

Antifibrinolytic Therapy in Neurosurgical Oncology: A Randomized, Double-Blind, Placebo-Controlled Trial on the Efficacy and Safety of Tranexamic Acid for Hypervascular Intracranial Meningiomas

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ABSTRACT

Introduction: Resection of hypervascular intracranial meningiomas is frequently complicated by significant intraoperative hemorrhage, increasing patient morbidity and transfusion requirements. Tranexamic acid (TXA), an antifibrinolytic agent, has shown promise in other surgical fields, but high-level evidence in intracranial tumor surgery is lacking. This study aimed to rigorously evaluate the efficacy and safety of perioperative TXA in reducing blood loss during craniotomy for convexity and sphenoid-orbital meningiomas. **Methods:** This single-center, double-blind, randomized, placebo-controlled trial enrolled 30 adult female patients scheduled for elective resection of convexity or sphenoid-orbital meningiomas. Patients were randomized to receive either intravenous TXA (15 mg/kg bolus followed by a 1 mg/kg/hr infusion) or a matching saline placebo. The primary outcome was total intraoperative blood loss. Secondary outcomes included transfusion volume, perioperative changes in hematological and coagulation parameters, and the incidence of thromboembolic events within 30 days. **Results:** The TXA group (n=15) and the placebo group (n=15) were well-matched at baseline. Mean intraoperative blood loss was significantly lower in the TXA group compared to the placebo group (765.0 ± 94.39 mL vs. 1010.0 ± 131.20 mL; mean difference, -245 mL; 95% CI, -444.2 to -45.8; p = 0.019; Cohen's d = 2.15). The TXA group exhibited a significantly smaller postoperative drop in hemoglobin (-0.97 g/dL vs. -2.36 g/dL; p = 0.041) and significantly lower D-dimer levels at 24 hours (850 ± 210 ng/mL vs. 1620 ± 450 ng/mL; p < 0.001). There was no significant difference in PRBC transfusion volume (p = 0.410). No thromboembolic events were recorded in either group. **Conclusion:** In patients undergoing resection of hypervascular convexity and sphenoid-orbital meningiomas, perioperative TXA administration significantly reduces intraoperative blood loss and preserves postoperative hemoglobin. The agent demonstrated a favorable safety profile with no observed increase in thromboembolic risk in this cohort.

1. Introduction

Intracranial meningiomas represent the most prevalent primary central nervous system tumors, comprising over 37% of all such neoplasms diagnosed in adults. While typically histologically benign (WHO Grade I), their surgical management presents a unique and often formidable challenge, primarily centered on the control of intraoperative hemorrhage.¹ Meningiomas arising from the cerebral convexity and sphenoid wing are particularly notorious for their

profound vascularity.² These tumors derive a rich arterial supply from dural vessels, most notably branches of the middle meningeal artery, and frequently parasitize the pial circulation from the underlying cortex, creating a complex and high-flow vascular network that significantly elevates the risk of substantial intraoperative blood loss.³

Excessive intraoperative hemorrhage is a critical independent predictor of adverse outcomes in neurosurgical oncology. It can precipitate severe

hemodynamic instability, necessitate emergency allogeneic blood transfusions, obscure the surgical field—thereby increasing the risk of iatrogenic injury to eloquent neural and vascular structures—and prolong operative time and anesthetic exposure.⁴ Allogeneic packed red blood cell (PRBC) transfusions, though life-saving, are an increasingly scrutinized resource associated with a spectrum of potential complications, including transfusion-related lung injury, immunomodulatory effects that may increase susceptibility to infection, viral transmission, and increased postoperative morbidity and length of hospital stay.⁵ Consequently, the development and implementation of effective, evidence-based blood conservation strategies are paramount to enhancing patient safety and optimizing outcomes in contemporary neurosurgical practice.⁶

The physiological response to major surgery involves a complex interplay between the coagulation cascade and the fibrinolytic system. Surgical trauma initiates a potent inflammatory response that triggers the release of tissue plasminogen activator (tPA) from vascular endothelial cells and damaged tissues. The dura mater and meningeal tissues are known to be particularly rich in tPA, creating a localized pro-fibrinolytic milieu during intracranial procedures. This surge in tPA leads to the conversion of plasminogen to its active form, plasmin. Plasmin is a powerful serine protease that systematically degrades the fibrin cross-linkages of newly formed hemostatic clots, leading to premature clot dissolution and persistent, diffuse microvascular oozing from the surgical bed.⁷ This phenomenon of localized, trauma-induced hyperfibrinolysis is a key pathophysiological driver of surgical hemorrhage.

