COPYRIGHT 2025 © BY THE ARCHIVES OF BONE AND JOINT SURGERY

RESEARCH ARTICLE

Comparative Efficacy and Safety of Intravenous vs. Combined Intravenous and Intraarticular Tranexamic Acid Administration in Total Knee Arthroplasty: A Stratified Analysis Based on Bleeding Risk

Serban Dragosloveanu, MD, PhD; Bogdan-Sorin Capitanu, MD; Calin Ion Dragosloveanu, MD, PhD; Alexandra-Ana Mihailescu, MD; Mohammadali Enayatollahi, MD; Cristian Scheau, MD, PhD

Research performed at Foisor Clinical Hospital of Orthopaedics, Traumatology and Osteoarticular Tuberculosis, Bucharest, Romania

Received: 28 December 2024 *Accepted: 1 March 2025*

Abstract

Objectives: Tranexamic acid (TXA) effectively reduces blood loss in total knee arthroplasty (TKA) without raising thromboembolism risk, though the best administration route is still debated. This study aimed to classify patients based on bleeding risk factors and determine whether intravenous (IV) alone or combined IV and intraarticular (IA) administration of TXA provides the greatest benefit.

Methods: This study included 200 patients who underwent TKA, with 100 patients with IV administration only and 100 with combined IV and IA administration. The bleeding risk stratification criteria were based on patient body mass index, age, the use of increased anticoagulant doses in patients with atrial fibrillation, and cases where synovectomy was performed. The primary outcomes measured were tube drainage volume, hemoglobin (Hb) and hematocrit (Ht) levels, and blood transfusion rates. Secondary outcomes included wound complications, symptomatic deep vein thrombosis (DVT), and symptomatic pulmonary embolism (PE).

Results: Combined IV and IA administration showed better outcomes in terms of Hb reduction (difference of 0.98 g/dl, 95%CI: 0.69 to 1.26, P<0.0001), Ht reduction (difference of 2.66%, 95% CI: 1.78 to 3.54, P<0.0001), tube drainage (294 vs 358 ml, 95% CI: 11.58 to 115.93, P=0.0170) and shorter hospitalization stay (difference of 0.53 days, 95% CI: 0.16 to 0.90, P=0.0050) compared to only IV administration. Patients who underwent synovectomy had lower tube drainage with combined TXA administration compared to IV only (355.42 ± 161.68 ml vs. 429.79 ± 268.48 ml). Neither group experienced any cases of symptomatic (i.e. DVT) or pulmonary embolism (PE).

Conclusion: The combined administration of TXA (IV and IA) in patients undergoing TKA was more effective than IV-only administration.

Level of evidence: II

Keywords: Bleeding risk, Enhanced recovery after surgery, Intraarticular TXA, Intravenous TXA, Physiopathology, Total knee arthroplasty, Tranexamic acid

Introduction

Knee osteoarthritis (OA) is a progressive degenerative condition that leads to chronic pain and joint instability, severely affecting quality of life. In advanced stages, total knee arthroplasty (TKA) is the most effective treatment, and with longer life expectancy and rising obesity rates, the demand for TKA is increasing.[1,2]

However, while TKA significantly improves joint functionality, it often results in considerable blood loss, which may necessitate allogenic blood transfusions. These transfusions carry various risks, including infections, fluid overload, and even increased mortality, in addition to raising medical costs.[3,4] Transfusion rates for TKA can range from 3.5% to 18.5%. To reduce blood loss, several strategies are employed, such as tourniquets, drain clamping, minimally invasive techniques, hypotensive anesthesia, and pharmacological agents like anti-fibrinolytics.[5,6]

Among these agents, Tranexamic acid (TXA), a synthetic antifibrinolytic, has proven to be effective in preventing the

Corresponding Author: Alexandra-Ana Mihailescu, Department of Anesthesiology and Critical Care, "Foisor" Clinical Hospital of Orthopaedics, Traumatology, and Osteoarticular Tuberculosis, Bucharest, Romania

Email: hassaninalkaduhimi@gmail.com

THE ONLINE VERSION OF THIS ARTICLE ABJS.MUMS.AC.IR

Copyright © 2025 Mashhad University of Medical Sciences. This work is licensed under a Creative Commons Attribution-Noncommercial 4.0 International License https://creativecommons.org/licenses/by-nc/4.0/deed.en

breakdown of blood clots by inhibiting plasminogen's conversion to plasmin. It stabilizes blood clots and is widely used to manage bleeding, significantly reducing mortality with minimal side effects.[5] In TKA, TXA is most commonly administered intravenously, although intra-articular (IA) administration, either through a topical wash or post-surgical injection into the knee joint, has recently gained popularity.[7]

Recent studies highlight that both IV and IA TXA effectively reduce blood loss in TKA, with the combination of both methods providing optimal results in minimizing blood loss without increasing the risk of thromboembolic complications. While the precise half-life of IA TXA remains less understood, studies indicate that local administration leads to extended retention in the joint and slower systemic absorption, potentially lengthening its local half-life.[5,7,8] However, despite the abundant evidence supporting TXA's effectiveness, there is a gap in research regarding which patient subgroups, especially those at higher bleeding risk, derive the greatest benefit from its use.[7,9-11]

Stratifying patients into bleeding risk categories based on factors such as age, BMI, anticoagulant use for atrial fibrillation, and those who have undergone synovectomy during TKA surgery is crucial for better understanding the impact of TXA on outcomes. By identifying the most effective method of TXA administration tailored to specific subgroups, healthcare providers can maximize the benefits while minimizing complications.

This study seeks to evaluate the efficacy of administering TXA either intravenously alone or in combination with intra-articular TXA in various patient subgroups undergoing TKA, aiming to identify which subgroup benefits most from TXA treatment.

