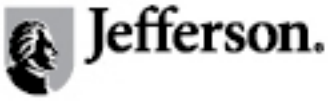

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Does 'excessive' anticoagulation predispose to periprosthetic infection?

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Does 'Excessive' Anticoagulation Predispose to Periprosthetic Infection?

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Abstract

Background: Although persistent drainage and hematoma formation are recognized risk factors for development of periprosthetic infection, it is not known that excess anticoagulation is a predisposing factor.

Methods: We conducted a 2 to 1 case-control study with 78 cases that underwent revision for septic failure. The controls underwent the same index procedure but did not develop consequent infection. Patient co-morbidities, medications, intraoperative, and postoperative factors were compared.

Results: Postoperative wound complications including development of hematoma and wound drainage were significant risk factors for periprosthetic infection. A mean INR >1.5 was found to be more prevalent in patients who developed of postoperative wound complications and subsequent periprosthetic infection.

Conclusions: Cautious anticoagulation to prevent hematoma formation and/or wound drainage is critical to prevent periprosthetic infection and its undesirable consequences.

Introduction

Despite immense improvements in prevention and treatment, the management of periprosthetic infection continues to be challenging[1-4]. The incidence of periprosthetic infection after primary arthroplasty is less than 1%[5] and up to 7%[6,7] after revision joint arthroplasty. Numerous risk factors for periprosthetic infection have been identified[8,9]. Immunocompromised status of the patient, skin lesions such as psoriatic plaques, and problems related to wound healing are some of the predisposing factors for periprosthetic infection following total joint arthroplasty[10-13].

In a previous case-controlled study, patients with delayed wound discharge, wound dehiscence and hematoma formation were found to have a higher incidence of periprosthetic infection[8]. Although the latter finding appears intuitive, the exact etiology of wound problems following joint arthroplasty was not elucidated in the stated study[8].

We hypothesized that patients receiving 'excessive' anticoagulation, defined as International Randomized Ration (INR) greater than clinically intended level, may be at risk of developing wound related problems which in turn predisposed them to periprosthetic infection. This case-control study was conceived to examine the correlation between anticoagulation and periprosthetic infection.

Materials and Methods

Study Group

Institutional review board approval was obtained prior to initiation of this case-control study. The cohort consisted of all patients who underwent primary or revision total knee or total hip arthroplasty for an aseptic diagnosis during the period of 2000 to

2005 and developed subsequent periprosthetic infection. The diagnosis of periprosthetic infection was reached on the basis of patients having at least three out of five of the following criteria: 1) abnormal serology (ESR >30 mm/hr; CRP >1mg/dl), 2) strong clinical and radiographic suspicion for periprosthetic infection, 3) positive joint aspiration culture, 4) evidence of purulence during the subsequent surgical intervention, and 5) positive intraoperative culture[14]. The patients with periprosthetic infection were then closely matched in a 2:1 ratio with those undergoing the same procedure who did not develop periprosthetic infection following their index surgery. The matching criteria included the underlying diagnosis, the type of prosthesis, mode of fixation, surgeon, height, weight, age, gender, and the year of surgery.

A thorough review of the medical records was performed to extract the relevant information, which included socio-demographic factors such as age, gender, body mass index, alcohol abuse and smoking habits. Information was also gathered regarding the medication history with special emphasis on steroid therapy and insulin requirement. Detailed information about the patient's medical history including inflammatory arthropathy, autoimmune disease, diabetes mellitus, malignancy, and any other concomitant medical conditions were gathered. A history of septic arthritis of the native joint or any other infection was considered relevant to our analysis. The postoperative course, and in particular the details of anticoagulation and the level of INR, for all these patients following their index primary arthroplasty was recorded. Detailed data regarding the intraoperative and postoperative course of these patients related to their index surgery was also collected which also included the National Nosocomial Infections Surveillance (NNIS) surgical index score[15]. The NNIS collates information on the comorbidities,

operative time, and the surgical wound classification and has been shown to be an important confounder for periprosthetic infection[8]. We documented the type, time of administration, and duration of prophylactic antibiotic that was given to the patients during the index arthroplasty. All intraoperative and postoperative transfusions of autologous or allogenic nature were also recorded.