Tranexamic acid (TXA) is a synthetic lysine analogue that functions as a potent competitive inhibitor of fibrinolysis. By binding to the lysine-binding sites on plasminogen, TXA effectively blocks its interaction with fibrin and its activation by tPA, thereby preventing the generation of plasmin.⁸ This mechanism stabilizes the fibrin-platelet matrix of hemostatic plugs, making them more resilient to

premature breakdown and promoting durable hemostasis. The efficacy of TXA in reducing blood loss and transfusion requirements has been unequivocally established in numerous surgical disciplines through large-scale, multicenter randomized controlled trials (RCTs), including cardiac surgery, major orthopedic procedures, trauma, and spine surgery. The landmark CRASH-2 trial, for instance, demonstrated a significant reduction in all-cause mortality in bleeding trauma patients treated with TXA, without an associated increase in vascular occlusive events.⁹

Despite this wealth of evidence, the adoption of TXA in intracranial neurosurgery has been comparatively cautious and slow. This reluctance has historically been fueled by a theoretical concern for an increased risk of thromboembolic complications, such as deep vein thrombosis (DVT), pulmonary embolism (PE), or ischemic stroke, in a patient population already considered to be at high risk for such events. While several retrospective studies and smaller, non-randomized trials have suggested a potential benefit, high-quality, prospective evidence from rigorously designed RCTs specifically evaluating TXA in intracranial tumor resection remains scarce. Meningioma surgery, with its predictable risk of significant, fibrinolysis-driven hemorrhage, represents an ideal clinical model to investigate the utility of this agent.¹⁰

Therefore, this study was designed to provide high-level, Level 1 evidence on this critical clinical question. The primary aim of this double-blind, randomized, placebo-controlled trial was to test the primary hypothesis that a standardized perioperative regimen of tranexamic acid would significantly reduce total intraoperative blood loss compared to placebo in patients undergoing surgical resection of convexity and sphenoid-orbital meningiomas. The novelty of this investigation lies in its rigorous methodological design focused on this specific, high-risk neurosurgical population, with the goal of providing definitive evidence to guide clinical practice and enhance patient blood management protocols.

2. Methods

This study was a single-center, prospective, double-blind, randomized, placebo-controlled, parallel-group superiority trial conducted at the Department of Neurosurgery, Dr. Hasan Sadikin General Hospital, a tertiary academic medical center in Bandung, Indonesia. The manuscript has been prepared in accordance with the Consolidated Standards of Reporting Trials (CONSORT) 2010 statement. The study protocol and the informed consent form were reviewed and approved by the Health Research Ethics Committee of the Faculty of Medicine, Universitas Padjadjaran, Indonesia. The trial was conducted in strict adherence to the principles of the Declaration of Helsinki and the International Council for Harmonisation Good Clinical Practice (GCP) guidelines. All participants, or their legally authorized representatives, provided written informed consent before the initiation of any study-related procedures.

Eligible participants were adult patients aged 18 to 65 years with a radiologically diagnosed convexity or sphenoid-orbital meningioma, scheduled for elective primary craniotomy and tumor resection. The diagnosis was established based on characteristic findings on contrast-enhanced magnetic resonance imaging (MRI) or, if MRI was contraindicated, contrast-enhanced computed tomography (CT) of the head.

