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Venous Thromboembolism and Mortality Associated With Tranexamic Acid Use During Total Hip and Knee Arthroplasty

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ABSTRACT

TKA and THA are associated with blood transfusion and risk for postoperative venothromboembolism (VTE). Reports show that tranexamic acid (TA) may be safe to use in high-risk orthopedic patients, but further data are needed to substantiate its use. All patients who underwent primary or revision TKA or THA in a five year period were retrospectively identified. In 13,262 elective TKA or THA procedures, neither the odds of VTE (OR = 0.98; 95% CI 0.67-1.45; $P = 0.939$) or adjusted odds of death (OR = 0.26; 95% CI 0.04-1.80; $P = 0.171$) were significant with TA administration. The major findings of this large, single center, retrospective cohort study show the odds of postoperative VTE and 30-day mortality were unchanged with TA administration.

There is compelling evidence demonstrating a beneficial blood-sparing effect of tranexamic acid (TA) administration in total joint arthroplasty, but unanswered questions remain regarding its potential safety [1–12]. It is well known that synthetic lysine antifibrinolytics such as tranexamic acid prevent clot breakdown by reducing fibrin degradation [13]. While this process reduces blood loss, there is concern that reduction in clot breakdown may increase the risk of postoperative venous thromboembolism (VTE) or death [14,15], especially in procedures associated with high risk for VTE (e.g., THA, TKA) or among "high risk" patients with pre-existing veno-occlusive diseases (e.g., myocardial infarction, stroke, previous VTE). Few studies have tried to directly address the question of TA use in these populations [16].

Total hip and knee arthroplasty have historically been associated with high transfusion rates. Approximately half of patients undergoing lower extremity joint arthroplasty required two units of packed red blood cells to maintain adequate hemoglobin levels [17]. Reported negative effects of blood transfusion include immunosuppression, transfusion reaction, and increased cost [15,18–21]. In addition, blood product transfusion may increase the risk of periprosthetic joint infection [22]. Tranexamic acid has the potential to reduce these transfusion-associated complications as well as decrease the cost of care. TA administration has been shown to reduce the direct hospital cost of joint arthroplasty in healthy patients, and may have an even greater impact in high morbidity patients [23].

While previous studies have reported the frequency of adverse thrombolic events in patients undergoing TKA and THA [24,25], no adequately powered prospective studies have specifically investigated the frequency of VTE in patients receiving TA. Studies examining the hemostatic role of TA have been powered to detect differences in blood loss and blood transfusion. These studies have not been adequately powered to detect frequencies of VTE and all-cause mortality in association with TA administration [1,2,4–6,8,10–12]. Another important limitation of previous investigations of TA in orthopedic surgery is that they have excluded patients with significant pre-existing cardiovascular and thromboembolic disease [2,3,26,27], leaving open the question of whether TA should be administered to high risk patients. Only a single preliminary study has evaluated the role of TA in high risk patients, showing a slight increase in the odds of postoperative VTE with TA administration [16]. Therefore, the objective of this large, single center, retrospective cohort study was to define the frequency of clinically-significant VTE and all-cause mortality within 30 days of surgery in patients who did and did not receive TA for primary and revision THA and TKA. We hypothesized that TA administration would not increase the frequency of VTE within 30 days of TKA or THA.

Material and Methods

After institutional review board approval, the Orthopedic Department Total Joint Registry (TJR) was searched to identify all patients

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who underwent primary or revision TKA or THA at our institution between January 1, 2005 and January 1, 2010. The TJR is a previously validated and comprehensive repository of data collected for each joint arthroplasty surgery performed at our institution since 1969 [28]. Data included within the TJR have been prospectively defined; and are collected by manual chart review, written patient questionnaire, and follow-up telephone surveys by full-time research assistants unaware of the current study hypothesis. Patients denying access to their medical or administrative records for research purposes were excluded as per Minnesota statute. Patients undergoing simultaneous bilateral procedures were also excluded, as was one patient undergoing both knee and hip arthroplasty due to osteosarcoma. For patients who underwent two joint arthroplasty surgeries within a 30 day period, only the second surgery was included in the analysis.

Patient demographic data (age, gender, weight, and height), date of surgery, surgeon, joint (TKA or THA), side of surgery (right or left), VTE and mortality were collected from the TJR. Height and weight were confirmed by electronic data mining of the medical record. After manual record extraction for missing values, a BMI was calculated for all but four patients who had missing height or weight information. The American Society of Anesthesiology Physical Status (ASA-PS) data were identified by electronic query of the anesthesia record and medical record.

The primary outcome variable was presence of clinically significant VTE within 30 days of the date of surgery. Cases of clinically significant VTE were identified from the TJR. The TJR has a dedicated support staff that read all follow-up notes, including phone conversations and radiologic reports each time a patient returns for follow-up. Thromboembolic events are recorded in the TJR if: 1) DVT and/or PE was documented in the medical record by the primary surgeon or 2) if there was radiologic evidence (i.e., ultrasound or computed tomography report) in the medical record documenting the presence of a DVT or PE. Although the collection methods of the TJR have been previously validated for other outcomes [24,29,30], additional validation of the TJR was confirmed through manual chart review of 200 randomly selected patients (100 patients with VTE, 100 patients without VTE). In all 200 patients, the TJR diagnosis of VTE (positive or negative) was confirmed. Patients experiencing multiple events were only counted once.

