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Complications - Infection

Rivaroxaban Use for Thrombosis Prophylaxis Is Associated With Early Periprosthetic Joint Infection

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ABSTRACT

Background: Periprosthetic joint infection is a disastrous complication after total hip arthroplasty (THA) and total knee arthroplasty (TKA). The use of certain agents to prevent deep vein thrombosis after arthroplasty has been linked to an increased risk of adverse effects including wound drainage and infection. Adverse effects of one alternative, rivaroxaban, was studied in a single community hospital.
Methods: International Classification of Diseases, Clinical Modification 9 codes were used to identify primary THAs and TKAs in an administrative database at one large-volume community hospital performed in 2012. Patients were divided into 2 groups: the study group received rivaroxaban, whereas the control group received another form of chemical thromboprophylaxis for at least 2 weeks postoperative. Demographics, risk factors, and illness severity scores were collected for each group. The primary measured outcome was the incidence of deep surgical site infection (SSI) within 30 days postoperative.
Results: A total of 639 TKA or THA patients were included, with 159 patients who received rivaroxaban and 480 who received another form of chemical thromboprophylaxis. There were no significant differences between groups regarding demographics, risk factors, or illness severity scores. Incidence of early deep SSI in the rivaroxaban group was higher than in the control group (2.5% vs 0.2%; $P < .015$).
Conclusion: The use of rivaroxaban for thromboprophylaxis led to a significantly increased incidence of deep SSI in a continuous series of patients undergoing primary THA and TKA in a single institution.

Primary total hip arthroplasty (THA) and total knee arthroplasty (TKA) are relatively safe procedures, with <1% of these procedures complicated postoperatively by periprosthetic joint infection [1,2]. Although its incidence is low, the effects are significant in terms of both morbidity [3] and economic burden [4]. Managing and/or eliminating risk factors that predispose a patient to periprosthetic joint infection is critically important.

The American College of Chest Physicians established national guidelines which recommend routine thromboprophylaxis with anticoagulants after THA and TKA [5]. Rivaroxaban (Xarelto; Bayer Schering Pharma, Berlin, Germany), an orally active direct factor Xa inhibitor, was recently approved by the Food and Drug Administration for the prevention of venous thromboembolism (VTE) in adults undergoing THA or TKA surgery in the United States [6]. The RECORD (Regulation of Coagulation in Orthopaedic Surgery to Prevent DVT and PE) trials demonstrated rivaroxaban to have superior efficacy compared to enoxaparin (Clexane/Lovenox; Sanofi-Aventis, Frankfurt, Germany) in preventing VTE with no significant increase in the major bleeding risk [7-10]. Although these studies favored rivaroxaban in terms of reduced VTE rates, wound infection and subsequent reoperation [11-13] were outcomes that were not fully evaluated by the RECORD trial design.

Previous studies have reported an increased incidence of infection [13] and subsequent reoperation [12,13] after the use of rivaroxaban for thromboprophylaxis in arthroplasty patients when compared with the use of low-molecular-weight heparin and enoxaparin. The purpose of this study was to further test those results by comparing the early deep postoperative surgical site infection and subsequent reoperation rates in THA and TKA

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patients treated with either oral rivaroxaban or any other form of chemical thromboprophylaxis.

Materials and Methods

After approval by the institutional review board, procedure codes from the 9th Revision of the International Classification of Diseases, Clinical Modification were used to query the administrative database at one large-volume community hospital to identify cases of a primary THA (procedure code: 81.51) or primary TKA (procedure code: 81.54) between January 2012 and December 2012, during which rivaroxaban was used as an option thromboprophylaxis. Patient charts were retrospectively reviewed using electronic medical records to verify the type of postoperative thromboprophylaxis used. The rivaroxaban group received 10-20 mg orally, once daily, within 24 hours postoperatively and continued for at least 14 days. The control group was composed of patients who received any other form of chemical thromboprophylaxis started within 24 hours postoperatively and continued for at least 14 days. Intermittent pneumatic compression devices and early mobilization were used as the standard postoperative protocol for hip and knee arthroplasties in both groups. No postoperative drains were used in either group. All patients received the standard dose of prophylactic perioperative antibiotics (cefazolin 1-2 g, replaced by vancomycin 1 g if penicillin allergy was present) for 24 hours.

Data elements collected included demographic data (age, gender, body mass index, length of stay), surgical data (type of procedure and procedure laterality), medication history (use of immunomodulators, steroids, or insulin at the time of surgery), and smoking history. The Charlson Comorbidity Index [14] was calculated for each patient admission. Patients with incomplete admission records were excluded.