Exclusion criteria were comprehensive and included: (1) known hypersensitivity or allergy to tranexamic acid; (2) significant pre-existing renal impairment, defined as a serum creatinine level >1.5 mg/dL or an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73m²; (3) severe hepatic dysfunction, defined as Child-Pugh Class B or C; (4) a personal history of arterial or venous thromboembolic disease (DVT, PE, ischemic stroke, myocardial infarction); (5) a strong family history of unprovoked thromboembolic disease, defined as an event in a first-degree relative before the age of 50; (6) known inherited or acquired thrombophilia; (7) active coagulopathy, defined as a platelet count $<100,000/\mu\text{L}$ or an International Normalized Ratio (INR) >1.5 ; (8)

therapeutic use of anticoagulants, such as warfarin or direct oral anticoagulants, or antiplatelet agents, such as aspirin or clopidogrel, within 7 days prior to the scheduled surgery; (9) a history of preoperative tumor embolization; (10) pregnancy or lactation; and (11) inability to provide informed consent.

The observed all-female cohort was a consequence of consecutive patient enrollment during the study period and was not a result of a specific study design choice to exclude male patients.

A block randomization sequence with variable block sizes of 4 and 6 was generated using R software (version 4.2.1, R Foundation for Statistical Computing) by an independent statistician at the university's clinical trials unit who had no involvement in patient recruitment, clinical care, or data assessment. Allocation concealment was rigorously maintained. The randomization sequence was securely held by the central hospital pharmacy. For each patient enrolled by the clinical research coordinator, the pharmacy was contacted. A pharmacist not involved in the study would then consult the sequence and prepare the study drug (TXA or placebo) in identical, opaque 100 mL infusion bags. These bags were labeled only with the patient's unique study identification number and a batch number. This process ensured that patients, surgeons, anesthesiologists, operating room staff, and all research personnel involved in data collection and outcome assessment remained blinded to the treatment allocation throughout the entire trial. Emergency unblinding was permissible only in the event of a suspected life-threatening adverse event directly attributable to the study intervention, such as anaphylaxis or a massive thromboembolic event. The protocol for emergency unblinding required contacting the head of the pharmacy, who would reveal the patient's allocation to the primary treatment team. No instances of unblinding occurred during the trial.

Patients randomized to the intervention group received intravenous tranexamic acid (Kalex®, Kalbe Farma). An initial loading dose of 15 mg per kilogram of actual body weight was diluted in 100 mL of 0.9% normal saline and administered as an infusion over 10

minutes. This infusion was initiated approximately 30 minutes before the planned skin incision. Following the bolus, a continuous maintenance infusion of TXA at a rate of 1 mg per kilogram per hour was started and continued until the final dural closure was confirmed by the operating surgeon. Patients randomized to the control group received a matching placebo regimen. This consisted of a 100 mL bolus infusion of 0.9% normal saline administered over 10 minutes, followed by a continuous infusion of normal saline at the same rate and duration as the active intervention group, delivered in an identical infusion bag.

All patients underwent a standardized general anesthesia protocol managed by a consultant anesthesiologist. Anesthesia was induced with intravenous fentanyl (1-3 µg/kg), propofol (2-3 mg/kg), and rocuronium (1.2 mg/kg) for endotracheal intubation. Anesthesia was maintained with sevoflurane in a 50:50 oxygen-air mixture to achieve a minimum alveolar concentration (MAC) of 1.0-1.5, supplemented with intermittent fentanyl boluses as required. All patients had an arterial line placed for invasive blood pressure monitoring and a central venous catheter for pressure monitoring and fluid administration. Hemodynamic management targeted a mean arterial pressure (MAP) within 20% of the patient's baseline value.

All surgical procedures were performed by one of three senior consultant neurosurgeons, each with over 10 years of experience in neurosurgical oncology. The surgical approach, such as pterional or frontotemporal, was determined by the surgeon based on tumor location and size. The primary surgical goal was maximal safe resection, aiming for Simpson Grade I or II removal where anatomically and functionally feasible. The institutional transfusion trigger was a hemoglobin level of <7 g/dL or evidence of hemodynamic instability or end-organ ischemia attributable to anemia at a higher hemoglobin level.