Socio-demographics

The infected group included 42 males (54%) and 36 females (46%). Fifty-six percent of the cases and 51% of the controls were considered obese at the time of index surgery (BMI >30 Kg/m^2). There was no significant difference in the mean BMI, smoking habit, and alcohol abuse between the cases and the controls (Table1).

Postoperative Protocols

All patients at our institution undergoing joint arthroplasty are placed on low dose warfarin (goal INR= 1.5) unless indicated otherwise. Warfarin is administered on the day of surgery and continued for a period of six weeks. Deviations from the latter occurred if: a) the patient was on anticoagulation prior to the surgery for conditions such as arrhythmia or replaced heart valve, b) had known allergy to warfarin, or c) developed thromboembolism in the postoperative period. In the latter three categories of patients subcutaneous and/or intravenous heparin was used as the sole or the bridging agent until adequate and full anticoagulation (goal INR=2-3) with the oral agent could be established.

Prophylaxis for infection using cephalosporin antibiotics (Ancef, 1 gram) or an alternative antibiotic for patients with penicillin allergy is also administered within 60 minutes of arthroplasty procedure and continued for 24 hours postoperatively. Antibiotic

was administered at a mean of 39 minutes (range, 0-60 minutes) prior to incision among the cases and controls respectively. Cephalosporin was the most frequently administered antibiotic in both groups [cases (72%); controls (88%)] followed by vancomycin [cases (18%); controls (8%)].

The wound management consisted of application of a sterile dressing that was placed over the wound in the operating room and usually kept for 24 hours. The wound was then inspected and covered by dry gauze that was changed at least twice daily during the hospital stay. The wound was monitored by the patient and/or the visiting nurses after discharge from hospital. Fluid discharge from the wound beyond postoperative day 7 was deemed clinically significant and abnormal.

Surgical Data

Degenerative joint arthritis was the most common diagnosis in both groups. Other diagnoses included post-traumatic arthritis (4 cases), and inflammatory arthropathy (two cases). Among the 78 patients in the infected group, 43 had undergone total knee arthroplasty (33 primary and 10 revisions), and 35 patients received total hip arthroplasty (12 primary and 23 revisions). The mean duration between index joint arthroplasty and the development of infection was 256 days (range, 4-1890 days). Gram-positive cocci were the most common infecting organisms including *Staphylococcus* coagulase negative (26%), *Staphylococcus aureus* (16%), Methicillin resistant *Staphylococcus aureus* [MRSA] (14%), and other *Streptococcus* species (13%).

Statistical Analysis

We performed descriptive statistics using SAS version 9.1 to determine the means, standard deviations, and the frequency distribution of the various variables

described above. The NNIS index score was stratified into two categories including 0 and greater than or equal to one. Unadjusted analysis was performed using Wilcoxon procedure to compare the means across the continuous variables among the cases and controls. Fisher exact test was used to compare the proportions across the categorical variables in the cases and controls. We analyzed continuous variables using t-statistics, while Chi-Square analysis was used for categorical variables. A p-value of <0.05 depicted statistical significance. Adjusted analysis was performed using multivariate stepwise logistic regression to determine the variables predicting infection in this study population.

Results:

Postoperative Course

Patients who subsequently developed infection had a more protracted hospitalization course with two times the number of postoperative complications ($p=0.02$) following their index arthroplasty compared to the control patients (Table 1). The mean hospital length of stay in the 78 patients with subsequent periprosthetic infection was significantly longer at 6 days (range, 1-11 days) compared to 4 days (range, 2-6 days) in the group of 156 patients without infection ($p<0.006$). Infected patients were 12.6 times more likely to develop hematoma compared to their respective controls and 16.8 times more likely to have persistent wound drainage. Although the cases had only slightly higher intraoperative blood loss, they had significantly higher postoperative transfusions compared to control patients (Table1). Wound dehiscence developed following the index arthroplasty in two patients both of whom later developed infection.

