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Low Risk of Thromboembolic Complications With Tranexamic Acid After Primary Total Hip and Knee Arthroplasty

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Abstract

Background The use of antifibrinolytic medications in hip and knee arthroplasty reduces intraoperative blood loss and decreases transfusion rates postoperatively. Tranexamic acid (TXA) specifically has not been associated with increased thromboembolic (TE) complications, but concerns remain about the risk of symptomatic TE events, particularly when less aggressive chemical prophylaxis methods such as aspirin alone are chosen.

Questions/purposes We determined whether the rate of symptomatic TE events differed among patients given intraoperative TXA when three different postoperative prophylactic regimens were used after primary THA and TKA.

Methods We retrospectively reviewed 2046 patients who underwent primary THA or TKA and received TXA from 2007 to 2009. The three chemical regimens included aspirin alone, warfarin (target international normalized ratio, 1.8–2.2), and dalteparin. Primary outcome measures were venous TE events, including symptomatic deep vein thrombosis (DVT) and pulmonary embolism (PE), and arterioocclusive events, including myocardial infarction

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and cerebrovascular accident. Patients judged to be at high risk for TE due to recent cardiac stent placement or strong personal/family history of TE disease were excluded.

Results For aspirin, warfarin, and dalteparin, the rates of symptomatic DVT (0.35%, 0.15%, and 0.52%, respectively) and nonfatal PE were similar (0.17%, 0.43%, and 0.26%, respectively). There were no fatal PE. Among the three groups, we found no difference in the rates of symptomatic DVT or PE with or without stratification by ASA score.

Conclusions A low complication rate was seen when using TXA as a blood conservation modality during primary THA and TKA with less aggressive thromboprophylactic regimens such as aspirin alone and dose-adjusted warfarin.

Level of Evidence Level III, therapeutic study. See the Instructions for Authors for a complete description of levels of evidence.

Introduction

Historically, THA and TKA have been associated with a substantial risk of blood transfusion resulting from perioperative blood loss. One strategy to decrease the amount of blood loss and lower the risk of transfusion is the use of an antifibrinolytic medication [11]. Antifibrinolytics inhibit clot degradation by preventing plasmin from cleaving fibrin and dissolving the incipient clot. Tranexamic acid (TXA) and ε-aminocaproic acid (EACA) are lysine analog antifibrinolytics that reversibly bind both plasmin and plasminogen. TXA is considerably more potent than EACA [8] and is currently FDA approved for use in patients with hemophilia to prevent hemorrhage during tooth extraction, although the use of this drug in other scopes of practice has been well studied for decades. Prospective studies in both the cardiovascular and orthopaedic literature have shown TXA and EACA reduce blood loss and postoperative transfusion rate largely without major complications [1–3, 10, 11, 18, 23, 24, 27–29]. In addition, many meta-analyses have substantiated these results [4, 14, 16, 17, 21, 26], including a recently updated Cochrane review synthesizing data from 252 randomized controlled trials and 25,000 patients [16]. However in 2005, 85% of a surveyed group of hip and knee orthopaedic surgeons had no experience with antifibrinolytics [22]. Aprotinin, a nonlysine antifibrinolytic, was more effective at decreasing blood loss but was associated with increased cardiovascular complications and death in patients undergoing cardiac surgery and was therefore removed from the market in 2008 [12]. While no similar increased cardiovascular risk has been found with TXA or EACA, some orthopaedic surgeons remain concerned these agents could elevate the risk of thromboembolic (TE) events such as deep vein thrombosis (DVT) and pulmonary embolism (PE) after THA and TKA [15].

After having used TXA successfully in clinical practice for nearly a decade, we sought to document the relative safety of this medication in association with primary hip and knee arthroplasty. Although TXA has not been associated with increased TE rates in the aforementioned studies [1–3, 10, 11, 18, 23], concern remains about the risk of symptomatic TE events, particularly when less aggressive chemical prophylaxis methods such as aspirin or warfarin with a target international normalized ratio (INR) of less than 2.5 are chosen.

We therefore asked: When TXA is used intraoperatively in primary THA and TKA, is there a difference in the risk of symptomatic venous or arterial TE events among three chemical prophylaxis regimens, namely aspirin, adjusted-dose warfarin with an INR of 1.7 to 2.2, and dalteparin (low-molecular-weight heparin)?

