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Comparison of Postoperative Bleeding in Total Hip and Knee Arthroplasty Patients Receiving Rivaroxaban, Enoxaparin, or Aspirin for Thromboprophylaxis

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Abstract

Background: Guidelines recommend the use of multiple pharmacologic agents and/or mechanical compressive devices for prevention of venous thromboembolism, but preference for any specific agent is no longer given in regard to safety or efficacy. **Objective:** To compare postoperative bleeding rates in patients receiving enoxaparin, rivaroxaban, or aspirin for thromboprophylaxis after undergoing elective total hip arthroplasty or total knee arthroplasty. **Methods:** This retrospective cohort analysis evaluated patients who received thromboprophylaxis with either enoxaparin, rivaroxaban, or aspirin. All data were collected from the electronic medical record. The primary outcome was any postoperative bleeding. **Results:** A total of 1244 patients were included with 366 in the aspirin, 438 in the enoxaparin, and 440 in the rivaroxaban arms. Those who received aspirin or enoxaparin were less likely to experience any bleeding compared to those patients who received rivaroxaban ($P < .05$). There was also a lower rate of major bleeding in these groups, but the differences were not significant. **Conclusions:** Aspirin and enoxaparin conferred similar bleeding risks, and both exhibited less bleeding than patients who received rivaroxaban.

Keywords

venous thromboembolism, rivaroxaban, enoxaparin, aspirin, deep vein thrombosis, pulmonary embolism, total hip arthroplasty, total knee arthroplasty, prophylaxis

Introduction

Total hip arthroplasty (THA) and total knee arthroplasty (TKA) occur frequently, with about 300 000 THA surgeries and more than 500 000 TKA surgeries performed annually in the United States.[1] This number is projected to rise to almost 600 000 annual THA surgeries and 3.5 million annual TKA surgeries by 2030.[1] Patients undergoing these procedures are at a significantly increased risk of developing postoperative complications, most notably venous thromboembolism (VTE).[2,3] The incidence of VTE after THA or TKA is reduced by the use of thromboprophylactics, such as vitamin K antagonists, unfractionated heparin (UFH), low-molecular-weight heparin (LMWH), direct oral anticoagulants (DOACs), or aspirin (ASA).[3] However, these medications have a number of limitations that impede their use, including increased bleeding risk. The potential for bleeding secondary to prophylaxis has been associated with prolonged recovery, infections, wound failure, and readmission.[4] Therefore, the risk versus benefit is a primary consideration when a provider chooses VTE prophylaxis in these patients.

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Prior to the 2012 update to the American College of Chest Physicians (ACCP) guidelines,[3] LMWH and warfarin were the commonly used options for VTE prophylaxis in THA and TKA patients in the United States.[5] In 2008 to 2009, the Regulation of Coagulation in Orthopedic Surgery to Prevent Deep Vein Thrombosis and Pulmonary Embolism (RECORD) 1 to 4 trials were published, which compared oral rivaroxaban 10 mg daily to enoxaparin (either 30 mg every 12 hours [q12h] or 40 mg q24h) for the prevention of VTE in THA and TKA patients.[6-9] Rivaroxaban was approved for this indication in the United States in 2011 as these trials showed similar rates of VTE with similar bleeding rates. Trials with other oral anticoagulants, including apixaban and dabigatran, also demonstrated similar efficacy with similar or decreased rates of major and minor bleeding.[10-15]

The arrival of the DOACs, the 2012 ACCP guideline update, the long-standing endorsement of other therapies, such as ASA, by the American Association of Orthopaedic Surgeons,[16] and other factors, such as broader specialty representation on ACCP committees, created opportunity for a paradigm shift in the interpretation of existing evidence. This broadened the options that were guideline endorsed, allowing providers even more options to manage thrombosis risk post-surgery. Although consensus was reached, debate still exists regarding ASA as evidenced by the statement in the ACCP guidelines, including a statement that read, "one panel member believed strongly that ASA alone should not be included as an option."[3(pe295S)] The addition of ASA as a recommended option only broadened the number of opinions.[17,18]

