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Perioperative Tranxemic Acid: A Game-Changer for Hip, Knee, and Spine Surgery Safety

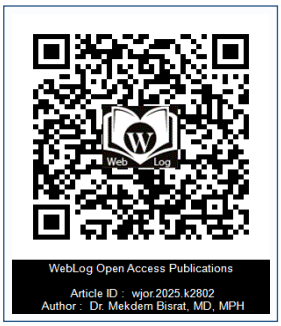
Dy'Quan Kearney[1], Amari Eubanks[1], Syed Fahad Gillani[4], Edward Arenas[1], Elijah McMillian[1], Mekdem Bisrat[2], Elizabeth Beyene[2] and Miriam Michael[2,3]*

[1]College of Medicine, Howard University, Washington, DC, USA

[2]Department of Internal Medicine, Howard University, Washington, DC, USA

[3]Department of Internal Medicine, University of Maryland School of Medicine, Baltimore, USA

[4]King Edward Medical University, Lahore, Pakistan



Abstract

Background: Tranexamic acid (TXA) is widely used in orthopedic surgeries to reduce blood loss, but concerns persist regarding its association with thromboembolic complications. This study aimed to compare the incidence of thromboembolic events in patients undergoing spine, knee, or hip surgeries with and without perioperative TXA administration.

Methods: Using TriNetX, a federated electronic health record network, we identified 406,609 matched patients in each cohort: one receiving TXA and one not receiving TXA during orthopedic surgery. Propensity score matching was performed on demographics and comorbidities. Outcomes included the incidence of thromboembolic events within one day post-surgery. Statistical analyses included risk ratio, odds ratio, Kaplan-Meier survival analysis, and t-tests.

Results: The TXA group demonstrated a lower incidence of thromboembolic events (0.060%) compared to the non-TXA group (0.089%), corresponding to a risk ratio and odds ratio of 1.478 (95% CI: 1.257, 1.739, $p < 0.0001$). Kaplan-Meier analysis did reveal a significantly higher event-free survival in the TXA group (99.940% *vs*. 99.911%, $p < 0.0001$).

Conclusions: This large-scale, real-world analysis demonstrates that TXA use in orthopedic surgery is associated with a significantly reduced risk of early postoperative thromboembolic events. The results support TXA's continued use in perioperative protocols, with no evidence of increased event burden among affected patients. Future studies should evaluate longer-term outcomes and specific surgical subtypes.

Keywords: Tranexamic Acid; Spinal Orthopedic Surgery; Total Knee Replacement; Total Hip Replacement; Thromboembolism; Deep Vein Thrombosis; Pulmonary Embolism

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Correspondence:
Dr. Mekdem Bisrat, MD, MPH, Department of Internal Medicine, Howard University, Washington, DC, USA, Tel: 240-425-2256; E-mail: mekdembisrat21@gmail.com

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Introduction

Tranexamic acid (TXA) is a lysine derivative used to stabilize blood clots and reduce blood loss [1]. Once blood clots are formed they must be broken down, this breakdown is initiated with a process known as fibrinolysis, the breakdown of blood clots by dissolving fibrin. The key enzyme responsible for fibrinolysis is plasmin. By inhibiting plasminogen, a precursor to plasmin, TXA directly suppresses fibrinolysis [1]. Due to the efficiency and direct impact TXA has on bleeding, it is most commonly used for nosebleeds and heavy menstrual cycles, but it has also been indicated to be used in trauma cases, postpartum hemorrhage, hemophilia patients, and orthopedic surgeries [2].

Many orthopedic surgeries tend to be associated with high levels of blood loss. Previous studies have shown that total knee replacement surgeries can lead to a blood loss of 726–1768 mL, and total hip replacement surgeries can lead to a blood loss of 1188–1651 mL [3]. Spinal surgeries also tend to be associated with high levels of blood loss, as the average blood loss in a spinal fusion surgery is 1122 mL [4]. TXA has the potential to lower blood loss during orthopedic surgeries. Meta-analysis conducted by Kim et al. found that the use of TXA during TKA resulted in 30% less blood loss and ultimately reduced blood transfusions [5]. In another study it was found that the use of TXA in fracture surgeries reduced blood loss by 330 mL and reduced the transfusion rate with a risk of 0.54 and decreased the drop of hemoglobin by 0.76 g/dL [6]. These studies indicate that TXA is effective at reducing blood loss and should be implemented in surgeries. Though TXA has been proven to

be effective, it is still underutilized by surgeons. A survey conducted in 2018 found that 57% of anesthesiologists were uncertain about the benefits and risks associated with using TXA preoperatively [7]. This study demonstrates the need to study TXA more, as it can significantly reduce bleeding during surgery and the need for blood transfusions.