Patients and Methods

We retrospectively reviewed all 2246 patients undergoing a primary THA or TKA at a single institution from 2007 to 2009 by three orthopaedic surgeons (RTT, MWP, RJS). We excluded all revisions and partial knee arthroplasties. Each surgeon followed a different TE prophylactic regimen except when comorbidities (ie, atrial fibrillation, prosthetic heart valve, thrombotic predisposition) necessitated the use of warfarin or heparin bridging therapies. As standard practice, the anesthesiologist administered TXA at a dose of 1 g intravenously at the beginning and closure of the case. We excluded 200 patients with a history of recent cerebrovascular accident (CVA), recent cardiac stent placement within 3 months, recent DVT or PE, or other anesthesiologic concern who did not receive TXA. Over that time period, 1250 primary THAs and 996 primary TKAs were performed. After excluding those not receiving TXA, 2046 patients were eligible for inclusion in the study. Patients received aspirin alone ($n = 579$), warfarin ($n = 692$), or dalteparin ($n = 775$). No patients were lost to followup, and no deaths occurred in the 90-day postoperative period. No patients were recalled specifically for this study; all data were obtained from the Mayo Clinic Joint Registry. A full chart review was performed on patients with a complication identified by the registry. The study was approved by our institutional review board.

All patients received a comprehensive, multidisciplinary approach to postoperative care with mechanical (sequential compressive device) prophylaxis in-house, regional anesthesia if appropriate, early mobilization with physical therapy, and medical optimization. Each surgeon used a standard prophylactic regimen. Aspirin treatment consisted

of 325 mg aspirin twice a day for 6 weeks beginning the night of surgery. In another cohort, warfarin was initiated with a pharmacist protocol and a target INR of 1.7 to 2.2 unless comorbidity required a higher therapeutic range with or without bridging. For those not requiring chronic anticoagulation, the INR was monitored for 3 weeks and then patients were placed on 3 weeks of twice daily 325 mg aspirin therapy. For the low-molecular-weight heparin arm, 2500 U dalteparin was injected the morning after surgery and then 5000 U for 9 more days. The remaining 5 weeks of prophylaxis was then switched to 325 mg aspirin twice a day. Primary outcome measures were any TE event in the 90-day postoperative period, including DVT, PE, myocardial infarction (MI), or CVA. Before surgery, patients were classified with an American Society of Anesthesiologists (ASA) physical status score by the anesthesia team and divided into two subgroups according to ASA score [6]: (1) those with ASA scores of less than 3 (1494 patients) and (2) those with ASA scores of 3 or greater (552 patients).

We used contingency table analysis and a Pearson chi-square test to assess differences among the three prophylactic regimens for any TE complication and individual complications. This was performed on the overall cohort and stratified between subgroups with an ASA score of less than 3 and 3 or greater. There were no missing data.

Results

When TXA was used intraoperatively in these primary THAs and TKAs, there was no detectable difference in the risk of symptomatic venous or arterial TE events among the three groups based on chemical prophylaxis regimen.

The rates of DVT were similar ($p = 0.61$) for aspirin alone (0.35%) compared to warfarin (0.14%) and dalteparin (0.52%) (Table 1). The rates of PE were also similar ($p = 0.68$): 0.17%, 0.43%, and 0.26% for aspirin, warfarin, and dalteparin therapy, respectively. There were no fatal PE. Four MIs and two CVAs occurred in the 90-day postoperative period. For the aspirin, warfarin, and dalteparin regimens, the rates of MI were similar ($p = 0.88$): 0.17%, 0.14%, and 0.26%, respectively, as were the rates of CVA ($p = 0.54$): 0.17%, 0.14%, and 0% (Table 1).

When stratified into two subgroups based on ASA score, we found no detectable differences in rates for DVT or PE (Table 2).

Discussion

Multiple meta-analyses and systematic reviews show antifibrinolytic medications such as TXA decrease blood loss and transfusion rates [4, 11–13, 15, 20]. TXA has a good safety profile, but for many orthopaedic surgeons, concerns remain about the risk of symptomatic TE events, particularly when less aggressive chemical prophylaxis methods such as aspirin or warfarin with a target INR of less than 2.5 are chosen after THA and TKA. We therefore determined whether the rate of symptomatic TE events differed among patients given intraoperative TXA when three different postoperative prophylactic regimens (aspirin, adjusted-dose warfarin, low-molecular weight heparin) were used after primary THA and TKA. In this group of 2046 patients who received intraoperative TXA, we found a consistently low risk for adverse TE events and that risk was not different among the three groups of patients based on the type of chemical prophylaxis.