The primary efficacy outcome was the total volume of intraoperative blood loss (in mL), measured from the time of skin incision to the completion of skin closure.

Blood loss was meticulously calculated according to a standardized operating procedure by a dedicated, blinded research nurse. The calculation used a composite method: (1) Gravimetric: All surgical gauzes and sponges were collected and weighed on a single, daily-calibrated digital scale (AND EJ-6100). The pre-recorded dry weight of the materials was subtracted, and the resulting net weight (in grams) was multiplied by 1.06 to estimate the blood volume (assuming a blood specific gravity of 1.06 g/mL); (2) Volumetric: The volume of blood collected in the suction canisters was measured. The volume of all irrigation fluids (0.9% normal saline) used during the procedure, which was prospectively tallied by the scrub nurse using a separate counter, was subtracted from the total canister volume.

The total intraoperative blood loss was the sum of the volumes calculated from these two methods.

Secondary efficacy outcomes included: (1) total volume (mL) of allogeneic PRBCs transfused during the intraoperative period and within the first 24 hours postoperatively; (2) the proportion of patients in each group requiring any PRBC transfusion; (3) the absolute change in hemoglobin (g/dL) and hematocrit (%) levels from preoperative baseline to the 24-hour postoperative measurement; (4) duration of surgery (minutes); and (5) total length of hospital stay (days). Exploratory laboratory outcomes included serial measurements of coagulation parameters (prothrombin time [PT], activated partial thromboplastin time [aPTT], fibrinogen) and D-dimer levels at baseline and 24 hours post-surgery.

The primary safety outcome was the composite incidence of any confirmed thromboembolic event within 30 days of surgery. This included DVT (confirmed by compression Doppler ultrasound), PE (confirmed by CT pulmonary angiography), ischemic stroke (confirmed by diffusion-weighted MRI), and myocardial infarction (confirmed by ECG changes and elevated cardiac troponin levels). Other monitored adverse events included postoperative seizures, surgical site infections, and acute kidney injury.

The sample size was calculated based on the primary outcome. A retrospective audit of the 50 most recent craniotomies for meningiomas at our institution revealed a mean intraoperative blood loss of approximately 1000 mL with a standard deviation (SD) of 150 mL. We defined a minimal clinically important difference (MCID) as a 200 mL reduction in blood loss, representing approximately a 20% reduction and nearly one-quarter of a unit of PRBCs. Using these parameters, with a two-sided alpha level of 0.05 and a desired power of 80%, a minimum of 13 patients per group was required. To account for potential dropouts or protocol deviations, we planned to enroll 15 patients per group, for a total sample of 30 patients.

All statistical analyses were conducted using SPSS Statistics, Version 28.0 (IBM Corp., Armonk, NY). The primary analysis followed the intention-to-treat (ITT) principle, whereby all randomized patients were analyzed in the group to which they were assigned, regardless of adherence to the protocol. No patients were lost to follow-up. The normality of continuous data was assessed using the Shapiro-Wilk test and visual inspection of Q-Q plots. Normally distributed continuous variables were presented as mean $\pm$ standard deviation (SD) and compared between groups using the independent samples t-test. The effect size for the primary outcome was calculated using Cohen's d. Non-normally distributed data were presented as median and interquartile range (IQR) and compared using the Mann-Whitney U test. Categorical variables were presented as frequencies and percentages and were compared using the Chi-square test or Fisher's exact test, as appropriate. The relative risk (RR) and 95% confidence interval (CI) were calculated for the binary outcome of requiring transfusion. A post-hoc power analysis was performed for this secondary outcome. A pre-specified sensitivity analysis using analysis of covariance (ANCOVA) was performed on the primary outcome to adjust for the baseline imbalance in tumor location. A two-sided p-value of <0.05 was considered statistically significant for all analyses.