One of the limitations to TXA is that it is known to cause seizures at high doses. When TXA was given at 80–109 mg/kg (high dose) the incidence of seizures greatly increased [8]. The effective dose of TXA was determined to be 10-15 mg/kg of body weight, which is well under the amount that was shown to induce seizures [8]. Another limitation to TXA is that physicians worry that the use of TXA during surgery could lead to complications such as venous thromboembolism [9]. Though venous thromboembolism (VTE) is a common concern, recent studies have indicated that the use of TXA does not increase the risk in healthy patients. In fact, a study on the use of TXA in trauma patients found that the risk factor for VTE was independent of the use of TXA [9]. These results are pivotal, as it counters one of the main arguments physicians have in the use of TXA. With further research to better understand the use of TXA and its side effects, it can have a major influence on surgical outcomes.

The purpose of this analysis is to further analyze the direct impact of TXA on VTE within the first 24 hours following surgery. This idea is important because TXA has a half life of 2 hours when given by IV and 11 hours when given orally [2]. Therefore to examine only the impact of TXA on the development of VTE, it is important to analyze these outcomes within the first 24 hours postoperatively when given TXA preoperatively. This would create a better understanding of the direct effects and minimize confounding factors.

Methods

Study Design

This retrospective cohort study utilized data from the TriNetX Global Collaborative Network, comprising 147 healthcare organizations (HCOs) and providing access to electronic medical records from a total of 148,972,479 patients. Patients that underwent spinal or knee orthopedic surgery were eligible for this study. Two cohorts were identified - patients who underwent recent surgery with tranexamic acid (TXA) and patients who underwent recent surgery without the use of tranexamic acid. Patients with a history of embolism or thrombosis prior to surgery were excluded from this study.

Patients were included in the TXA cohort if they recently experienced arthrodesis (surgical immobilization of a joint) of the lumbar with and without laminectomy or discectomy (UMLS CPT codes: 22612, 22630, 22633, 22551, 22558, 27446, 27447, 27130) and they took TXA (NLM:RXNORM:10691) pre-operatively or during the surgery. Patients with acute or chronic embolism and thrombosis, acute or chronic pulmonary embolism, or a personal history with other venous thrombosis and embolism prior to the instance of surgery were excluded. A total of 380,879 patients were included in this cohort.

Patients were included in the non TXA cohort if if they recently experienced arthrodesis (surgical immobilization of a joint) of the lumbar with and without laminectomy or discectomy (UMLS CPT codes: 22612, 22630, 22633, 22551, 22558, 27446, 27447, 27130) and they did not use TXA pre-operatively or during the surgery. Patients with acute or chronic embolism and thrombosis, acute or chronic pulmonary embolism, or a personal history with other venous thrombosis and embolism prior to the instance of surgery were excluded. A total of 783,540 patients were included in this cohort.

The index event was defined as any thromboembolism or thrombosis onset 24 hours after surgery. The primary outcome was acute or chronic embolism or thrombosis defined by the following ICD codes and conditions: acute or chronic thromboembolism or thrombosis of veins (ICD-10 codes I82.4x, I82.5x, I26, I27.82, etc).

Data Analysis

To reduce confounding, a 1:1 propensity score matching was performed using the following covariates: age at index, sex, race, ethnicity, chronic kidney disease, lupus erythematosus, Crohn's disease, and Ulcerative Colitis. Matching resulted in balanced cohorts of 406,609 patients each, ensuring comparability. The increase in total matched patients increased for the group that did not receive TXA due to the TriNetX platform's propensity score matching algorithm, which draws from the entire patient population that meets the inclusion/exclusion criteria at the time of matching. TriNetX identified additional eligible patients during matching that were not included in the original cohort count due to dynamic data availability or system-level filtering, allowing a larger matched sample to be constructed with balanced characteristics. In addition, a total of 1,086 patients were excluded from the non-TXA group and 943 patients from the TXA group were also excluded from the final outcome analyses due to having a thromboembolic event prior to the time window, leaving the matched cohort at 405,666 patients in the TXA group and 405,532 in the non-TXA group.

