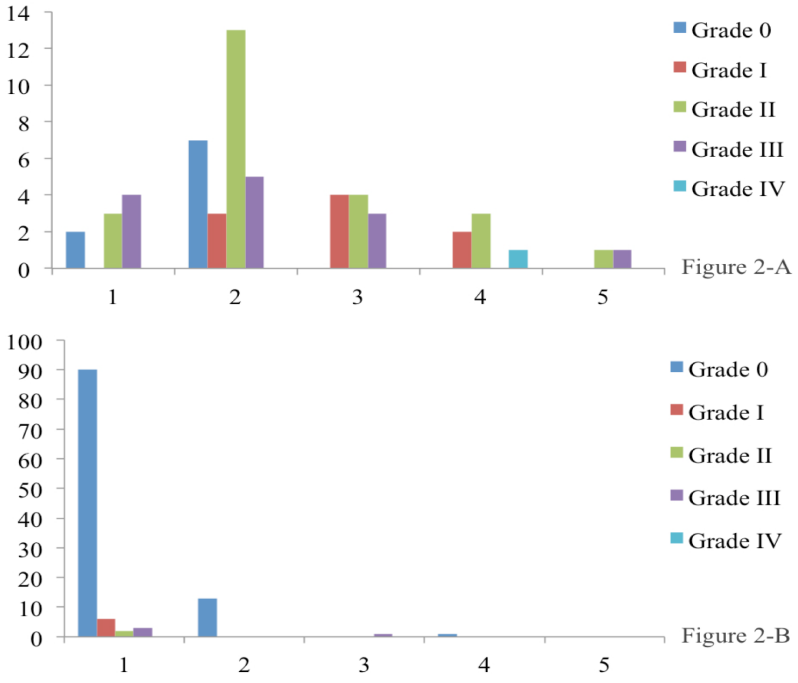

Figure 2. Distribution of grades of heterotopic ossification (HO) in Periprosthetic joint infection (2-A) and aseptic (2-B) groups per number of surgical procedures demonstrates high grade HO (III and IV) tended to occur more frequently (yet not exclusively) in patients with increased number of surgical procedures, especially in PJI patients. X-axis represents number of surgeries and Y axis represents number/ proportion of patients.

Table 2. Duration of surgical procedures and number of blood transfusions per HO class in PJI and aseptic groups. * Numbers represent mean with range in parentheses. ** No range is presented because there is just one case in the group

	Total number of surgical procedures*		Total duration of surgical procedures*		Number of blood transfusions*	
	PJI patients	Aseptic patients	PJI patients	Aseptic patients	PJI patients	Aseptic patients
Class 0 (No HO)	1.8 (1-2)	1.2 (1-4)	353 (90-566)	182 (84-462)	1 (0-2)	0.2 (0-1)
Class I	2.9 (2-4)	1 (1-1)	522 (323-856)	160 (113-211)	1.9 (0-3)	0
Class II	2.4 (1-5)	1 (1-1)	464 (140-1447)	172 (113-231)	1.2 (0-4)	0.5 (0-1)
Class III	2.1 (1-5)	1.5 (1-3)	416 (122-823)	238 (38-634)	1 (0-5)	1 (1-1)
Class IV	4 **	-	712 **	-	3 **	-
Average	2.4 (1-5)	1.2 (1-4)	449 (90-1447)	185 (38-634)	1.25 (0-5)	0.25 (0-2)

were significantly higher in the PJI group compared with the aseptic group (*P<0.001* for both comparisons). The difference was consistently present for both variables in all classes of HO [Table 2]. The number of surgeries, the total duration of procedures and the number of transfusions were all significantly correlated with HO formation in the univariate analysis (*P<0.001*), with correlation co-efficient of 0.53, 0.44 and 0.42, respectively.

In the multivariate analysis, PJI was independently associated with HO formation with odds ratio of 9.3 (95% CI: 2.9-29.9, *P<0.001*). The number of surgical procedures showed statistical trend with formation of any type of HO (Odds ratio per surgical procedure: 1.8, 95% CI: 0.92-3.5, *P=0.08*) yet the number of blood transfusion and the total duration of surgical procedures were not independent risk factors for formation of HO.