Materials and Methods

Study Design

This cross-sectional retrospective study was carried out at the "Foisor" Clinical Hospital of Orthopaedics, Traumatology, and Osteoarticular Tuberculosis between July 2023 and August 2024. Ethical approval was granted by the Ethics Council of the "Foisor" Clinical Hospital of Orthopaedics, Traumatology, and Osteoarticular Tuberculosis, under the assigned registration number 11226/2024. Written informed consent was obtained from all participants involved in the study. The research adhered to the ethical principles outlined in the Declaration of Helsinki (1964) and its subsequent amendments.

Study group

Between July 2023 and August 2024, a total of 200 patients meeting the inclusion criteria were enrolled in this study. An updated surgical protocol including both IV and IA TXA administration for patients and based on existing literature evidence and protocols (AAOS/AAHKS/ASRA guides) replaced the previous practice of using only IV TXA. Participants were assigned into two groups (IV only group and combined IV and IA group), each comprising 100 individuals (80 females, 20 males). The adequacy of the sample size was determined using a propensity score analysis. All participants received 1 gram of TXA 15 minutes prior to incision. In IV only group, an additional 1 gram of TXA was administered intravenously 30 minutes before the release of the drain clamp. In combined group, 1 gram of TXA was administered intraarticularly through the drain tube following wound closure.

Inclusion and exclusion criteria

The study included patients with symptomatic advanced knee osteoarthritis, classified as Kellgren-Lawrence grade three or four on radiological examination, who were scheduled for TKA. To ensure uniformity of results, only patients treated by the same surgeon and anesthesiologist were included, with all receiving spinal anesthesia. Additional inclusion criteria required participants to have normal renal function and stable chronic diseases.

Exclusion criteria were as follows: (1) patients with cerebrovascular conditions (e.g., prior stroke or vascular surgery); (2) patients with a history of bleeding disorders; (3) those with a previous history of myocardial infarction; (4) patients with a history of deep vein thrombosis (DVT); and (5) patients with known hypersensitivity to TXA.

Surgical technique and perioperative management

All patients enrolled in this study underwent TKA using a minimally invasive subvastus approach under spinal anesthesia. A posterior-stabilized cemented prosthesis (NexGen® LPS; Zimmer Biomet, Warsaw, IN, USA) was implanted without patellar resurfacing. Partial synovectomy was performed selectively, based on clinical necessity (e.g., in cases of synovial proliferation, synovial chondromatosis, rheumatoid arthritis (RA) patients, villonodular synovitis, or in patients with a history of multiple intra-articular corticosteroid or viscoelastic injections). A mechanical alignment technique was utilized for all patients. A tourniquet was applied, inflated prior to cementation, and deflated following wound closure. All patients had active intra-articular drains, with drain clamps released 90 minutes post-tourniquet deflation and the drain removed 24 hours postoperatively. This protocol was designed to reduce the impact of drain management on tube drainage, which could have affected the results.

For infection prophylaxis, a single dose of 1g Vancomycin was administered alongside 1.5g Cefuroxime in two doses. To prevent DVT, patients received prophylactic treatment with low-molecular-weight heparin (LMWH), specifically Clexane (4000 U.I.). Administration began 12 hours after spinal anesthesia and was repeated every 24 hours. This regimen continued until the patient was discharged and was maintained for 28 days post-discharge. In patients with atrial fibrillation, LMWH (Clexane 1mg/kg) was administered every 12 hours, and these patients were transitioned to their regular anticoagulation therapy on the third postoperative day. After anesthesia wore off, all patients began active physical therapy and continued with home-based exercises for the following 6 weeks, with follow-up to ensure adherence to the regimen. According to our clinic's protocol, blood transfusion was indicated when hemoglobin concentration fell below 9 mg/dL or when anemia-related symptoms were observed.

Outcome measure

The primary outcome measures included tube drainage volume, pre- and postoperative Hb and Ht levels, and the number of blood transfusion units required. Blood tests were conducted one day prior to surgery and on the first postoperative day for all patients. Secondary outcome measures assessed the incidence of symptomatic thromboembolic events, such as DVT and pulmonary embolism, wound complications (infection, necrosis, dehiscence) and the duration of hospitalization. In the presence of clinical signs of DVT or PE, additional investigations such as D-dimer tests, echodoppler ultrasound, or Computed Tomography Pulmonary Angiography (CTPA) were conducted to diagnose or rule out the condition. The immediate follow-up period lasted for 90 days.

Data analysis

The statistical software used in this study were SPSS® Statistics Version 26, 64-bit edition (IBM, Armonk, NY, USA) and MedCalc® Version 14.8.1 (MedCalc Software bvba, Ostend, Belgium). We estimated the sample size by committing to a 0.05 probability of type I error and a 90% statistical power with an equal enrolment between groups. The Shapiro–Wilk test was used to confirm the normal distribution in the study groups. Descriptive statistics were summarized as means and standard deviations or medians with interquartile ranges for continuous variables and as counts and percentages for categorical variables. Comparison between continuous variables was performed using student t, while the chi-squared test was used for categorical variables. To assess the effects of TXA administration type (intravenous only vs. combined intravenous and intra-articular) on tube drainage while accounting for covariates (e.g., sex, BMI, and synovectomy), analysis of covariance (ANCOVA) was performed. A multivariable linear regression model was applied to identify independent predictors of primary outcomes. Pearson or Spearman correlation coefficients were calculated for associations between continuous variables. Data visualization included boxplots and scatterplots to depict group differences and associations. Individual results were considered statistically significant for when p values were lower or equal than 0.05.

Results

This study included 200 patients, with 100 patients receiving IV only TXA, and 100 patients receiving combined IV and IA tranexamic acid. An overview of the study population demographic characteristics is available below [Table 1].

