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Rivaroxaban Versus Enoxaparin for Venous Thromboembolism Prophylaxis after Hip and Knee Arthroplasty

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ABSTRACT

The oral Factor Xa inhibitor rivaroxaban (Xarelto) has been the pharmacologic agent used for venous thromboembolism (VTE) prophylaxis after primary hip and knee arthroplasty (THA/TKA) at our institution since February 2012. The purpose of our study was to compare rates of VTE and major bleeding between rivaroxaban and our previous protocol of enoxaparin after THA/TKA. A retrospective cohort study was performed including 2406 consecutive patients at our institution between 1/1/11 and 9/30/13. Patients who did not have unilateral primary THA/TKA or who received other anticoagulants were excluded. Of the 1762 patients included, 1113 patients (63.2%) received enoxaparin and 649 patients (36.8%) received rivaroxaban. This study found no demonstrable differences between these two anticoagulants in rates of VTE, infection, reoperation, transfusion, or major bleeding. Therapeutic, Retrospective comparative study, Level III.

Venous thromboembolism (VTE) prophylaxis is one of the most controversial topics in hip and knee arthroplasty. The ideal anticoagulant medication would be easy to administer and have low rates of deep venous thrombosis (DVT), pulmonary embolus (PE), bleeding, and wound complications. With the current agents available, however, the challenge is to find the balance of low rates of VTE while minimizing bleeding and wound complications.

Rivaroxaban (Xarelto; Bayer Schering Pharma, Berlin, Germany) is a Factor Xa inhibitor which may have benefits for pharmacologic VTE prophylaxis after primary total hip and knee arthroplasty (THA and TKA, respectively). This oral medication is easy to administer and does not require laboratory monitoring due to its predictable pharmacodynamics and pharmacokinetics [1]. Most of the evidence regarding this new medication consists of the RECORD studies [2–5] and multiple publications that pool data from these same studies [6–12]. Combined, this literature suggests favorable results with decreased VTE rates and no change in bleeding or infectious complications compared to enoxaparin. However, shortly after the introduction of rivaroxaban in Europe, two recent studies raised concerns about wound complications with use of rivaroxaban. A single-institution retrospective study revealed a higher rate of return to the operating room for wound complications [13]. This was followed by a study of all British National Health Service (NHS) hospitals that began using rivaroxaban, which found higher rates of wound complications with rivaroxaban compared to enoxaparin with no difference in reoperation rates [14]. Given the recent independent studies which showed differing results from the industry-sponsored phase III trials, additional independent studies of this medication are necessary.

Prior to February 2012, our institution administered enoxaparin for routine VTE prophylaxis after primary THA and TKA. Enoxaparin is a subcutaneously injected medication which activates antithrombin III. In February 2012, our institution changed the VTE prophylaxis protocol to include the routine use of rivaroxaban. The purpose of our study was to compare rates of VTE and rates of major bleeding between rivaroxaban and enoxaparin after primary THA and TKA.

Materials and Methods

A retrospective cohort study was conducted according to IRB protocol including 2406 consecutive patients who underwent primary THA or TKA. Patients were included beginning with the calendar year prior to implementation of the rivaroxaban protocol (between 1/1/11 and 9/30/13). Data were collected from 6 fellowship trained surgeons at 2 academically affiliated hospitals. All patients underwent surgery at a large urban tertiary care center or a suburban community hospital in a large metropolitan area.

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Patients were excluded who had a bilateral procedure, complex procedure, unicompartmental knee arthroplasty, hip hemiarthroplasty, resurfacing arthroplasty, or revision surgery. Patients who were concurrently on other anticoagulants were excluded, such as acetylsalicylic acid (Aspirin), clopidogrel, fondaparinux, or warfarin. Patients with a pre-operative creatinine of 1.2 mg/dL or greater were excluded. At our institution, patients with renal insufficiency are routinely placed on enoxaparin, due to the medical team's greater familiarity with this medication in these situations. Both drugs are renally excreted and this exclusion criterion served to minimize the effect of this potential confounder. Patients without at least 6 weeks of follow-up were excluded.

Patients received pharmacologic VTE prophylaxis beginning the morning after surgery with either enoxaparin (40 mg subcutaneous [SQ] daily for 21 days for THA patients, 30 mg SQ twice daily for 14 days for TKA patients) or rivaroxaban (10 mg oral daily for 35 days for THA patients, 10 mg oral daily for 12 days for TKA patients). Patients in both groups wore thromboembolism-deterrent stockings until 2 weeks post-operatively and wore intermittent pneumatic compression devices during their hospital stay. Both groups received 24 h of post-operative antibiotics.

Chart review recorded demographics, comorbidities, surgery performed, length of stay (LOS), symptomatic DVT, symptomatic PE, transfusion, number of units of packed red blood cells transfused, hemorrhagic cerebrovascular event (CVA), superficial infection, deep periprosthetic infection, and reoperation. Patients were not screened for DVT or PE unless they were symptomatic. Superficial infection was defined as infection superficial to the fascia including patients who underwent reoperation for irrigation and debridement superficial to the fascia. Patients were identified as having deep infection if they required reoperation extending deep to the fascia—including deep irrigation and debridement, with or without modular component exchange, or if they required removal of components for infection.

Statistical Methods

T-tests were used to compare continuous variables between treatment groups and Chi-square tests were used, with Cochran corrections as appropriate, to compare categorical variables between treatment groups. For this analysis, the American Society of Anesthesiologists (ASA) score was considered a categorical variable. Alpha = 0.05.