The appeal of ASA is likely the low cost coupled with the perception that bleeding risk is lower compared to traditional anticoagulants. There is mixed evidence in regard to the safety and efficacy of ASA when compared to other agents.[5,19-21] Complicating this decision further is the trade-off of risk and benefit as clinicians should be cautious because choosing a perceived lower risk with 1 agent may increase the risk of a preventable harmful outcome with another. Previous studies showed similar rates of major bleeding between ASA, UFH, LMWH, and warfarin.[20,21] A study by Brown was able to show that ASA was associated with lower operative site bleeding events compared to LMWH ($P < .0001$), with no significant difference observed in total bleeding.[22] In addition, a multivariate analysis showed that ASA was an independent predictor of decreased costs for these surgeries, mainly attributed to a shorter length of initial hospitalization.[23] However, a more recent network meta-analysis calls into question the assumption that ASA has lower or similar bleeding rates due to the paucity of methodologically sound data.[24] Furthermore, those authors call into question contemporary guidelines, including the ACCP guidelines, which offer no clear preferential recommendations regarding particular agents other than 2B or 2C recommendations of "preference" favoring more traditional LMWH over other options, including ASA. Furthermore, no clear guidance on risk stratification is provided, ultimately leaving the decision of risk versus benefit to the subjective discretion of the provider.

The recently published Extended Venous Thromboembolism Prophylaxis Comparing Rivaroxaban to Aspirin Following Total Hip and Knee Arthroplasty II (EPCAT II) data add an additional layer to this complex question in that they evaluated a combination regimen that included both rivaroxaban for 6 days followed by low-dose (81 mg) ASA versus a traditional rivaroxaban regimen of 10 mg daily.[25] Although this does support the hypothesis that ASA is an effective chemoprophylactic option, the possibility still exists that higher dosed ASA regimens, without lead-in potent anticoagulation, could be still be less efficacious or carry a higher safety risk or both. One editorialist points out that the EPCAT II data also failed to evaluate any additive benefit of mechanical prophylaxis, which was utilized in only about 15% of trial participants.[26]

In 2014, a study at our institution compared a local cohort of patients who received rivaroxaban to the historical RECORD trials and observed a statistically significant increase in "real-world" bleeding events.[27] In order to evaluate whether this outcome was valid, we compared a local enoxaparin group to the historical enoxaparin groups in the RECORD trials and then also to the local rivaroxaban patients.[28] This study found increased bleeding in the local rivaroxaban patients compared to that in local enoxaparin, while similar bleeding rates existed between the local and historical enoxaparin patients. To further assess the safety of utilizing ASA for thromboprophylaxis in a similar patient population, the purpose of this study was to compare postoperative bleeding rates in patients receiving ASA to patients who received enoxaparin or rivaroxaban after undergoing elective THA or TKA.

Methods

This was a retrospective study approved by the local institutional review board. This study collected patient information from 2 regional institutions within 1 local health-care system. Both institutions are designated as Orthopedic Centers of Excellence. One institution is a 261-bed community hospital that performs approximately 100 THA and 200 TKA surgeries annually. The other institution is a 488-bed community teaching facility that performs approximately 250 THA and 400 TKA surgeries annually. Patients admitted to either of the 2 study institutions between January 1, 2012, and January 25, 2016, were screened for inclusion in the study.

The study population consisted of patients who were 18 years or older, underwent elective THA or TKA, and received ASA, enoxaparin, or rivaroxaban for postoperative thromboprophylaxis. Dosages of VTE prophylaxis were as follows: ASA orally 325 mg 2 times a day, rivaroxaban 10 mg orally daily for creatinine clearance (CrCl) >30 mL/min, and enoxaparin subcutaneously either 30 mg q12h or 40 mg q24h for CrCl >30 mL/min or 30 mg q24h if CrCl <30 mL/min. The dosage of enoxaparin was at the discretion of the treating physician, but the order set recommended 30 mg q12h (CrCl >30 mL/min) for this patient population. Duration of VTE prophylaxis was determined by the treating physician; however, all VTE prophylaxis regimens are

Table 1. Baseline Demographics and Hospital Length of Stay.