Following identification of all primary or revision TKA or THA procedures during the 5-year study period, patients who received TA were identified by electronic query of the perioperative datamart. The Perioperative datamart is the access layer of an institutional data warehouse containing detailed information regarding aspects of a patient's surgical encounter (e.g., demographic information, procedural descriptions, locations, start and stop times, detailed physiologic information including vital signs, ventilator data, laboratory information, and fluid, transfusion and medication administration information) [31]. The decision to administer TA was based on surgeon request and judgment of the attending anesthesiologist. Per standard TA protocol, 1000 mg was infused prior to incision and 1000 mg was infused immediately prior to closure. The primary regimen of postoperative anticoagulation was determined using patient medication administration records and/or hospital discharge summaries. Patients were assigned to the following monotherapy anticoagulation groups: aspirin, heparin, low molecular weight heparin (LMWH), or warfarin. If a patient received LMWH as a bridge to warfarin anticoagulation, they were assigned to the warfarin group. A patient who received both warfarin and aspirin following surgery was assigned to the warfarin group. Patients receiving LMWH followed by aspirin were assigned to the LMWH group.

Statistical Analysis

The primary aim of this study was to calculate the frequency and risk of clinically-significant VTE in patients who received TA and in those patients who did not receive TA. Similarly, the secondary aim was to calculate the frequency and risk of all-cause mortality in both the TA cohort and non-TA cohort.

Because many patients (>15%) had more than one surgery included in the cohort, the analysis was performed using a generalized linear model framework utilizing generalized estimating equations to properly account for the within-patient correlation. Within this analysis framework, the association of TA use (as well as other risk factors including demographics, patient characteristics, and surgical factors) with the primary outcomes of (1) VTE within 30 days of surgery, and (2) all-cause death within 30 days of surgery were evaluated using logistic regression. Odds ratios are reported with 95% confidence intervals. Because of differences in the populations that received TA and did not receive TA, a propensity score was developed to estimate the probability that a patient received TA conditional on observed patient and surgical data. The propensity score was generated using a logistic regression model, with TA or no TA as the outcome variable, and demographic, clinical, and surgical data as the independent variables. The fitted values from this model represent the propensity that a patient received TA given the observed demographic, clinical, and surgical factors. This propensity score was included as an adjusting covariate in the final multivariable model for each outcome along with an indicator for TA to minimize the potential bias between the TA and no TA groups. Data were summarized as mean (standard deviation) for continuous variables, and count (percentage) for categorical outcomes, unless otherwise noted. All statistical tests were two-sided and *P*-values less than 0.05 were considered significant. All analysis was conducted in SAS version 9.2 (SAS Institute, Inc., Cary, NC).

Results

During the study period, a total of 14,100 cases were initially identified. After exclusions, a total of 13,262 elective TKA or THA procedures in 11,175 unique patients were analyzed (Fig. 1). Patient demographic information is summarized in Table 1. At the time of surgery, 71% of subjects were over the age of 60 (median age 67 years). Tranexamic acid was administered intraoperatively in 2785 procedures (21%).

A total of 196 VTE events were identified for an overall frequency of 1.48%. Thirty-seven VTE events (1.3%) were identified among 2785 procedures in which patients received TA, while 159 VTE events (1.5%) were identified among 10,477 procedures in which patients did not re-

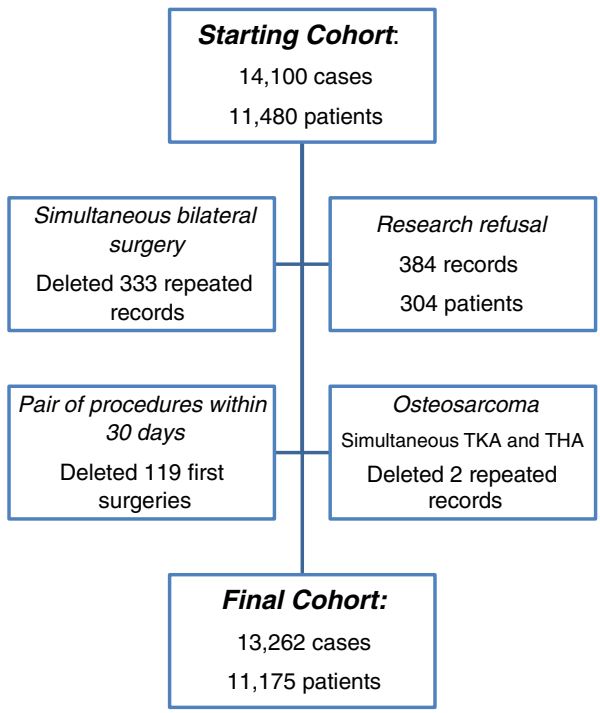

Fig. 1. Determination of final study cohort.