Statistical Analysis

TriNetX's analytical tools were used for propensity score matching and statistical analyses. Risk calculations such as absolute risk, risk difference, risk ratio, and odds ratio provided an assessment of the proportion of patients diagnosed with postoperative thromboembolic events in each cohort. Survival analysis used Kaplan-Meier survival curves with long-rank testing and hazards ratios to estimate the time period to diagnose. Frequency comparisons evaluated the number of degeneration related diagnoses during the study period. Statistical significance was determined at a two-sided p-value < 0.05.

Ethical Considerations

This retrospective study is exempt from informed consent. The data reviewed is a secondary analysis of existing data, does not involve intervention or interaction with human subjects, and is de-identified according to the de-identification standard defined in the HIPAA Privacy Rule.

Index Event and Time Window

The index event was defined as the date of the qualifying orthopedic surgical procedure. Outcomes were analyzed within a time window spanning from the day of surgery to the day after, capturing early postoperative thromboembolic events.

Outcome Definitions

The primary outcome was a composite of thromboembolic complications, including deep vein thrombosis and pulmonary embolism, defined using ICD-10 codes. Events were counted if they occurred within the defined time window.

Propensity Score Matching

To reduce confounding, 1:1 propensity score matching was performed between the TXA and no-TXA groups using logistic

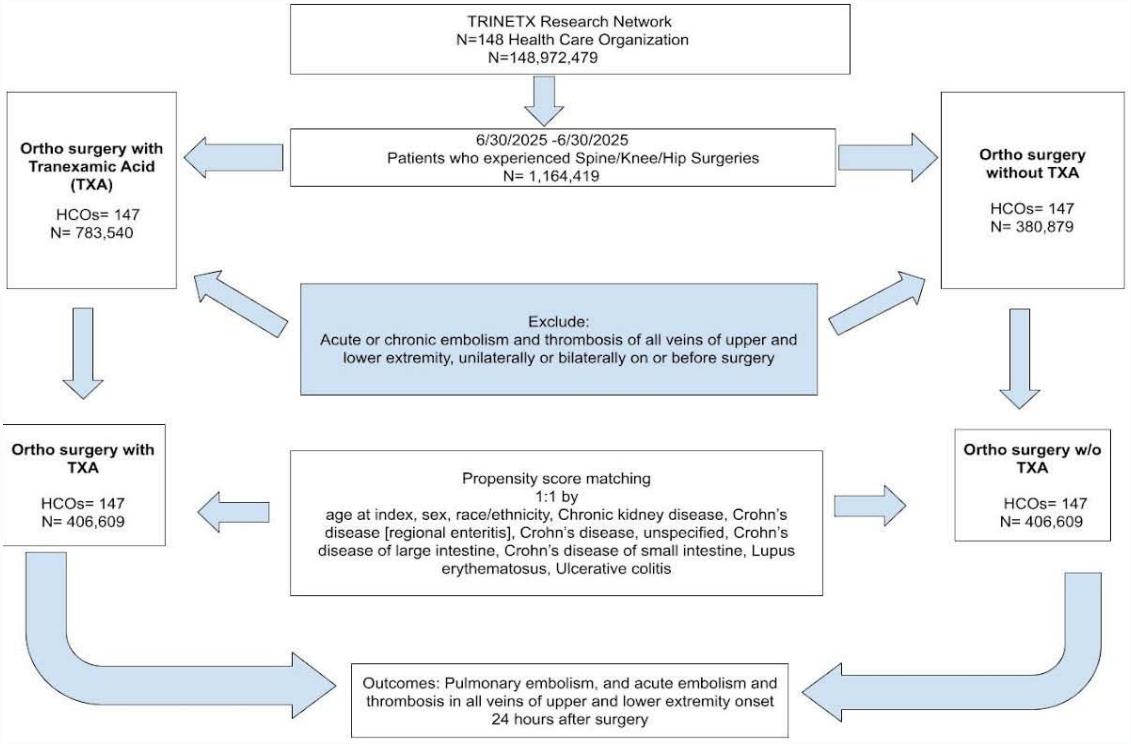

Figure 1: Cohort Selection Flow Diagram.

regression. Matching variables included age, sex, race/ethnicity, and baseline comorbidities (including chronic kidney disease, lupus, and inflammatory bowel diseases). After matching, each cohort consisted of 406,609 patients.

Statistical Analysis

We conducted risk analysis to estimate the proportion of patients with events in each cohort and calculated risk ratios (RR), odds ratios (OR), and their 95% confidence intervals (CI). The statistical significance of the proportions was tested using a Z-test. Kaplan-Meier survival analysis assessed the time-to-event distribution, with differences between survival curves tested via the log-rank test. Hazard ratios (HR) were calculated with Cox proportional hazards models. A t-test was used to compare the number of outcome instances per patient. Significance was set at $p < 0.05$. Analyses were performed using the TriNetX analytics platform.