Variable	Aspirin, n = 366	Enoxaparin, n = 438	Rivaroxaban, n = 440	*P* Value
Age in years, mean (range)	65.8 (30-92)	66.7 (35-91)	65.4 (29-93)	.08
Female (%)	223 (60.9)	289 (66.0)	285 (64.8)	.308
Caucasian (%)	366 (100.0)	343 (99.1)	415 (94.3)	<.001
Weight in kg, mean (range)	87.9 (46-155)	90.6 (36-154)	89.1 (37-173)	.178
THA (%)	188 (51.4)	141 (32.2)	167 (38.0)	<.001
TKA (%)	178 (48.6)	297 (67.8)	273 (62.0)	<.001
SCr in mg/dL, mean (range)	0.8 (0.3-1.7)	1.0 (0.3-3.0)	0.9 (0.5-2.2)	<.001
Hgb in g/dL, mean (range)	11.2 (5.7-15.3)	10.5 (6.6-15.1)	10.6 (6.0-15.1)	<.001
Length of stay in days, mean (range)	2.0 (1-10)	4.6 (2-15)	3.6 (1-16)	<.001

Abbreviations: Hgb, hemoglobin; SCr, serum creatinine; THA, total hip arthroplasty; TKA, total knee arthroplasty.

ordered via standardized order sets with suggested durations of 12 and 35 days for TKA and THA, respectively. Patients were excluded if they were diagnosed with active bleeding prior to surgery, received another anticoagulant for greater than 24 hours, were admitted directly to the intensive care unit, had an international normalized ratio of greater than 1.5 on the day of surgery, had an estimated CrCl of less than 30 mL/min, or received concomitant protease inhibitor therapy.

The primary outcome was any postoperative bleeding. This was defined as a composite of clinically overt fatal bleeding, critical organ bleeding, bleeding requiring the transfusion of 2 or more units of blood, bleeding that necessitated operation, and bleeding outside the surgical site that was associated with a hemoglobin (Hgb) decrease of $\geq$2 g/dL, and clinically relevant nonmajor bleeding (CRNMB). The outcome of CRNMB was defined consistent with the RECORD trials and included multiple source bleeding events, unexpected hematoma, excessive wound hematoma, nose bleeding, vaginal/semen bleeding, surgical site bleeding, gingival bleeding, macroscopic hematuria, rectal bleeding, coughing or vomiting blood, or intraarticular bleeding with trauma. Secondary outcomes included individual components of the primary outcome, as well as the receipt of blood transfusions and rate of 30-day readmissions for any reason. Baseline demographics collected were age, sex, race, weight, type of operation, baseline serum creatinine (SCr), pre- and postoperative Hgb, and length of stay.

To achieve 80% power using a 2-sided α value of .05, assuming a 5% absolute difference as being clinically relevant, it was determined that 435 patients per group would be required. Categorical variables were analyzed with a logistic regression analysis. A χ^2 or Fisher exact test was used for categorical demographic data as appropriate. An analysis of variance (ANOVA) with post hoc tests was used for continuous data. All analyses were performed using SPSS software, version 23 (IBM Corporation, New York, New York). All reported *P* values were 2 sided, with a value of less than .05 considered statistically significant.

Results

A total of 1244 patients were included in the final analysis, with 366 patients receiving ASA. These patients were compared to the 2 cohorts of patients previously identified who had received rivaroxaban (440) and enoxaparin (438). Complete baseline demographics are listed in Table 1. The mean age of the ASA, rivaroxaban, and enoxaparin groups was 65.4, 66.7, and 65.8 years, respectively. The majority of patients were female in all groups and almost all were Caucasian. The ASA group was relatively even in the number of THAs versus TKAs. Baseline SCr and Hgb differed minimally between groups, and these differences were not thought to be clinically meaningful. Patients who received ASA had shorter hospital length of stay when compared to patients who received enoxaparin or rivaroxaban ($P < .001$).