There was a significantly higher number of reoperations following the index surgery in the group of patients who later became infected (total of 14 reoperations) compared to the control patients (total of 3 reoperations) (OR=11.2, p<0.0001). The indication for reoperation included evacuation of hematoma (9 patients), debridement and wash out of draining wound (3 patients), and debridement and closure for wound dehiscence (2 patients) in the infection group. Among the controls, only two patients underwent evacuation of hematoma, while one was reoperated for delayed wound healing.

Stratified Analysis For Anticoagulation

Although the mean INR at all time points was higher in the cohort of patients who developed periprosthetic infection compared to those who did not develop infection, this difference was not found to be statistically different (p=0.06). However, the INR level was statistically higher in patients with wound related problems who later developed infection compared to patients who did not develop infection (p=0.03). In addition, a significantly greater percentage of infected patients (17%) had an INR level >1.5 at hospital discharge compared to the control group (8%) (Chi-Sq=4.39; p=0.04) (Figure 1). Similarly, there were twice as many infected patients (21%) with a mean INR > 1.5 compared to the control group (11%) (Chi-Sq=3.97; p=0.05) (Figure 1). An INR >1.5 at day of discharge was more prevalent in the group with wound complications (22%) compared to patients with uncomplicated postoperative course with regard to wound healing (8%) (p=0.005).

There were 13 patients in the periprosthetic infection cohort who had received injectable anticoagulant in addition to or in lieu of oral anticoagulation in the

postoperative period that included subcutaneous low-molecular weight heparin (1 case), and intravenous heparin (12 cases). Heparin was administered as prophylaxis for cardiac conditions (arrhythmia and prosthetic heart valves). No patient in this cohort developed pulmonary embolus. Out of the 13 cases that were heparinized, nine patients developed postoperative wound complications including hematoma (3), persistent wound drainage (5), and delayed wound healing (1).

Multivariate Analysis

A multiple logistic regression analysis was performed after adjusting for the various variables. Concomitant comorbidities as measured by ASA (OR=2.07; 95% CI 1.08-.97; p=0.03), postoperative transfusions (OR=1.63; 95% CI 1.14-2.33; p=0.007), postoperative wound complications including development of hematoma (OR=27.02; 95% CI 11.04-91.59; p=0.0002) and wound drainage (OR=32.20; 95% CI 8.7-119.17; p<0.0001) were significant risk factors for periprosthetic infection.

Discussion

Total joint arthroplasty is a successful surgical procedure that continues to confer functional improvement and alleviation of pain for majority of patients with disabling arthritis[16-19]. The outcome of this otherwise successful operation is occasionally compromised by complications such as periprosthetic infection[20-22].

Although implementation of strategies such as clean air operating room, administration of perioperative antibiotics, and body exhaust systems have all contributed to prevention of this dreaded complication, periprosthetic infection still continues to occur after total joint arthroplasty[4,5,7]. A recent study from the Mayo Clinic found that

periprosthetic infection has become one of the major causes of failure of total knee arthroplasty[23]. The findings of the latter study are truly concerning and raise the question as to why the incidence of periprosthetic infection may be on the rise. The other pertinent and inter-related issue is the identification of factors that predispose the patients to periprosthetic infection.

There is a multitude of reasons that may explain the development of infection following joint arthroplasty in general and the increase in the incidence of this complication in particular. First, it may relate to the fact that joint arthroplasty is currently performed in a wide spectrum of patients including immunocompromised patients with concomitant comorbidities such as diabetes, malignancy, and steroid use, which have all been identified as important predisposing factors for periprosthetic infection[8]. Second, improvements in prosthetic design and surgical techniques may have reduced the incidence of mechanical complications, bringing infection to the forefront of major complications. There may be other explanations also[10]. Based on our anecdotal observation, we believed that patients receiving 'excessive' anticoagulation such as intravenous heparin or high dose oral anticoagulant agents during the postoperative period were at high risk of developing wound related problems that could have in turn resulted in subsequent periprosthetic infection. This study confirmed the latter and revealed some important findings.