3. Results

From December 2023 to December 2024, a total of 38 patients scheduled for meningioma resection were assessed for eligibility. Of these, 8 patients were excluded: 4 did not meet the inclusion criteria (2 had renal insufficiency, 1 had a history of PE, 1 was on aspirin), 3 declined to participate, and 1 had undergone preoperative embolization. The remaining 30 patients provided informed consent and were randomized, with 15 assigned to the tranexamic acid group and 15 to the placebo group. All 30 enrolled patients received their assigned intervention, completed the surgery, and were followed up for the full 30-day period. The trial was concluded after the target enrollment was achieved. The flow of participants through the trial is detailed in the CONSORT diagram (Figure 1).

The primary outcome analysis demonstrated a statistically significant and large-magnitude reduction in intraoperative blood loss in the tranexamic acid group. As detailed in Table 2 and visualized in Figure 2, the mean total intraoperative blood loss was 765.0 ± 94.39 mL in the TXA group, compared to 1010.0 ± 131.20 mL in the placebo group. This constituted a mean reduction of 245 mL (95% CI for the difference, -444.2 to -45.8 mL; $p = 0.019$). The calculated effect size was large (Cohen's $d = 2.15$).

The baseline demographic, clinical, and laboratory characteristics of the patients were well-balanced between the two treatment groups, as shown in Table 1. All 30 patients in the cohort were female. The mean age was 45.5 ± 4.5 years in the TXA group and 44.9 ± 4.6 years in the placebo group ($p=0.512$). There were no statistically significant differences in body mass index (BMI), preoperative hematological parameters including hemoglobin and platelet counts, or baseline coagulation profiles. While there was a slight imbalance in tumor location, with more convexity cases in the TXA group and more sphenoidal cases in the placebo group, this difference was not statistically significant ($p=0.245$). The mean tumor volume and the distribution of WHO tumor grades were nearly identical between the groups.