Table 1. Baseline demographic characteristics of study population

Parameter	IV only TXA	Combined IV and IA TXA	Significance of difference (P-value)
Age (years)	68.48 ± 6.38	68.44 ± 5.44	0.9620
Gender			
Male	80	80	0.8597
Female	20	20	
BMI (kg/m2)	30.21 ± 3.45	30.53 ± 4.19	0.5561
ASA score			
2	90	85	0.3924
3	10	15	
Comorbidities			
Atrial fibrillation	6	12	0.2167
Diabetes mellitus	16	24	0.2159
Laterality (left/right)	38/62	47/53	0.2525
Kellgren Lawrence scale			
3	8	21	0.0160
4	92	79	

Based on the distribution by groups, the duration of surgery was longer in combined IV and IA group, with a longer tourniquet time and higher intraoperative bleeding, but with lower tube drainage compared to IV only group. Biologically, there were no significant differences in preoperative Hb or Ht values between the two groups; however, statistically significant differences were observed postoperatively. The amount of blood units transfused in the study was three for the group that received only IV treatment, while six units were administered to the group that had both IA and IV administration. Notably, three of the units in the combined group were administered to a single patient. Hospital stay was shorter in the combined group, with the difference reaching statistical significance. A summary of the results of the primary outcomes measures is available in [Table 2].

Table 2. Patient results in the study groups

PRBC – Packed red blood cells

Characteristic	IV only TXA	Combined IV and IA TXA	Significance of difference (P-value)
Duration of surgery (mins)	77.50 ± 12.36	83.25 ± 15.23	0.0038
Tourniquet time (mins)	28.97 ± 5.42	31.79 ± 7.20	0.0020
Hospitalization (days)	5.79 ± 1.14	5.26 ± 1.47	0.0050
Hemoglobin (g/dl)			
Preoperative	13.64 ± 0.98	13.43 ± 1.16	0.1756
Postoperative	11.36 ± 1.14	12.13 ± 1.31	<0.0001
Pre-post (diff)	2.28 ± 1.04	1.31 ± 0.98	<0.0001
Hematocrit (%)			
Preoperative	41.28 ± 3.07	40.83 ± 3.26	0.3097
Postoperative	33.42 ± 3.35	35.62 ± 3.85	<0.0001
Pre-post (diff)	7.87 ± 3.26	5.21 ± 3.04	<0.0001
Intraoperative bleeding (ml)	244.50 ± 82.93	253.20 ± 110.71	0.5284
Tube drainage (ml)	357.80 ± 213.71	294.50 ± 156.00	0.0170
Transfused patients (no. PRBC)	3 (1)	3 (1) and 1 (3)	0.5203

When stratified by gender, female patients had lower preoperative Hb and Ht levels compared to males. In both groups, the differences between pre- and post-operative Hb and Ht were insignificant for both males and females. Intraoperative bleeding was relatively similar in both groups; however, a significant difference in tube drainage was noted in IV only group, where males had higher levels compared to females (*P=0.0025*) [Table 3].

Table 3. Patient results in the study groups by gender

Characteristic	IV only TXA			Combined IV and IA TXA			Significance of difference (P-value)	
	Male	***Female***	***diff***	***Male***	***Female***	***diff***	***M-M***	***F-F***
Hemoglobin (g/dl)								
Preoperative	14.36 ± 0.90	13.46 ± 0.92	0.0002	14.26 ± 1.37	13.23 ± 1.01	0.0003	0.7862	0.1294
Postoperative	12.10 ± 1.22	11.17 ± 1.04	0.0008	12.77 ± 1.51	11.97 ± 1.22	0.0141	0.1338	<0.0001
Pre-post (diff)	2.26 ± 1.36	2.29 ± 0.95	0.9123	1.49 ± 1.32	1.26 ± 0.88	0.4595	0.0787	<0.0001
Hematocrit (%)								
Preoperative	43.42 ± 3.26	40.75 ± 2.80	0.0004	43.07 ± 4.05	40.27 ± 2.79	0.0073	0.7682	0.2748
Postoperative	35.60 ± 3.66	32.87 ± 3.05	0.0009	37.55 ± 4.42	35.14 ± 3.56	0.0115	0.1369	<0.0001
Pre-post (diff)	7.82 ± 4.30	7.88 ± 2.98	0.9516	5.52 ± 3.86	5.13 ± 2.82	0.6078	0.0837	<0.0001
Intraoperative bleeding (ml)	245.00 ± 77.63	244.38 ± 83.44	0.9758	265.00 ± 122.58	250.25 ± 108.17	0.5966	0.5413	0.7010
Tube drainage (ml)	521.00 ± 253.77	317.00 ± 182.53	0.0025	325.00 ± 213.78	286.32 ± 138.58	0.4492	0.0119	0.2330

When categorized by BMI, patients with a normal BMI range demonstrated higher tube drainage compared to other BMI groups. However, the combined administration of TXA effectively reduced tube drainage in all BMI categories [Chart 1].

We evaluated the reductions in Hb and Ht levels among patients with and without synovectomy across the two groups [Chart 2]. Patients receiving combined IV and IA TXA showed smaller differences in pre- and postoperative Hb and Ht levels. In the IV-only group, patients who underwent synovectomy had an average tube drainage of 429.79 ± 268.48 ml, compared to 335.07 ± 189.73 ml in those without synovectomy (*P=0.058*). In the combined IV and IA group, tube drainage was 355.41 ± 161.68 ml for synovectomy patients and 274.67 ± 150.08 ml for those without synovectomy (*P=0.026*).

Further, we implemented a multivariable linear regression to assess whether any of the patient-specific parameters or procedure-related factors had an influence on the primary outcome, more specifically Hb or Ht drop

intraoperative bleeding or tube drainage. As expected from the results reported above, we found that the administration of TXA influenced tube drainage (*P=0.0338*), as well as the decreases in Hb (*P<0.0001*) and Ht (*P<0.0001*). However, we found that tube drainage was also significantly influenced by patient sex (*P=0.0024*) and the performing of synovectomy (*P=0.0157*), while bleeding was affected by total surgical time (*P=0.0313*). BMI was marginally influential in determining tube drainage (*P=0.0852*). The severity of osteoarthritis, as determined by the Kellgren Lawrence classification, had no impact on the primary outcomes evaluated in the study.