The results of this study can be found in Table 2. Based on a logistic regression analysis of the 3 independent groups, patients who received rivaroxaban were twice as likely to experience any bleeding compared to those patients who received ASA therapy (odds ratio [OR]: 2.19, 95% confidence interval [CI]: 1.07-4.46). There was a similar rate of major bleeding in the ASA and enoxaparin groups. Despite higher rates of major bleeding in the rivaroxaban group (OR = 5.05, 95% CI: 0.61-42.1), the difference was not significant. No other differences were detected between the 3 treatments in regard to outcomes associated with bleeding.

The number of patients requiring blood transfusions was elevated in both the enoxaparin and rivaroxaban groups compared to those who received ASA; however, this was likely due to a change in practice versus an increased rate of bleeding events. A 1-way ANOVA with post hoc analyses indicated that length of stay was significantly different between each of the 3 study groups with the shortest length of stay, in days, being associated with ASA (mean = 2.0), followed by rivaroxaban (mean = 3.6) and lastly enoxaparin (mean = 4.6), with a *P* value <.001 for all comparisons. Patients were 3.7 (95% CI: 1.8-7.7) times more likely to be readmitted within 30 days when taking ASA compared to enoxaparin. No difference in 30-day readmission rates existed between the ASA and rivaroxaban groups (Table 3).

Reason for readmission was not collected in patients receiving rivaroxaban; however, for those receiving enoxaparin, 2 patients were readmitted for an infected joint, 1 to rule out VTE, and none were readmitted for bleeding complications. In the ASA group, 5 patients were admitted for an infected joint, 5 to rule out VTE, and 3 for bleeding, with 2 of those being listed as a gastrointestinal bleed.

Table 2. Bleeding Outcomes for Patients Who Received Enoxaparin and Rivaroxaban Relative to Those Who Received Aspirin Therapy.

Variable	Aspirin, n = 366, n (%)	Enoxaparin, n = 438, n (%)	OR (95% CI)	Rivaroxaban n = 440, n (%)	OR (95% CI)
Any bleeding[a]	11 (3.3)	10 (2.2)	0.75 (0.32-1.79)	30 (6.8)	2.19 (1.07-4.46)
Major bleeding	1 (0.3)	1 (0.2)	0.84 (0.05-13.4)	6 (1.4)	5.05 (0.61-42.1)
Bleeding into a critical organ	0 (0)	1 (0.2)	–	0 (0)	–
Bleeding leading to reoperation	0 (0)	0 (0)	–	3 (0.7)	–
Clinically overt bleeding → decreased hemoglobin	0 (0)	0 (0)	–	3 (0.7)	–
Clinically overt bleeding → transfusion ≥2 units	1 (0.3)	0 (0)	–	3 (0.7)	2.51 (0.26-24.19)
Clinically relevant nonmajor bleeding	10 (3.0)	9 (2.1)	0.75 (0.3-1.86)	24 (5.5)	2.1 (0.97-4.35)
Receipt of blood transfusions	19 (5.2)	158 (36.1)	10.3 (6.2-17.0)	111 (25.2)	6.2 (3.7-10.3)

Abbreviations: CI, confidence interval; OR, odds ratio.
[a]Defined as clinically relevant nonmajor bleeding plus major bleeding.

Table 3. Thirty-Day Readmission Rates for Patients Who Received Enoxaparin and Rivaroxaban Relative to Those Who Received Aspirin.