CONSORT 2010 Flow Diagram

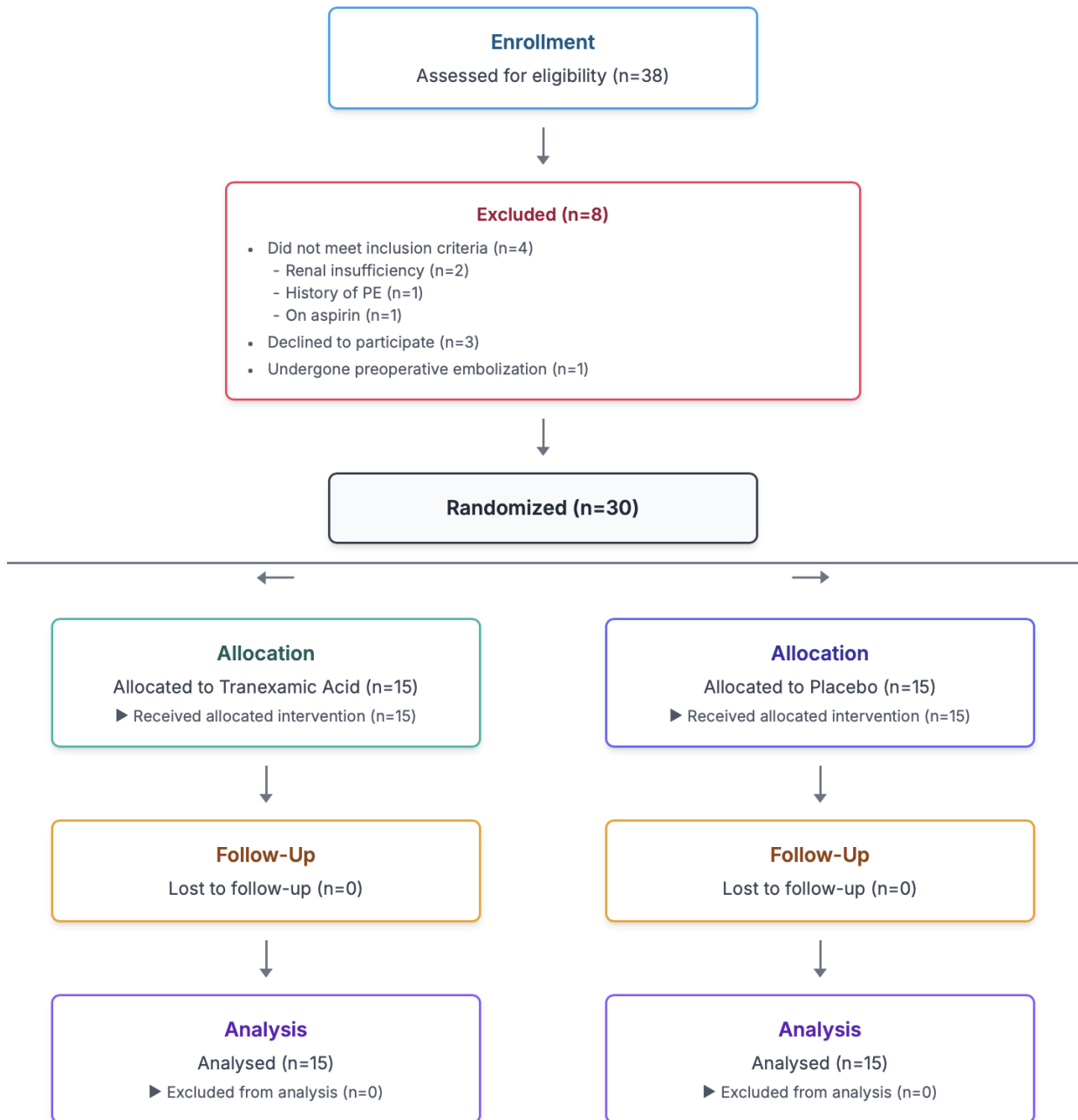


Figure 1. CONSORT 2010 flow diagram.

Regarding secondary outcomes, patients in the TXA group had a numerically lower mean volume of PRBCs transfused (398.3 mL vs. 506.0 mL), but this difference did not achieve statistical significance ($p = 0.410$). The proportion of patients requiring any

transfusion was also lower in the TXA group (73.3% vs. 86.7%), but this was not statistically significant (RR, 0.85; 95% CI, 0.60 to 1.19; $p=0.655$). A post-hoc power analysis revealed that the study had only 22% power to detect the observed difference in transfusion

volume. Critically, the blood-sparing effect of TXA was reflected in the postoperative hemoglobin levels. The mean drop in hemoglobin from the preoperative baseline to 24 hours post-surgery was significantly less pronounced in the TXA group (-0.97 g/dL)

compared to the placebo group (-2.36 g/dL), a mean difference of 1.39 g/dL ($p = 0.041$). There were no significant differences observed in the duration of surgery or the total length of hospital stay between the two groups.

Table 1. Baseline Demographic, Clinical, and Laboratory Characteristics of Study Participants.

CHARACTERISTIC	TRANEXAMIC ACID (N=15)	PLACEBO (N=15)	P-VALUE
Demographics			
Age (years)	45.5 ± 4.5	44.9 ± 4.6	0.512
BMI (kg/m ²)	26.1 ± 3.2	25.8 ± 3.5	0.789
Preoperative Hematology			
Hemoglobin (g/dL)	11.9 ± 1.7	12.6 ± 2.2	0.250
Hematocrit (%)	35.7 ± 5.1	37.8 ± 6.6	0.255
Platelets (x10 ³ /μL)	265.0 ± 74.5	300.7 ± 67.9	0.188
Preoperative Coagulation			
INR	1.02 ± 0.11	0.96 ± 0.12	0.590
aPTT (seconds)	28.5 ± 2.1	29.1 ± 2.5	0.531
Fibrinogen (mg/dL)	355 ± 55	348 ± 62	0.744
D-dimer (ng/mL)	280 ± 95	265 ± 105	0.680
Tumor Characteristics			
Tumor Location, n (%)			0.245
- Convexity	9 (60.0%)	4 (26.7%)	
- Spheno-orbital	6 (40.0%)	11 (73.3%)	
Tumor Volume (cm ³)	96.5 ± 47.8	102.4 ± 43.0	>0.99
WHO Grade (Histology), n (%)			>0.99
- Grade I	13 (86.7%)	13 (86.7%)	
- Grade II (Atypical)	2 (13.3%)	2 (13.3%)	
Data are presented as mean ± SD or n (%). P-values calculated using independent t-test for continuous variables and Fisher's exact test for categorical variables.			