Inclusion and Exclusion Criteria

See Figure 1.

Results

Pre-operative TXA use in patients undergoing orthopedic hip, spine, and knee surgeries was associated with a decreased risk of developing venous thromboembolism (VTE) within 24 hours after surgery. In the group that did not receive TXA (Cohort 1), 362 out of 405,532 patients (0.089%) developed a VTE within the 24-hour postoperative window. In contrast, among patients who received TXA (Cohort 2), 245 out of 405,666 (0.06%) experienced a VTE in the same timeframe. These values reflect outcomes among matched patients following conditional exclusions. Risk percentages for each group are illustrated in Figure 2. This analysis yielded a risk ratio of 1.478 (95% CI: 1.257–1.738), an odds ratio of 1.478 (95% CI: 1.257–1.739), and a risk difference of 0.029% (95% CI: 0.017%–0.041%; z = 4.755; $p < 0.0001$) (Table 1). These findings indicate that patients who received TXA prior to orthopedic surgery had approximately a 32.6% lower risk of developing a VTE compared to those who did not receive TXA.

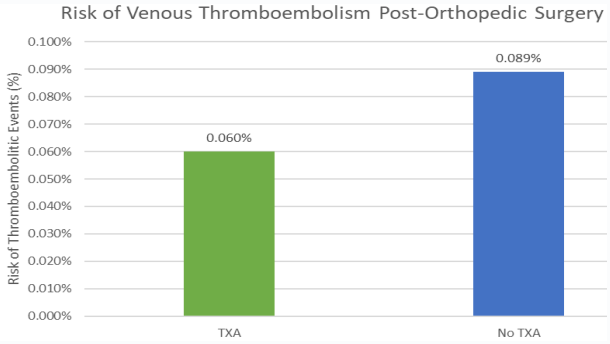

Figure 2: Column chart comparing the risk of thromboembolic events following orthopedic surgery in groups that received or did not receive TXA.

To further evaluate time-to-event differences between the groups, a Kaplan-Meier survival analysis was conducted.The probability of surviving 24 hours without a thromboembolic event with TXA was slightly greater than not having TXA, but still showed statistical significance (99.940% *vs.* 99.911%, log-rank test: $\chi 2 = 22.612$, df = 1, $p < 0.001$). A hazard ratio of 1.478 demonstrated an increased hazard with not using TXA compared to surgeries that utilized TXA, but this number was not statistically significant ($p = 0.199$). Overall, there is a statistically significant difference in the survivability of the two cohorts, but there is not a significant instantaneous hazard between groups (Figure 3).

Overall, the results outlined in Table 1 demonstrate that TXA

Table 1: Comparison of postoperative venous thromboembolic outcomes in TXA *vs* No-TXA groups.

Measure	TXA Group	No-TXA Group
Patients in Group (Matched)	406,609	406,609
Patients Included in Analysis	405,666	405,532
Number of Events	245	362
Risk (%)	0.0226%	0.0368%
Survival Probability (%)	99.940%	99.911%

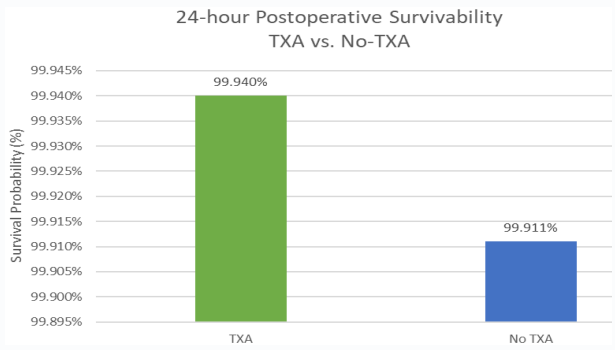

Figure 3: Column chart comparing the survival probability, or the chance that patients will be outcome free for 24 hours post surgery in patients that did or did not receive TXA.

administration in the setting of orthopedic surgery is associated with a statistically significant reduction in the early postoperative risk of thromboembolic events without an increase in the frequency of events among those affected. These findings remained consistent across some of the statistical approaches, including risk comparison and survival analysis. These results therefore support the safety and efficacy of TXA in this context.