Where results were not statistically significant, a post-hoc power analysis was performed. In addition, a minimum sample size was calculated to achieve power = 0.08 at alpha = 0.05, given the current data's variances and differences between means.

Source of Funding

There were no external sources of funding associated with this study.

Results

Of the 2406 patients who had hip or knee arthroplasty at our institution during the study period, 1762 patients met inclusion criteria. The following patients were excluded from the study: 141 patients had a bilateral procedure, complex procedure, unicompartmental knee arthroplasty, hip hemiarthroplasty, resurfacing arthroplasty, or revision surgery; 292 patients required continuation of prior anticoagulant medication post-operatively for medical reasons; and 211 patients had pre-operative creatinine greater than 1.2. Of the 1762 patients ultimately included in the study, 1113 patients (63.2%) received enoxaparin and 649 patients (36.8%) received rivaroxaban for VTE prophylaxis.

There were no differences in gender ($P = 0.989$, post-hoc power = 0.047), body mass index (BMI) ($P = 0.170$, post-hoc power = 0.144), ASA score ($P = 0.965$, post-hoc power = 0.047), or procedure performed ($P = 0.845$, post-hoc power = 0.051) between the 2 groups. The rivaroxaban group was younger, with mean age of 64.7 (± SD 10.4), compared to the mean age of 66.0 (± 10.7) in the enoxaparin group ($P = 0.011$). Pre-operative creatinine was higher in the enoxaparin group with mean creatinine of 0.80 (± 0.19) compared to mean creatinine of 0.73 (± 0.19) in the rivaroxaban group ($P < 0.001$). There was no difference in length of stay (LOS) between the groups ($P = 0.433$, post-hoc power = 0.050). These results are summarized in Table 1.

With the numbers available for study, there were no demonstrable differences in rates of venous thromboembolic disease with similar rates of DVT ($P = 0.208$, post-hoc power = 0.226) and PE ($P = 0.437$, post-hoc power = 0.113). There was no difference in major bleeding with similar rates of transfusion ($P = 0.372$; post-hoc power = 0.135), bleeding requiring transfusion of 2 or more units of packed red blood cells ($P = 0.971$, post-hoc power = 0.047), and hemorrhagic cerebrovascular events (CVA) ($P = 1.00$). The minimum sample size to achieve adequate statistical power ranged from 2798 to 347,691 patients. These results are summarized in Table 2.

There was no difference in rates of superficial infection ($P = 0.748$, post-hoc power = 0.058), deep infection ($P = 0.989$, post-hoc power = 0.047), or reoperation ($P = 0.904$, post-hoc power = 0.049). An analysis of all patients who required reoperation is summarized in Table 3.

Discussion

This study showed that a pharmacologic VTE prophylaxis protocol with the use of rivaroxaban was as efficacious as enoxaparin at preventing post-operative symptomatic DVT and PE. The DVT rate of the enoxaparin group was 1.8% compared to 0.9% in the rivaroxaban group ($P = 0.208$) and the PE rate of the enoxaparin group was 0.7% compared to 0.3% in the rivaroxaban group ($P = 0.437$). A recent retrospective, industry-sponsored registry study by Beyer-Westendorf et al found a statistical decrease in symptomatic DVT in 54 of 1495 patients (3.6%) who received enoxaparin compared to 20 of 1043 (1.9%) patients who received rivaroxaban, and PE rates of 0.54% and 0.19% in the enoxaparin and rivaroxaban groups, respectively [15]. In contrast, our study found lower overall rates of DVT in both treatment cohorts than were seen in the Beyer-Westendorf study. Moreover, unlike in Beyer-Westendorf et al, we were unable to demonstrate a difference in DVT rates between treatment groups.

The ultimate goal of pharmacologic VTE prophylaxis after arthroplasty surgery is prevention of PE, most importantly fatal PE. In many studies, rates of DVT have been used as a surrogate outcome measure for the efficacy of medications used for pharmacologic VTE prophylaxis, and studies that do not identify statistically significant differences in PE suggest this is because of inadequate power. However, in a large meta-analysis of the available level I studies comparing apixaban and rivaroxaban to enoxaparin in 24,385 patients, Russell et al found no difference in rates of PE (Odds Ratio [OR] 0.6, 95% Confidence Interval [CI] 0.17–2.13, $P = 0.43$) [8]. These results are consistent with our study, which found no statistically demonstrable difference in PE rates between the enoxaparin and rivaroxaban groups.

There is variability in the literature regarding the definition of bleeding complications and the rates of bleeding complications after primary hip and knee arthroplasty. This variability makes it difficult to directly compare our transfusion rates to other studies. In a pooled analysis of 9581 patients from the RECORD 1, 2, and 3 studies, the transfusion rates were 49.8% in the enoxaparin group and 49.7% in the rivaroxaban group [6]. In our study, rivaroxaban was not associated with an increase in bleeding events compared to enoxaparin. The transfusion rate in the enoxaparin group was 13.3% compared to 15.0% in the rivaroxaban group ($P = 0.372$). Major bleeding requiring transfusion of 2 or more units of packed red blood cells occurred in 9.9% of patients receiving enoxaparin compared to 9.7% of patients receiving rivaroxaban ($P = 0.971$). There were no patients with post-operative hemorrhagic stroke in either group. At our institution, we transfuse patients who are symptomatic with hemoglobin less than 8 and asymptomatic with hemoglobin less than 7. During the time period of our study, the clinical