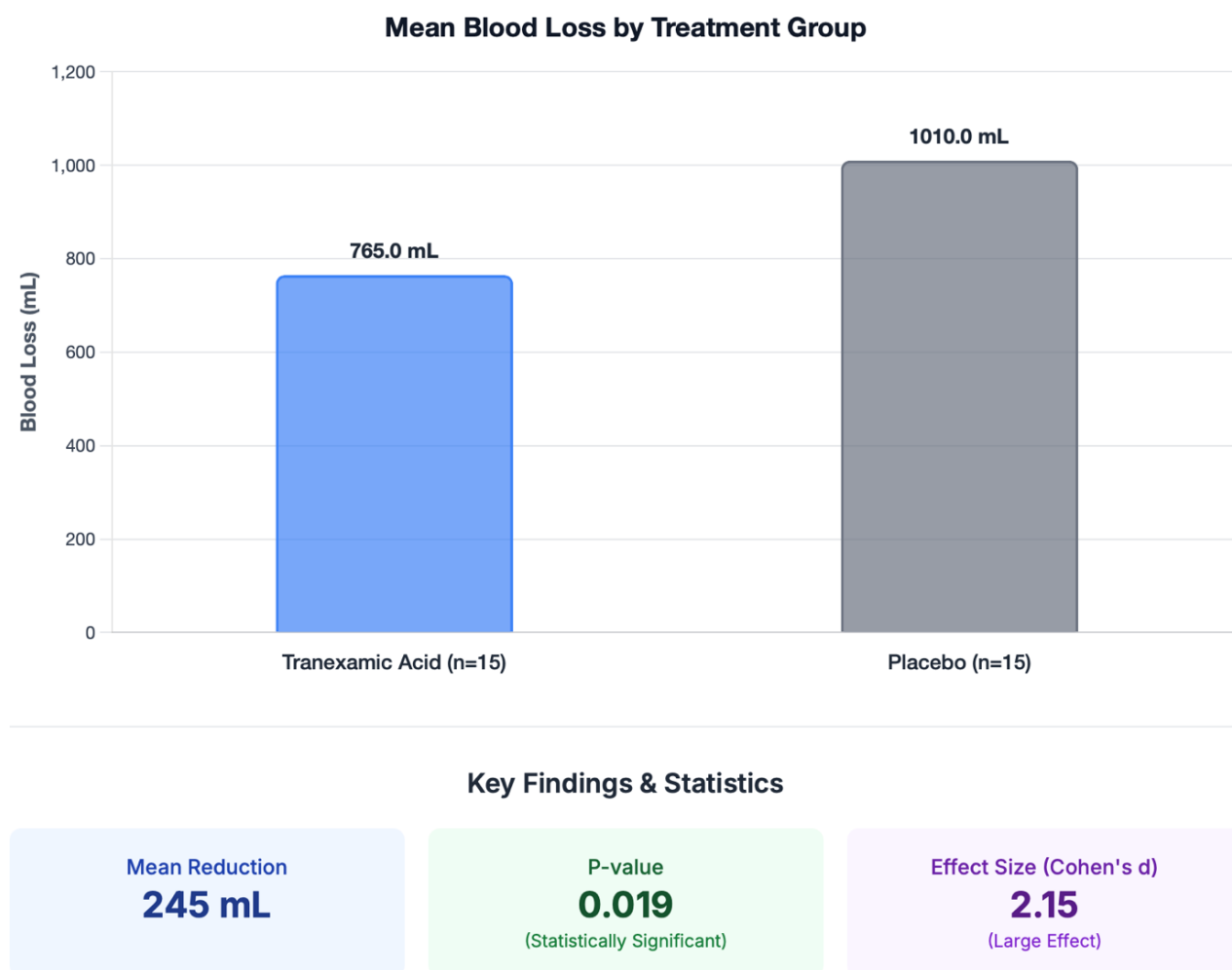


Figure 2. Intraoperative blood loss by treatment group.