The incidence of periprosthetic infection was found to be significantly higher in the group of patients who had a protracted postoperative course related to wound problems. The latter is intuitive and has in fact been previously reported[8]. The study, however, did reveal that there was a direct correlation between 'excessive' anticoagulation and

development of wound related problems that lead to development of subsequent periprosthetic infection. Excessive anticoagulation was either as a result of administration of intravenous agents such as heparin to prevent important and potentially life threatening complications or it resulted from administration of oral agents (warfarin in this case) at a level that was higher than clinically intended.

The finding that wound complications and subsequent deep infection are associated with 'excessive' anticoagulation is important and at the same time worrisome. Recent recommendations of American College of Chest Physicians (ACCP) explicitly state that only agents with proven efficacy should be utilized as prophylaxis against thromboembolic disease following total joint arthroplasty[24]. The criteria set forth by the ACCP, do not recognize low dose warfarin as an effective agent and recommend a higher level of INR (2 to 2.5). The recommendation also endorses low molecular weight heparin as an effective agent. The major concern posed by the orthopedic community with regard to the recommendations of the ACCP relates to the potential for development of wound related problems such as hematoma and wound drainage that may ensue after aggressive anticoagulation regimen. The current study confirms that such problems do occur even after administration of low dose warfarin. Hence, wound related problems and subsequent infection is likely to be more prevalent after higher doses of anticoagulants or injectable agents, as the incidence of bleeding, persistent wound drainage, and hematoma formation has been shown to be higher with injectable agents compared to oral anticoagulants[25,26]. A previous study has also demonstrated that patients receiving intravenous heparin in the postoperative period were more likely to suffer medical and orthopedic complication[27]. The latter study did not however find a correlation between

anticoagulation and implant related infection. Our study, for the first time to our knowledge, demonstrates a direct correlation between administration of excessive anticoagulation and the development of periprosthetic infection.

The findings of this study need to be interpreted with some caveat in mind. This is a retrospective study with all the innate limitations of such a study design with regard to uniformity of data collection. Second, it is possible that factors other than excessive anticoagulation may have lead to the development of periprosthetic infection in this cohort. This study sought to collect information on all predisposing factors that could possibly contribute to the development of periprosthetic infection. One of those may have been the presence of concomitant comorbidities such as diabetes or steroid use. Although the ASA score was higher in the infected group, there did not seem to be a difference in the prevalence of diabetes or other 'predisposing conditions' between the two groups. The only exception is that a higher number of patients in the infected group were receiving oral steroid, as treatment for pulmonary conditions, than the control group. This difference could plausibly be an important confounding variable. There was also a significant difference in the ASA score between the two groups. This could however be explained by the higher incidence of cardiorespiratory conditions among the infected cohort which in turn lead to more of these patients requiring intravenous anticoagulation. More patients in the infected cohort required allogenic transfusion in the postoperative period. Although allogenic transfusion by the virtue of immunonodulation[28] can potentially predispose patients to a higher incidence of infection, this correlation has not been proven. Instead we believe the higher need for transfusion in the infected cohort is

the reflection of the problem with bleeding, hematoma formation, and persistent wound discharge which in turn lead to the need for reoperation and further blood loss.

Despite all the aforementioned limitations, this study serves to highlight an important, and in our opinion a critical, fact. There needs to be an acceptable balance between efforts to prevent thromboembolism and the potential for causing serious harm to patients undergoing total joint arthroplasty. With the continuing improvements in surgical and anesthesia techniques allowing earlier rehabilitation and faster recovery leading to a reduced potential for development of thromboembolism, the benefits of aggressive prophylactic anticoagulation should be weighed against the rising problem of periprosthetic infection.

Legends:

Figure 1: The mean International Normalized Ratio (INR) for patients which developed periprosthetic infection (experimental group) compared to those who did not develop infection (control group).