Variable	Aspirin, n = 366, n (%)	Enoxaparin, n = 438, n (%)	OR (95% CI)	Rivaroxaban, n = 440, n (%)	OR (95% CI)
30-day readmissions	29 (8.0)	10 (2.3)	0.27 (0.13-0.56)	28 (6.4)	0.79 (0.46-1.35)

Abbreviations: CI, confidence interval; OR, odds ratio.

Discussion

Any postoperative bleeding, defined in this study as a composite of clinically overt fatal bleeding, critical organ bleeding, bleeding requiring transfusion of 2 or more units of blood, bleeding that necessitated reoperation, bleeding outside the surgical site that was associated with a Hgb decrease in 2 g/dL, or CRNMB, was lower in the ASA group compared to those who received rivaroxaban but similar to those patients who received enoxaparin. The absolute difference in these bleeding rates, as the primary composite outcome, was 3.5% (3.3% for ASA vs 6.8% for rivaroxaban), resulting in a number-needed-to-harm of 29. Most would consider this to hold clinical significance; however, any potential harm would have to be weighed against potential benefit.

Major bleeding rates alone were low overall at 0.3% for ASA, 0.2% for enoxaparin, and 1.4% for rivaroxaban patients. The numeric difference between ASA and enoxaparin compared to rivaroxaban was lower but not significant; however, this trial was not powered to detect differences in major bleeding rates alone. Additionally, this trial did not assess efficacy outcomes, and to our knowledge, no direct comparisons between rivaroxaban and ASA for efficacy exist for orthopedic VTE prophylaxis.

Interestingly though, both rivaroxaban and apixaban have been shown to be more efficacious than ASA without an increased risk of bleeding in 2 different patient populations.[29,30] In the Apixaban Versus Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment (AVERROES) study, which included patients with atrial fibrillation deemed inappropriate candidates for warfarin therapy, those who received low-dose apixaban had improved efficacy outcomes, specifically stroke and systemic embolization, without an observed increased risk in bleeding outcomes.[29] In the Reduced-dosed Rivaroxaban in the Long-term Prevention of Recurrent Symptomatic Venous Thromboembolism (EINSTEIN CHOICE) study, which evaluated the long-term prevention of VTE, rivaroxaban at both 20 mg and 10 mg daily conferred a lower risk of developing fatal or nonfatal VTE than did ASA with a similar risk of major bleeding.[30]

The decision of the best VTE prophylactic agent in the high-risk orthopedic population is also confounded by the differences of opinion between those providers who emphasize prevention of VTE over nonmajor bleeding events. In fact, many providers cannot agree on a valid outcome to measure VTE with historical guidelines including any event along the gamut from asymptomatic objectively confirmed DVT to fatal PE, with varying results and opinions from analyses.[31,32] A lack of validated bleeding risk assessments is also a barrier to clinicians identifying subpopulations who may or may not benefit from a particular therapy, and it is the experience of the authors that most orthopedic providers use a standardized approach for all patients without an individualized assessment and risk stratification, in the absence of such a clinical tool.

These results are also interesting in that between those patients who received enoxaparin compared to ASA, there was not an increased risk for bleeding, and in fact, the patients who received enoxaparin had a lower bleeding rate than those who received ASA. This finding is consistent with prior studies that have not found a decreased bleeding risk with ASA compared to other anticoagulants.[20,21] A more recent retrospective database analysis found similar findings relative to transfusions,[33] but our data add to this finding in that we also include a comparison to rivaroxaban.

Of note, the primary contemporary evidence often referenced for ASA in this population are data from the Pulmonary Embolism Prevention trial.[34] There were multiple limitations in the research methodology, despite the fact it was a large population. Additionally, it has been demonstrated that ASA is not benign and that bleeding risk is as much a concern with ASA, as it is with more traditional anticoagulants.[5,35]

While efficacy was not a focus of our study, we did observe more patients in the ASA group being readmitted to rule out VTE, although none actually had an objective event. This begs the question of whether or not providers are less confident in the effects of ASA and have a lower threshold for evaluating symptoms in patients who have been discharged on an ASA regimen compared to a more traditional anticoagulant approach. Additionally, we noted more admissions for wound infections, which could be directly related to bleeding, in those patients receiving ASA compared to enoxaparin. Unfortunately, as data collection was done in 3 separate cohorts, reason for readmission, which was not a primary or secondary endpoint of the study, was not recorded for the rivaroxaban group.