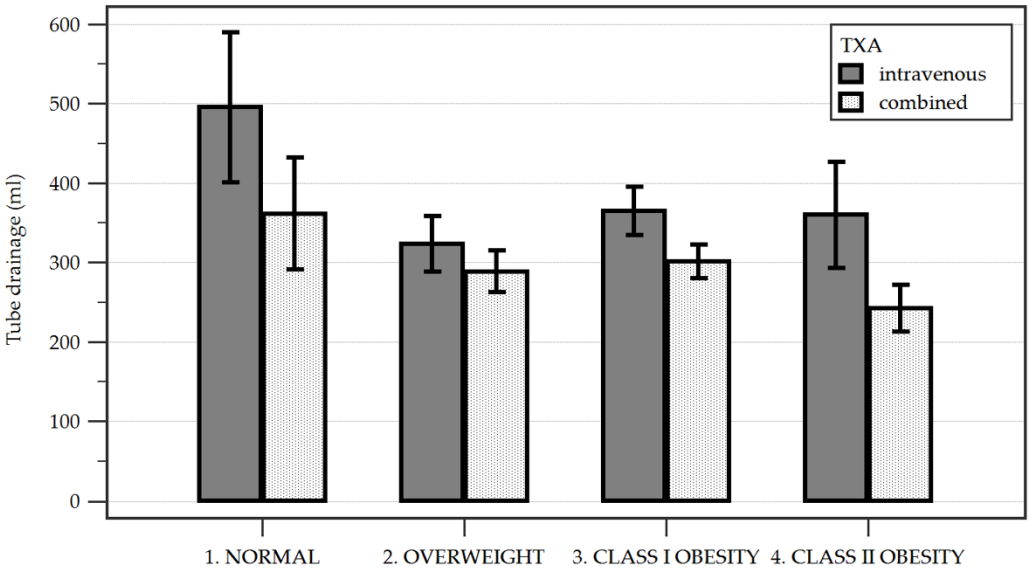

Chart 1. Tube drainage volume (ml) grouped by BMI classification for both groups

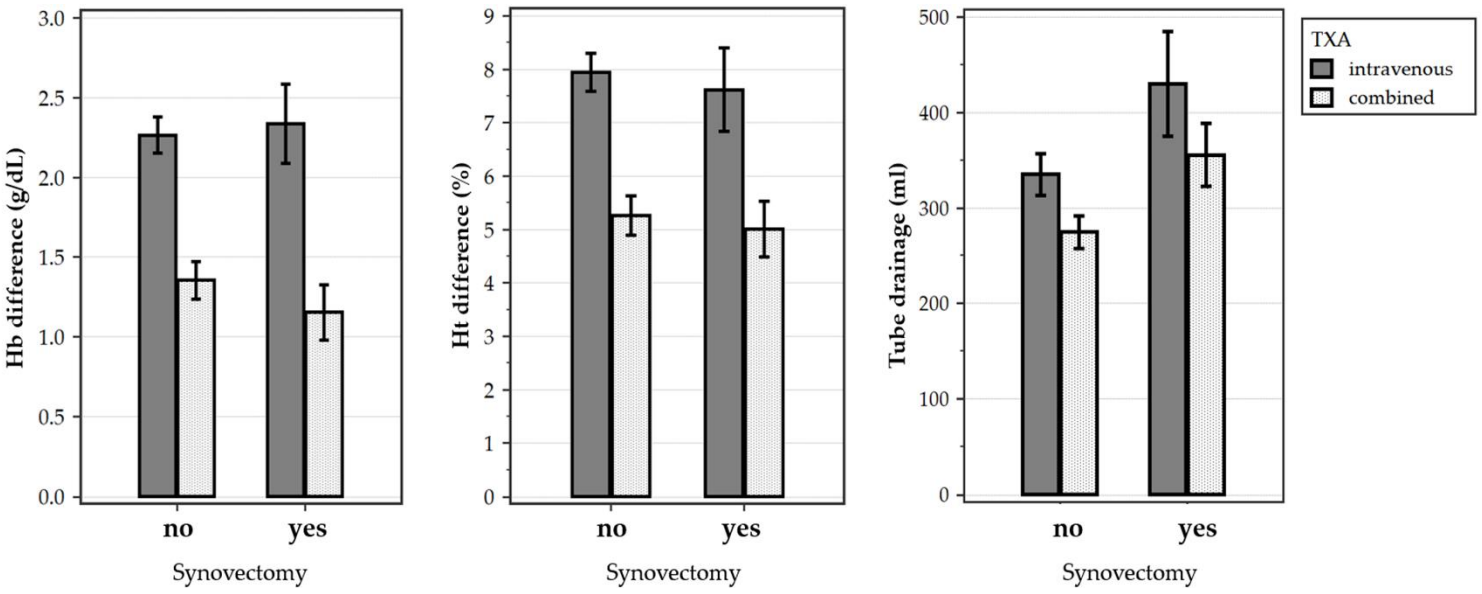

Chart 2. Hemoglobin and hematocrit pre-postoperative differences alongside the tube drainage in patients with and without synovectomy in the two groups

We conducted an ANCOVA to examine the effect of TXA administration on tube drainage while controlling for demographic and clinical covariates (sex, BMI, diabetes, atrial fibrillation, synovectomy). The model was statistically significant, $F(6,193) = 4.975$, *P<0.001*, with an adjusted R^2 of 0.107, indicating that the covariates and TXA administration type accounted for approximately 10.7% of the variance in tube drainage. Pairwise comparisons revealed that intravenous TXA was associated with significantly higher tube drainage compared to combined TXA administration (mean difference = 62.93 mL, p = 0.015). Significant covariates included gender (*P=0.003*) and synovectomy (*P=0.014*). However, BMI (*P=0.069*) and atrial fibrillation (AFib) (*P=0.089*) did not significantly impact tube drainage albeit having values <0.1. Although Levene's test indicated unequal variances (*P=0.001*), the homogeneity of regression slopes assumption was met (*P=0.167*). These results highlight the impact of TXA administration type and select patient-specific factors on postoperative tube drainage.