Discussion

The incidence of HO following revision total hip arthroplasty has been reported to be between 4 to 30 % (10, 11). While revision surgery has been implicated as a risk factor for HO formation, in a series of patients undergoing revision total knee arthroplasty with minimum two-year follow up, Barrack et al found that revision due to infection was significantly associated with higher risk for HO formation compared with aseptic failure (76% versus 47%, respectively) (11-13). However, they did not find any correlation with the number of surgical procedures or duration of surgery. In another study on patients undergoing computed tomography (CT)-assisted hip aspiration prior to revision surgery, the incidence of HO (detected on CT images) in patient with PJI was higher than non-infected patients (5/33 versus 2/30) but the difference was not statistically significant due to small sample size (14). Based on our prior observations in patients with PJI of the hip and considering these signals, this case-controlled study was conceived to examine the potential relationship between diagnosis of PJI and the higher frequency of HO formation. In addition, the influence of the number of surgical procedures, total duration of surgeries and the number of transfusions on formation of HO was examined.

Our study confirms that PJI is a considerable risk factor for HO formation, statistically independent of the number of surgical procedures, the duration of surgeries and the number of RBC transfusions. This association between HO formation and diagnosis of PJI can be viewed from different standpoints. First, PJI and HO share some patient-related risk factors such as the old age, male gender and increased BMI (5, 15-17). Second, this association may be due to the considerable surgery-related tissue injury consisting of more aggressive and extensive soft tissue debridement, higher number of surgical procedures within short period of time (either due to treatment strategies with multiple procedures such as two-stage arthroplasty or because of persistent or recurrent PJI) and the lengthier surgical procedures. This fact is reflected by our data showing substantial difference between the PJI and the aseptic groups with regards to the number of surgeries, the total duration of surgeries and the number of RBC transfusions. Local trauma has been proposed to be associated with signals that lead to increased activity of inflammatory and osteoinductive factors (such as prostaglandin E2 and bone morphogenetic proteins) and differentiation of the mesenchymal stem cells into osteoprogenitor cells (1). Additionally, PJI per se is a cause of prolonged local inflammatory reaction causing fibroblast proliferation and excessive formation of extracellular matrix. Both of these factors can promote metaplastic changes and subsequent formation of heterotopic ossification (18). These findings support the theory that HO can be an unexpected ossification that results from deviation of a normal adaptive response for cells with a regenerative potential (19). The triggering factors, such as presence of infection by itself and the surgical trauma, can initiate an interaction between local and systemic signals that within an osteoconductive environment facilitate the differentiation of stem cells into osteoblasts (20). Expression of bone morphogenetic proteins (BMPs) are one of these signals with a role in the repair mechanisms seen in the connective, the vascular and the osseous tissues, as well as transcription of genes that lead to osteoblast differentiation of progenitor cells (21-23).

We aimed to eliminate the confounding influence of unknown constitutional risk factors by excluding patients

with HO prior to revision surgery or those patients who are known to be at increased risk of HO formation such as those with ankylosing spondylitis. Thus, this could cause the real incidence of HO be underreported in our study. However, the incidence of HO in our patients with PJI of the hip still seems to be higher than patients with PJI of the knee as reported by Barrack et al (84 versus 76%) (13). This finding is in parallel with the difference of HO following primary total hip (5-90%) and total knee (5-39%) replacement, though comparative studies are lacking (1).

We recognize some limitations to this study. First, this is a retrospective study with potential for recall bias. Second, we were unable to include all 116 patients with PJI who were treated during the study period either due to inadequate follow-up or inability to find matching controls. Third, the relatively small size of our cohort may have resulted in a type II error that failed to reveal the statistical significance of some factors such as the number of surgical procedures, the duration of surgery and the number of blood transfusions. However, based on the numbers available, these confounders had far weaker association with HO formation than diagnosis of PJI. Although we do not exclude the potential confounding influence of other yet to be recognized risk factors of HO in our study (such as the type of infecting organism in the PJI group or the etiology of failure in the aseptic group), we believe the observed association between diagnosis of PJI and HO formation is of considerable clinical importance. Forth, due to inadequate data, we were unable to assess the functional outcome and therefore focused on radiographic HO. High grade HO is associated with decreased range of motion in the hips yet its impact on the functional outcome is controversial (24, 25). Finally, this study evaluates the formation of HO at six months. It is possible that continuation of the study to a longer term of follow-up may have revealed different findings. The reason for choosing six months as the follow-up of this study is based on the reports in the literature that suggest that HO maturation generally happens in the first three months after surgery (1). Despite these considerations, we believe our study conveys an important message in that patients with diagnosis of PJI of the hip are at considerable risk for formation of HO and this association does not seem to be fully explained by the increased number or the complexity of surgical procedures in PJI patients.

The diagnosis and surgical treatment of PJI increases the risk of HO formation and the potential of negative influence on the range of motion and functional outcomes. Surgeons must be aware of this higher risk and patients should be counseled despite having been adequately treated for PJI.

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