Discussion

Thromboembolic complications, including deep vein thrombosis (DVT) and pulmonary embolism (PE), are among the most serious and potentially fatal outcomes following major orthopedic surgeries, especially of the spine, hip, and knee. These events arise from a combination of factors such as prolonged immobility, the inflammatory response to tissue trauma, venous stasis during surgery, and the release of thromboplastin from soft tissue and bone. The incidence of asymptomatic DVT without prophylaxis after major lower limb orthopedic surgery ranges from 30% to 80% [10].

Tranexamic acid (TXA), an antifibrinolytic agent that prevents clot breakdown by inhibiting the binding of plasminogen to fibrin, is widely used in orthopedic surgeries to reduce blood loss. However, concerns remain regarding its potential to increase thromboembolic risk by stabilizing clots. Previous studies have reported mixed outcomes. For instance, Babtain et al. found no significant association between TXA and venous thromboembolism (VTE) [12], while another study reported a higher VTE rate with TXA use (15.3% *vs.* 7.4%) [13]. These discrepancies highlight the need to evaluate TXA's safety profile in different contexts.

Our propensity score-matched retrospective cohort study found that TXA use was associated with a significantly lower incidence of postoperative thromboembolic events: 0.060% in the TXA group versus 0.089% in the non-TXA group, with an odds ratio of 1.478. Kaplan-Meier analysis confirmed that patients in the TXA group had a higher 24-hour event-free survival probability (99.940% *vs.* 99.911%). These findings are consistent with a meta-analysis by Fillingham et al., which suggested that TXA may reduce VTE risk in orthopedic patients [11].

A possible explanation for these findings lies in TXA's broader physiologic effects. TXA reduces the need for blood transfusions, a known risk factor for VTE. One systematic review showed that TXA reduced transfusion need by one-third [14], and transfusion itself increases VTE risk nearly threefold [15]. Furthermore, TXA may exert anti-inflammatory effects by upregulating anti-inflammatory genes [16], potentially further reducing thromboembolic risk in the postoperative setting.

To isolate the immediate postoperative effects of TXA, our study focused on VTE events occurring within 24 hours of surgery. This timeframe aligns with the pharmacokinetics of TXA, which is renally cleared within approximately 24 hours [17]. The early divergence of survival curves in our analysis reinforces the hypothesis that TXA offers protective effects shortly after surgery.

The pharmacologic mechanism of TXA, namely, clot stabilization without systemic prothrombotic effects, helps explain the observed reduction in thromboembolic events. Greater blood loss and fluid shifts in patients not receiving TXA may trigger compensatory responses that elevate thrombotic risk [18]. Studies suggest that TXA does not increase systemic thromboembolism risk when appropriately used, especially in patients without prior clotting disorders [19].

Our findings align with other literature suggesting that TXA does not elevate thrombotic risk despite its antifibrinolytic action [20, 21]. Additionally, we found no evidence that TXA use increases recurrence of thromboembolic events, based on the similar number of total events across cohorts.

Nonetheless, some studies offer contrasting results. Sara P. et al. analyzed a small sample (217 TXA users) from trauma centers and reported a threefold increase in odds of VTE among TXA recipients [22]. Similarly, increased VTE risk was observed over a 30-day period in patients undergoing total knee and hip arthroplasty [23]. These findings could be influenced by factors such as TXA dosage, patient age, and length of follow-up.

In conclusion, our data support the use of TXA in orthopedic surgery not only for blood conservation but also for its favorable thrombotic safety profile. These findings have practical implications for perioperative decision-making and underscore the need to consider multiple physiologic and pharmacologic pathways when evaluating thromboembolic risk.

Strengths, Limitations, and Future Directions

The strength of this analysis lies in its large sample size and rigorous propensity score matching. However, the short 1-day follow-up period may underestimate the occurrence of delayed complications. Further research with extended time windows and exploration of subgroup differences (e.g., spine *vs.* joint surgery) would enhance understanding of TXA's safety and efficacy across diverse orthopedic populations.

Conclusion

This large-scale, real-world analysis demonstrates that TXA use in orthopedic surgery is associated with a significantly reduced risk

of early postoperative thromboembolic events. The results support TXA's continued use in perioperative protocols, with no evidence of increased event burden among affected patients. Future studies should evaluate longer-term outcomes and specific surgical subtypes.

Declarations

Use of Generative AI

Generative artificial intelligence (AI), specifically OpenAI's ChatGPT, was used to assist in refining the language, and grammar of the manuscript. All content was reviewed, validated, and approved by the authors to ensure accuracy, originality, and adherence to ethical standards. No AI tool was used to generate data, perform analysis, or draw scientific conclusions.

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