The primary outcome measured was early deep postoperative surgical site infection. Patients who presented with clinical signs of wound infection (ie, persistent wound drainage) within 30 days of surgery were diagnosed with a potential early postoperative surgical site infection. These patients all subsequently underwent reoperation where each infection was defined as deep through evidence of intra-articular extension and joint aspiration. Microbiological specimens (fluid and/or tissues) were taken (by intra-articular aspiration preoperatively or from deep tissues during reoperation) and sent for cell count, differential, and cultures.

Statistical Analysis

Continuous variables were described using means and standard deviations or medians and interquartile ranges, as appropriate. Categorical variables were described using counts and percentages. Comparisons of continuous variables between patients with and without rivaroxaban treatment were done using Wilcoxon's rank-sum test. Comparisons of categorical variables were made using either Pearson's chi-squared test or Fisher's exact test, as appropriate. All analyses were performed using R software (version 3.0.2; Vienna, Austria). A significance level of 5% was used for all testing.

Results

Twelve surgeons performed 742 THA and TKA procedures during the study period, 103 of which were excluded because of incomplete records, leaving 639 procedures included in the study. None of the excluded patients had reoperation within 30 days; however, they were missing information regarding demographics or comorbidities. Of the 103 excluded patients, 27 were treated with rivaroxaban, whereas remaining 76 were treated with another chemical form of prophylaxis. For the 639 patients included in the study group, 159 patients were in the study group and were treated with rivaroxaban, whereas remaining 480 were in the control group. One of the patients in the rivaroxaban group received 20 mg of oral rivaroxaban daily, whereas remaining 158 received 10 mg daily. In the control group, distribution of the thromboprophylaxis agents used was as follows: 322 patients received enoxaparin, 161 received aspirin, 33 received warfarin, 3 received dabigatran, and 1 received heparin. Fifty patients in both groups received more than one type of chemical thromboprophylaxis.

Table 1
Patient Demographics.

Variable	With Rivaroxaban (n = 159)	No Rivaroxaban (n = 480)	*P* Value
Gender			
Male	63 (39.6%)	210 (43.8%)	.41
Female	96 (60.4%)	270 (56.3%)	
Body mass index[a]	31 (27.5, 35)	32 (27, 38)	.21
Age (y)[a]	61 (54, 68)	62 (56, 70)	.052
Length of stay[a]	3 (3, 3)	3 (3, 3)	.56

[a] Data reported as median (25th percentile, 75th percentile).

There were no statistically significant differences in demographics between the 2 groups (Table 1). Median length of hospital inpatient stay was identical in both groups at 3 days ($P = .56$). The proportions of THA and TKA in both groups were similar ($P = .67$; Table 2), with more TKA than THA in each. There were no significant differences between the groups in terms of smoking, the use of insulin, the use of immunosuppressive drugs, or Charlson Comorbidity Index (Table 2).

In the rivaroxaban group, 4 of 159 patients (2.5%) had an early deep surgical site infection with subsequent reoperation, while 1 of 480 patients in the control group experienced this complication (Table 3; $P = .015$). Details of these 5 patients with infection are described in Table 4. All of the patients diagnosed with an early deep surgical site infection had at least 2 positive preoperative or intraoperative intra-articular aspirate cultures with the same bacteria and received only one type of chemical thromboprophylactic drug as indicated in Table 4. When stratified by type of procedure, the difference between the groups treated with and without rivaroxaban was no longer statistically significant (Table 3).

Table 2
Univariate Comparison Between Groups of Patients Treated With and Without Rivaroxaban.

Variable	With Rivaroxaban (n = 159)	No Rivaroxaban (n = 480)	*P* Value
Current smoker	2 (1.3%)	14 (2.9%)	.38
Immunomodulator use	1 (0.6%)	3 (0.6%)	.99
Steroid use	20 (12.6%)	47 (9.8%)	.40
Insulin use	23 (14.5%)	68 (14.2%)	.99
Procedure			
Total hip arthroplasty	72 (45.3%)	206 (42.9%)	.67
Total knee arthroplasty	87 (54.7%)	274 (57.1%)	
Laterality			
Left	66 (41.5%)	224 (46.7%)	.52
Right	84 (52.8%)	232 (48.3%)	
Bilateral	9 (5.7%)	24 (5.0%)	
Charlson Comorbidity Index[a]	2 (1, 3)	2 (1, 3)	.07

[a] Data reported as median (25th percentile, 75th percentile).