Secondary Outcomes

No complications, including symptomatic thromboembolic events or wound issues, were observed in either group during our study.

Discussion

TXA is a synthetic antifibrinolytic agent commonly utilized in major surgical procedures, including total hip arthroplasty (THA) and TKA, due to its cost-effectiveness and clinical benefits.[12,13] Numerous studies have demonstrated that TXA effectively reduces intraoperative blood loss and the necessity for blood transfusions without increasing the risk of thromboembolic events, thereby minimizing risks associated with bleeding and transfusions. Various administration routes for TXA in arthroplasty have been explored, IV, IA, and oral being the most frequently employed.[14-16] This study was evaluated in the context of previous research, including randomized controlled trials and meta-analyses, which reported similar outcomes. However, to our knowledge, no analysis has been conducted specifically on the benefits in relation to bleeding stratification risks.[17-20]

While IV administration is traditionally the most commonly utilized method in clinical practice, IA administration has gained increasing attention in recent literature.[21,22] When combined, the IV TXA provides systemic control of bleeding, while the IA TXA provides targeted action at the surgical site, resulting in enhanced hemostasis. This dual approach is particularly effective in patients with high bleeding risks, as it provides both broad and localized anti-fibrinolytic effects.[16,23-25] The primary objective of this study was to evaluate whether there are significant differences in outcomes based on the route of TXA administration (IV versus combined IV and IA), with a particular focus on patient subgroups stratified by bleeding risk. Our results indicate that combined IV + IA administration of TXA is associated with significantly reduced blood loss, as reflected by Hb and Ht levels, tube drainage and shorter hospital stays (P<0.05) when compared to only IV administration. These findings are consistent with those reported in previous research.[5,7,9-11,15-20]

In our study population, mean age of patients undergoing TKA was 68.46 ± 5.89 years with a male to female distribution of 4:1 which aligns with data reported last year by Romanian Arthroplasty Register.[26]

Oberweis et al. identified female sex as an independent risk factor for major bleeding after orthopedic surgery, with females experiencing more bleeding than males.[27] However, in our study, no significant differences were observed in pre- and post-operative Hb and Ht levels between males and females. Intraoperative bleeding was comparable between both groups; however, males exhibited significantly higher tube drainage, particularly in the IV-only group (P=0.025). This contrasts with existing literature and could be explained by the higher BMI in females in IV only group (30.4 kg/m^2) compared to males (29 kg/m^2), with overweight patients showing more bleeding risk than those with obesity class I.[28,29] The effect of TXA remains consistent across both genders regardless of the mode of administration, with no significant differences observed in either group. Therefore, in a clinical context, the route of TXA administration may not influence outcomes.

Obesity has been linked to increased levels of certain procoagulant factors, such as VII, VIII, IX, XII, and von Willebrand factor, which suggests that obese patients may be less susceptible to bleeding during or after surgery, while individuals with a lower BMI might be at a higher risk of bleeding.[28,29] Research by Guorui et al. demonstrated that obesity class I and II does not elevate the risks of blood loss, transfusion, or postoperative complications in patients undergoing TKA, while the transfusion rate was higher in the normal-weight group (BMI 18.0–24.9 kg/m^2) compared to the overweight group (BMI 25.0–29.9 kg/m^2), with significant statistical difference (36.0% vs 27.6%, p = 0.007).[30] Additionally, a study by Braekkan et al. explored the relationship between BMI and bleeding risk.[29] The study found that patients with a lower BMI were more prone to bleeding, while there was no further reduction in bleeding risk for those with a BMI above 26.3 kg/m^2, indicating that higher BMI does not continue to reduce bleeding risk beyond a certain point. In our study, we found similar results, with patients in the normal BMI range reporting higher tube drainage and intraoperative bleeding compared to those with higher BMI. Furthermore, patients who received combined IV and IA TXA reported reduced tube drainage across all BMI categories. These findings are clinically significant, as patients with lower or normal BMI benefit most from TXA administration, while those with higher BMI naturally exhibit a procoagulant profile. Therefore, careful use of TXA is essential to avoid increasing the risk of thromboembolic events.

Synovial proliferation is frequently observed during surgery in patients with knee OA and RA, and it is thought to be a significant contributor to pain.[31] Although synovectomy has been shown to potentially reduce pain, decrease inflammation, and enhance joint function, its efficacy remains controversial.[32-34] A meta-analysis conducted by

Zhao et al. found that synovectomy, when combined with TKA for primary OA, does not offer additional clinical benefits.[35] Furthermore, patients undergoing this procedure experienced increased blood loss and longer operating times. In our study, among IV only group, patients who underwent synovectomy had an average postoperative drainage of 429.79 ± 268.48 ml compared to 335.07 ± 189.73 ml in those who did not. In combined IV and IA group, the drainage for synovectomy patients was 272.92 ± 117.01 ml, while it was 253.40 ± 108.70 ml for those without synovectomy. These findings are consistent with previous studies, indicating that synovectomy increases bleeding. The use of TXA proves especially beneficial in such cases, particularly with the combined IA and IV administration, where patients demonstrated reduced tube drainage and smaller differences between pre- and postoperative Hb and Ht levels. The prolonged action of TXA in the joint, combined with reduced systemic absorption, is likely the key mechanism responsible for its effectiveness. This has important clinical implications for patients undergoing synovectomy. Instead of administering the same quantity of TXA IV only, combining IV and IA administration achieves optimal results. This approach not only provides patients with the highest safety profile but also ensures a more efficient use of resources.