There are limitations to our study. The first relates to statistical power since a sizable cohort is required to detect small differences among events that occur less than 1% of the time. However, with a power of 80%, 424 patients in each group would be required to detect a difference of 3% among complications. This reflects symptomatic DVT incidence and thus our study is adequately powered in this regard. In contrast, detecting a 1% change in an event occurring 0.1% of the time would require 936 patients in each group. The latter is more closely reflective of PE rates and indicates this study may not adequately minimize the

Table 1. Summary of rates and statistical analysis of three prophylactic regimens

Regimen	Rate (%)			
	DVT	PE	MI	CVA
Aspirin	0.35	0.17	0.17	0.17
Warfarin	0.14	0.43	0.14	0.14
Dalteparin	0.52	0.26	0.26	0
p value	0.48	0.68	0.88	0.54

DVT = deep vein thrombosis; PE = pulmonary embolism; MI = myocardial infarction; CVA = cerebrovascular accident.

Table 2. Summary of DVT and PE rates with stratification by ASA score

Regimen	Rate (%)			
	ASA score < 3		ASA score ≥ 3	
	DVT	PE	DVT	PE
Aspirin	0.45	0.23	0	0
Warfarin	0	0.23	0.39	0.78
Dalteparin	0.65	0.16	0	0.63
p value	0.26	0.96	0.56	0.60

ASA = American Society of Anesthesiologists; DVT = deep vein thrombosis; PE = pulmonary embolism.

risk of a Type II error for this event. Second, although the joint registry provides a formal, organized system to follow outcomes of patients, it requires the accurate reporting of complications occurring in the postoperative period. This difficulty is highlighted by the fact that many times patients are from different geographic regions and may be followed locally. This may underreport the number of complications. We focused on the 90-day risk of each of the outcome variables and had complete records for all patients. The ASA physical status score, as a general sense of patient morbidity, does not account for the many gradations of moderate illness between a score of 2 (mild systemic illness) and 3 (severe systemic illness), nor does it differentiate between patients at a higher risk of TE events per se. Third, confounding variables may exist with individual surgeon technique within specific prophylactic groups, as well as the lack of documenting unique, presurgical medical conditions that may predispose patients to TE events such as a previous DVT or PE.

Despite previous suppositions that clots formed in the venous circulation are not commonly platelet based but rather protein and erythrocyte based [5], aspirin therapy alone reduces the risk of both DVT and PE. In the Antiplatelet Trialists' Collaboration Part III review of 52 trials and 8400 patients [25], DVT and PE risks were nearly halved with aspirin in a wide range of surgical patients, with a greater reduction in higher-risk orthopaedic patients compared to placebo. Furthermore, in the Pulmonary Embolism Prevention multicenter trial of 17,444 patients with hip fractures undergoing elective arthroplasties randomized to either low-dose aspirin (160 mg) or placebo, DVT and PE risks were reduced with aspirin by 29% and 43%, respectively [25]. However, controversy continues with regard to the appropriate postoperative prophylactic regimen as evidenced by discordant guidelines by both the American Academy of Orthopaedic Surgeons (AAOS) in 2009 and the American College of Chest Physicians (ACCP) in 2008 for patients with a standard risk of venous TE [9, 13, 15, 20]. Even in patients receiving TXA to prevent blood loss, our rates of DVT and PE in the aspirin prophylactic regimen were similar to those for warfarin and dalteparin and did not change when stratified by ASA score. Dorr et al. [7] found a similar rate (0.4%) of clinically symptomatic DVT utilizing a standard low- versus high-risk venous TE assessment for prophylaxis and the majority of patients received antiplatelet therapy alone. However, a recently published prospective study [19] compared venous TE rates between utilization of the AAOS PE risk stratification versus the ACCP anticoagulation guidelines and showed an increased rate of any venous TE complication (7.9% compared to 1.2%). Specifically for symptomatic PE and DVT, both rates were 4.6% in the AAOS PE risk-stratified group compared to 0.7% in the ACCP group. This continues to raise questions about the efficacy of aspirin therapy alone in total joint arthroplasty but also the inadequate detection and appropriate stratification of higher-risk patients.

Surgeons and hospitals may be interested in considering the use of an antifibrinolytic agent such as TXA as part of a strategy to decrease blood loss and decrease transfusion after hip and knee arthroplasty. We have used TXA in our practice for the past decade with supportive data from the literature documenting its effectiveness. Our study begins to answer, but certainly is not definitive in answering, questions on the safety of TXA in elective hip and knee arthroplasty. In this study, we found TXA was associated with a low risk of symptomatic TE events when used with three different chemical prophylactic regimens after routine primary THA and TKA. During the time frame of our study, TXA was not routinely used in patients judged to be at high risk of TE disease and so we lack the ability to comment scientifically on the relative safety of TXA in patients with a recent cardiac stent, a recent history of another TE event, or a strong family history of TE complications. However, for the vast majority of patients undergoing elective THA or TKA in our practice, TXA is used as part of a comprehensive strategy to decrease blood loss and transfusion.

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