There was a statistically higher rate of blood transfusions in the rivaroxaban and enoxaparin groups compared with the ASA group (25.2% vs 36.1% vs 5.2%, $P < .05$, respectively). The authors are confident that this could be attributed to a change in blood transfusion guidelines published in 2012, which raised the recommended transfusion threshold to an Hgb value of less than 7 mg/dL.[36] The majority of the patients in the ASA group were included after June 2015, coinciding with a local practice change, while the historical enoxaparin and rivaroxaban groups included patients as late as August 2011, prior to the publication of new transfusion guidelines. Given this confounder, the data regarding blood transfusions are less helpful than the observed event rates.

Our findings differ in that based on our definition, consistent with other trials, rates of bleeding were not greater with enoxaparin compared to ASA but were higher with rivaroxaban relative to ASA. We would point out that not all anticoagulants are the same and that clinicians and investigators alike should not evaluate all anticoagulants within and between classes without comparative data, such as these presented here.

One concerning finding was the higher readmission rates in the cohort of patients who received ASA therapy. This is coupled with a significantly shorter length of stay for these patients compared to both the enoxaparin and the rivaroxaban cohort. Potential explanations for this include a paradigm shift in patient care leading to earlier discharge from hospital, a change in dosage formulation from injectable to oral therapies over time, need for patient education with injectable compared to oral agents, or physician comfort (or discomfort) with new prophylactic options compared to historical treatments. Although it is outside the scope of this publication, one future researchable hypothesis could be whether or not length of stay for a high-risk orthopedic procedure is truly inversely related to the likelihood for 30-day readmission as was observed in this sample of patients.

The limitations of this trial include the limited patient population from 2 community hospitals within a single health-care system, as well as potential loss to follow up postsurgery. Variances in surgical techniques and medications that could have been used in the periprocedural period were not taken into consideration for the purposes of this study, secondary to limitations within the local electronic medical record. Additionally, due to limitations in the electronic medical record, information regarding tranexamic acid use was unable to be retrieved. It is less likely that patients receiving either rivaroxaban or ASA had a difference, but this is an assumption based on practice patterns given those data are unavailable.

Another limitation is the failure to identify the target of 435 patients for inclusion in the ASA group; however, a difference was still detected in the primary outcome between the rivaroxaban and ASA groups. Given the small difference between the enoxaparin and ASA groups (2.2% vs 3.3%, respectively), it is unlikely that evaluating the additional 80 patients would result in a significant difference between the groups. Even if one assumed a doubling of the rate of the primary outcome in those additional patients, the result would still be insignificant.

Conclusion

Despite these and other published data, it is still not clear that 1 agent is superior in terms of collective efficacy and safety compared to other recommended agents. This study illustrates that bleeding risk is present with all 3 classes of thrombophylactics studied and that those patients who received either ASA or enoxaparin were at similar risks of having a bleeding event following TKA or THA. Stratifying patients based on known risks and benefits of bleeding and VTE prophylaxis, respectively, would be an optimal approach, until validated risk stratification systems are available for routine use.

Authors' Note

Ethical approval to conduct this study was obtained from the East Tennessee State University institutional review board (1015.13sw). Informed consent for patient information to be published in this article was not obtained because the East Tennessee State University institutional review board granted a waiver of informed consent based on U.S. 45 CFR 46.116(d). Some of these data were presented in abstract format at the Southeastern Residency Conference, April 28-29, 2016, in Athens, Georgia.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Dr Stewart is a member of the speakers' bureau for Janssen Pharmaceuticals. No other authors declare to have conflicting interests.

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