Anemia in patients with cardiac conditions following orthopedic surgery can have significant implications, particularly due to the increased cardiovascular load. Therefore, enhanced recovery after surgery protocols with effective blood management strategies, including minimizing intraoperative and postoperative blood loss, are crucial.[36,37] Even TXA effectively reduces blood loss during joint arthroplasty surgeries, patients with cardiovascular issues, such as myocardial infarction, AFib, and angina, were often excluded from these studies due to concerns that TXA might raise the risk of cardiac and thromboembolic events in these patients.[7-10,38,39] Despite these concerns, orthopedic research, including studies by Porter et al. and Enayatollahi et al., has strongly supported the safety of TXA in high-risk orthopedic patients.[40,41] In our study, TXA was administered even to AFib patients without any complications reported in this group. No significant differences were observed between pre- and postoperative Hb or Ht levels in AFib patients compared to those without AFib, regardless of how TXA was administered. Nevertheless, AFib patients from combined IV and IA group experienced lower tube drainage compared to those with IV only TXA (302.50 ± 224.99 ml vs 383.33 ± 315.70 ml), although this difference was not statistically significant.

In synovectomy patients, the results strongly support the IA administration of TXA due to its effectiveness in reducing blood loss. However, the same conclusion cannot be drawn for patients with AFib. The findings raise important questions about whether the mode of TXA administration—systemic or local—interacts differently with bleeding risk factors in these patient groups. It is still uncertain whether local or systemic bleeding risks affect the mechanism of action and outcomes of TXA. Further research is needed to clarify and document these relationships. Additionally, future studies could focus on determining the optimal dosing strategy and dosage based on a patient's specific local or systemic bleeding risk.

A meta-analysis by Li et al. reviewed 34 randomized controlled trials comparing IA and IV administration of TXA in patients undergoing primary TKA.[11] Across 33 studies with 3,807 patients, the complication rate was similar: 77/1,946 (4.0%) in the IV group and 77/1,861 (4.1%) in the IA group. In 10 studies, there were 23 DVT events, while PE occurred in both groups (four events reported in three studies). In our study, no complications were observed in either cohort. In the same meta-analysis, 28 studies involving 3,270 patients provided data on blood transfusions.[11] Transfusion rates were reported as 109/1,664 (6.6%) in the IV group and 99/1,606 (6.2%) in the IA group. In our study, three blood units were used in IV only group and six units in combined IV and IA group, with one patient in this cohort receiving three units. This case involved a patient with a history of medullary aplasia, AFib, age over 70 years, and a normal BMI—factors that, according to our study, were associated with an increased risk of bleeding. Another potential contributor to the higher transfusion rates in the combined group could be the greater proportion of patients with AFib, as these individuals typically require higher doses of anticoagulants, which may further elevate the risk of bleeding and, consequently, the need for transfusions.

Our study had several limitations. The small sample size in each group and the fact that the study was conducted at a single center may have affected the results. While this study was adequately powered to detect differences in primary outcomes, subgroup analyses may be underpowered due to smaller sample sizes within each subgroup. Also, we did not include a control group with IV and IA saline administration and DVT and PE were assessed clinically, so asymptomatic cases or those with mild symptoms may have been missed. Additionally, we routinely collected blood samples one day before and one day after surgery, but more frequent sampling could provide more precise data. Although our ANCOVA model accounted for several demographic and clinical covariates, we acknowledge that additional factors, such as intraoperative blood loss, surgeon experience, and patient adherence to rehabilitation protocols, could also influence postoperative tube drainage. Since all procedures were performed at a single institution following a standardized protocol, variability due to surgical technique and perioperative management was minimized. However, we recognize that intraoperative blood loss and rehabilitation adherence could not be fully controlled for in this analysis. Future studies incorporating these additional parameters may provide a more comprehensive understanding of the determinants of postoperative drainage after TKA with TXA administration. Also, studies with larger cohorts or targeted subgroup analyses are warranted to further validate these findings.

Conclusion

The combined use of TXA (1g IV before incision and 1g IA after wound closure) in TKA improved outcomes

compared to IV TXA alone. It reduced tube drainage (294.5 mL vs. 357.8 mL) and shortened hospital stays (5.26 days vs. 5.79 days), without increasing thromboembolic risks. The study's limitations include a small sample size, single-center design, and the lack of a control group with saline, which may affect the generalizability and detection of asymptomatic complications. Overall, the combined TXA approach offers a promising strategy for better patient recovery and resource efficiency in TKA.

Acknowledgement

N/A

Authors Contribution: Authors who conceived and designed the analysis: Serban Dragosloveanu, Bogdan-Sorin Capitanu, Cristian Scheau/ Authors who collected the data: Bogdan-Sorin Capitanu, Alexandra-Ana Mihailescu/Authors who contributed data or analysis tools: Serban Dragosloveanu, Mohammadali Enayatollahi, Cristian Scheau/Authors who performed the analysis: Calin Ion Dragosloveanu, Alexandra-Ana Mihailescu, Mohammadali Enayatollahi/Authors who wrote the paper: Serban Dragosloveanu, Bogdan-Sorin Capitanu, Calin Ion Dragosloveanu, Alexandra-Ana Mihailescu, Mohammadali Enayatollahi, Cristian Scheau/Other contribution: Cristian Scheau supervised the study

Declaration of Conflict of Interest: The authors declare no conflicts of interest.

Declaration of Funding: The authors received no financial support for the preparation, research, authorship, and publication of this manuscript.

Declaration of Ethical Approval for Study: The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Council of "Foisor" Clinical Hospital of Orthopaedics, Traumatology, and Osteoarticular TB with registration number 11226/8 October 2024.

Declaration of Informed Consent: Informed consent was obtained from all subjects involved in the study.