Table 1: Details of Various Parameters in the Cohort

Abbreviations: BMI = Body Mass Index; ASA = American Society of Anesthesiologists; NNIS = National Nosocomial Infection Surveillance; PE= Pulmonary Embolus; DVT= Deep Vein Thrombosis; UTI= Urinary Tract Infection

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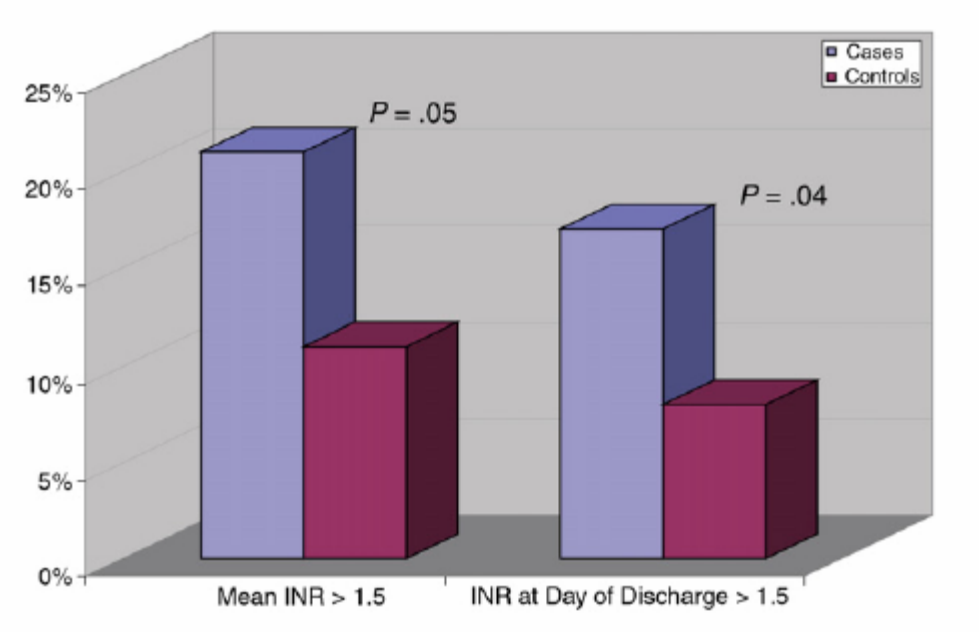
Cases
Controls
25%
20%
15%
10%
5%
0%
P = .05
P = .04
Mean INR > 1.5
INR at Day of Discharge > 1.5

Figure1

Variables	Cases N=78	Controls N=156	p-value
Socio-Demographics			
Age in Years(Mean ± SD)	66 ± 10	66 ± 10	0.91
BMI Kg/m^2 (Mean ± SD)	32 ± 9	32 ± 7	0.76
Alcohol Abuse	1 (1%)	0%	0.16
Heavy Smoker	6 (8%)	15 (10%)	0.63
Comorbidities			
ASA score (Mean ± SD)	2.6 ± 0.57	2.4 ± 0.56	**0.01**
Diabetes mellitus	14 (18%)	22 (14%)	0.56
≥3 co-morbidities	33 (42%)	56 (36%)	0.39
Steroid Therapy	8 (10%)	5 (3%)	**0.03**
Insulin use	2 (3%)	3 (2%)	0.75
NNIS ≥1	50 (64%)	73 (47%)	**0.01**
Surgical Data			
Blood loss (Mean ± SD)	354 ± 602	270 ± 341	0.17
Operative time (Mean ± SD)	114 ± 49	114 ± 91	0.97
Total Transfusion (Mean ± SD)	0.78 ± 1.15	0.39 ± 0.79	**0.002**
Allogenic Transfusion	10 (13%)	3 (2%)	**0.0006**
Autologous Transfusion	47 (60%)	111 (71%)	0.09
Postoperative Complications			
Wound Hematoma	11 (14%)	2 (1%)	**0.0001**
Wound Drainage	24 (31%)	4 (3%)	**0.0001**
Other complications(PE,DVT,UTI)	18 (23%)	18 (12%)	**0.02**

Table1