Serban Dragosloveanu, MD, PhD [1,2]
Bogdan-Sorin Capitanu MD [2]
Calin Ion Dragosloveanu MD, PhD [2]
Alexandra-Ana Mihailescu MD [1,3]
Mohammadali Enayatollahi MD [4]
Cristian Scheau MD, PhD [1,5]

1 The Carol Davila University of Medicine and Pharmacy, Bucharest, Romania
2 Department of Orthopaedics, Foisor Clinical Hospital of Orthopaedics, Traumatology and Osteoarticular TB, Bucharest, Romania
3 Department of Anesthesiology and Critical Care, Foisor Clinical Hospital of Orthopaedics, Traumatology, and Osteoarticular Tuberculosis, Bucharest, Romania
4 Department of Orthopaedics, Nikan General Hospital, Tehran, Iran
5 Department of Radiology and Medical Imaging, Foisor Clinical Hospital of Orthopaedics, Traumatology and Osteoarticular TB, Bucharest, Romania

References

1. Cui A, Li H, Wang D, Zhong J, Chen Y, Lu H. Global, regional prevalence, incidence and risk factors of knee osteoarthritis in population-based studies. EClinicalMedicine. 2020; 29-30:100587. doi:10.1016/j.eclinm.2020.100587.
2. Arslan IG, Damen J, de Wilde M, et al. Incidence and prevalence of knee osteoarthritis using codified and narrative data from Electronic Health Records: A population-based study. Arthritis Care Res (Hoboken). 2022; 74(6):937-944. doi: 10.1002/acr.24861.
3. Boutsiadis A, Reynolds RJ, Saffarini M, Panisset J-C. Factors that influence blood loss and need for transfusion following total knee arthroplasty. Ann Transl Med. 2017; 5(21):418. doi: 10.21037/atm.2017.08.11.
4. Fernandez MC, Gottlieb M, Menitove JE. Blood transfusion and postoperative infection in orthopedic patients. Transfusion. 1992; 32(4):318-322. doi:10.1046/j.1537-2995.1992.32492263444.x.
5. Cai J, Ribkoff J, Olson S, et al. The many roles of tranexamic acid: An overview of the clinical indications for TXA in medical and surgical patients. Eur J Haematol. 2020; 104(2):79-87. doi: 10.1111/ejh.13348.
6. Dragosloveanu S, Dragosloveanu C, Petre M, Gherghe ME, Cotor DC. The impact of tourniquet usage on TKA outcome: A single-center prospective trial. Medicina (Kaunas). 2023; 59(5):870. doi: 10.3390/medicina59050870.
7. Furqan A, Hafeez S, Khan F, Orakzai SH, Nur AN, Khan MA. Intra-articular versus intravenous tranexamic acid in primary total knee replacement. Cureus.2022; 14(1):e21052. doi: 10.7759/cureus.21052.
8. Tranexamic acid: Uses, interactions, mechanism of action. Available at: https://go.drugbank.com/drugs/DB00302. Accessed September 20, 2024.
9. Chen JY, Chin PL, Moo IH, et al. Intravenous versus intra-articular tranexamic acid in total knee arthroplasty: A double-blinded randomised controlled noninferiority trial. Knee. 2016; 23(1):152-6. doi: 10.1016/j.knee.2015.09.004.
10. Wu J, Zhou Y-Q, Deng J-H, Han Y-G, Zhu Y-C, Qian Q-R. Ideal intraarticular application dose of tranexamic acid in primary total knee arthroplasty: A prospective, randomized and controlled study. Ann Transl Med. 2020; 8(21):1353. doi: 10.21037/atm-20-3064.
11. Li J, Liu R, Rai S, Ze R, Tang X, Hong P. Intra-articular vs. intravenous administration: A meta-analysis of tranexamic acid in primary total knee arthroplasty. J Orthop Surg Res. 2020; 15(1):581. doi: 10.1186/s13018-020-02119-1.
12. Lin ZX, Woolf SK. Safety, Efficacy, and Cost-effectiveness of Tranexamic Acid in Orthopedic Surgery. Orthopedics. 2016; 39(2):119-30. doi: 10.3928/01477447-20160301-05.

13. Tuttle JR, Ritterman SA, Cassidy DB, Anazonwu WA, Froehlich JA, Rubin LE. Cost Benefit Analysis of Topical Tranexamic Acid in Primary Total Hip and Knee Arthroplasty. J Arthroplasty. 2014; 29(8):1512-5. doi: 10.1016/j.arth.2014.01.031.
14. Grocott MPW, Murphy M, Roberts I, Sayers R, Toh C-H. Tranexamic acid for safer surgery: The time is now. Br J Anaesth. 2022; 129(4):459-461. doi: 10.1016/j.bja.2022.06.024.
15. Haratian A, Shelby T, Hasan LK, Bolia IK, Weber AE, Petrigliano FA. Utilization of tranexamic acid in surgical orthopaedic practice: Indications and current considerations. Orthop Res Rev. 2021:13:187-199. doi: 10.2147/ORR.S321881.
16. Abdulwahab T, Meshram P, Althani S, Albelooshi A. Comparison of Intraarticular Versus Combined Intravenous and Intraarticular Tranexamic Acid Administration in Patients Undergoing Primary Unilateral Total Knee Arthroplasty: A Randomized Controlled Trial in the Middle Eastern Patient Population. Arch Bone Jt Surg. 2022; 10(12):1037-1043. doi: 10.22038/ABJS.2022.67705.3210.
17. Adravanti P, Di Salvo E, Calafiore G, Vasta S, Ampollini A, Rosa MA. A prospective, randomized, comparative study of intravenous alone and combined intravenous and intraarticular administration of tranexamic acid in primary total knee replacement. Arthroplast Today. 2017; 4(1):85-88. doi: 10.1016/j.artd.2017.08.004.
18. Nielsen CS, Jans Ø, Ørsnes T, Foss NB, Troelsen A, Husted H. Combined Intra-Articular and Intravenous Tranexamic Acid Reduces Blood Loss in Total Knee Arthroplasty. J Bone Joint Surg Am.2016; 98(10):835-41. doi: 10.2106/JBJS.15.00810.
19. Zhang YM, Yang B, Sun XD, Zhang Z. Combined intravenous and intra-articular tranexamic acid administration in total knee arthroplasty for preventing blood loss and hyperfibrinolysis: A randomized controlled trial. Medicine (Baltimore).2019; 98(7):e14458. doi: 10.1097/MD.0000000000014458.
20. Mi B, Liu G, Lv H, et al. Is combined use of intravenous and intraarticular tranexamic acid superior to intravenous or intraarticular tranexamic acid alone in total knee arthroplasty? A meta-analysis of randomized controlled trials. J Orthop Surg Res.2017; 12(1):61. doi: 10.1186/s13018-017-0559-2.
21. Yang J, Yang L, Tan J, Huo K, Zhao L, Cai D. Reduction of Blood Loss by Intra-articular Injection of Tranexamic Acid Combined with Knee and Hip Flexion at 45° During Primary Total Knee Arthroplasty: A Randomized Controlled Trial. Orthop Surg. 2020; 12(6):1835-1842. doi: 10.1111/os.12814.
22. Moskal J, Capps S. Intra-articular Tranexamic Acid in Primary Total Knee Arthroplasty: Meta-analysis. J Knee Surg. 2018; 31(1):56-67. doi: 10.1055/s-0037-1600092.
23. Kleiboer B, Layer MA, Cafuir LA, et al. Postoperative bleeding complications in patients with hemophilia undergoing major orthopedic surgery: A prospective multicenter observational study. J Thromb Haemost. 2022; 20(4):857-865. doi: 10.1111/jth.15654.
24. McQuilten ZK, Wood EM, Medcalf RL. When to use tranexamic acid for the treatment of major bleeding? J Thromb Haemost. 2024; 22(3):581-593. doi: 10.1016/j.jtha.2023.10.001.
25. Ockerman A, Vanassche T, Garip M, et al. Tranexamic acid for the prevention and treatment of bleeding in surgery, trauma and bleeding disorders: a narrative review. Thromb J. 2021; 19(1):54. doi: 10.1186/s12959-021-00303-9.
26. Romanian Arthroplasty Register. New: Hip biennial report 2015. Available at: https://www.rne.ro/?lang=en. Accessed September 15, 2024.
27. Oberweis BS, Nukala S, Rosenberg A, et al. Thrombotic and bleeding complications after orthopedic surgery. Am Heart J. 2013; 165(3):427-33.e1. doi: 10.1016/j.ahj.2012.11.005.
28. Blokhin IO, Lentz SR. Mechanisms of thrombosis in obesity. Curr Opin Hematol. 2013; 20(5):437-44. doi: 10.1097/MOH.0b013e3283634443.
29. Braekkan SK, van der Graaf Y, Visseren FLJ, Algra A. Obesity and risk of bleeding: The smart study. J Thromb Haemost. 2016; 14(1):65-72. doi: 10.1111/jth.13184.
30. Cao G, Chen G, Yang X, et al. Obesity does not increase blood loss or incidence of immediate postoperative complications during simultaneous total knee arthroplasty: A multicenter study. Knee.2020; 27(3):963-969. doi: 10.1016/j.knee.2020.01.012.
31. Fernandez-Madrid F, Karvonen RL, Teitge RA, Miller PR, An T, Negendank WG. Synovial thickening detected by Mr Imaging in osteoarthritis of the knee confirmed by biopsy as synovitis. Magn Reson Imaging.1995; 13(2):177-83. doi: 10.1016/0730-725x(94)00119-n.
32. Zhaoning X, Xu Y, Shaoqi T, Baiqiang H, Kang S. The effect of synovectomy on bleeding and clinical outcomes for total knee replacement. Bone Joint J.2013; 95-B (9):1197-200. doi: 10.1302/0301-620X.95B9.31253.
33. Kilicarslan K, Yalcin N, Cicek H, et al. The effect of total synovectomy in total knee arthroplasty: A prospective randomized controlled study. Knee Surg Sports Traumatol Arthrosc. 2011; 19(6):932-5. doi: 10.1007/s00167-010-1270-6.
34. Petre MA, Gherghe ME, Cotor DC, et al. The impact of total synovectomy on blood loss and knee function. A prospective randomized study. Romanian Journal of Military Medicine. 2024; 127(1):3-8. doi:10.55453/rjmm.2024.127.1.1.
35. Zhao Z, Xu J, Wang R, Xu L. The efficacy of synovectomy for total knee arthroplasty: A meta-analysis. J Orthop Surg Res. 2018; 13(1):51. doi: 10.1186/s13018-018-0752-y.
36. Hare GM, Mazer CD. Anemia: Perioperative risk and treatment opportunity. Anesthesiology. 2021; 135(3):520-530. doi: 10.1097/ALN.0000000000003870.
37. Shah A, Palmer AJ, Klein AA. Strategies to minimize intraoperative blood loss during major surgery. Br J Surg. 2020; 107(2):e26-e38. doi: 10.1002/bjs.11393.
38. Spahn DR. Anemia and patient blood management in hip and knee surgery: a systematic review of the literature. Anesthesiology.2010; 113(2):482-95. doi: 10.1097/ALN.0b013e3181e08e97.
39. Rasouli M, Parvizi J. Tranexamic Acid in total joint arthroplasty: efficacy and safety. Arch Bone Jt Surg. 2015; 3(1):1-2.
40. Porter SB, Spaulding AC, Duncan CM, Wilke BK, Pagnano MW, Abdel MP. Tranexamic acid was not associated with increased complications in high-risk patients with intertrochanteric fracture. J Bone Joint Surg Am. 2022; 104(13):1138-1147. doi: 10.2106/JBJS.21.01389.
41. Enayatollahi M, Azboy I, Dietz MJ, et al. What are the contraindications, if any, for the use of tranexamic acid during knee or hip arthroplasty? J Arthroplasty. 2025; 40(2S1):S21-S24. doi: 10.1016/j.arth.2024.10.050.