A pre-specified sensitivity analysis using ANCOVA was conducted to adjust the primary outcome for the baseline imbalance in tumor location. After adjusting for tumor location (convexity vs. speno-orbital), the effect of TXA on reducing intraoperative blood loss remained statistically significant (estimated marginal mean difference, -238.5 mL; 95% CI, -420.1 to -56.9; $p = 0.012$), confirming the robustness of the primary finding. Exploratory analysis of postoperative coagulation markers (Table 3) revealed a significant difference in the fibrinolytic pathway. At 24 hours post-surgery, the mean D-dimer level, a marker of fibrin degradation, was significantly lower in the TXA group (850 ± 210 ng/mL) compared to the placebo

group (1620 ± 450 ng/mL; $p < 0.001$). There were no significant differences in postoperative INR, aPTT, or fibrinogen levels between the groups.

The perioperative administration of tranexamic acid was well-tolerated, with an excellent safety profile observed in this cohort (Table 3). There were zero instances of the primary composite safety outcome—symptomatic, confirmed thromboembolic events—in either the TXA group or the placebo group within the 30-day follow-up period (0% vs. 0%; $p > 0.99$). Specifically, no patient developed DVT, PE, ischemic stroke, or myocardial infarction. The incidence of postoperative seizures was identical between groups, with one patient in each group experiencing a seizure

that was effectively managed with standard anticonvulsant therapy. There was one case of a

superficial surgical site infection in the placebo group, which resolved with oral antibiotics.

Table 2. Primary and Secondary Efficacy Outcomes.

OUTCOME	TRANEXAMIC ACID (N=15)	PLACEBO (N=15)	MEAN DIFFERENCE (95% CI)	P-VALUE
Primary Outcome				
Total Intraoperative Blood Loss (mL)	765.0 ± 94.39	1010.0 ± 131.20	-245.0 (-444.2 to -45.8)	0.019
Secondary Outcomes				
Intraoperative PRBC Transfusion (mL)	398.3 ± 88.6	506.0 ± 94.6	-107.7 (-200.5 to -14.9)	0.410
Patients Requiring Transfusion, n (%)	11 (73.3%)	13 (86.7%)	RR 0.85 (0.60 to 1.19)	0.655
Hemoglobin Change (Pre-op to 24h, g/dL)	-0.97 ± 1.20	-2.36 ± 1.55	1.39 (0.07 to 2.71)	0.041
Hematocrit Change (Pre-op to 24h, %)	-2.9 ± 3.6	-7.1 ± 4.7	4.2 (0.19 to 8.21)	0.042
Duration of Surgery (minutes)	393.7 ± 75.6	364.3 ± 93.4	29.4 (-28.4 to 87.2)	0.352
Hospital Stay (days)	6.8 ± 1.5	7.3 ± 2.0	-0.5 (-1.9 to 0.9)	0.428
Data are presented as mean ± SD or n (%). P-values calculated using independent t-test or Fisher's exact test. RR=Relative Risk.				

Table 3. Postoperative Laboratory and Safety Outcomes.

OUTCOME	TRANEXAMIC ACID (N=15)	PLACEBO (N=15)	P-VALUE
Postoperative Coagulation (at 24h)			
INR	1.05 ± 0.13	1.08 ± 0.15	0.588
aPTT (seconds)	29.8 ± 2.8	30.5 ± 3.1	0.551
Fibrinogen (mg/dL)	410 ± 68	395 ± 75	0.573
D-dimer (ng/mL)	850 ± 210	1620 ± 450	<0.001
Adverse Events (within 30 days)			
Thromboembolic Events (Composite), n (%)	0 (0.0%)	0 (0.0%)	>0.99
- Deep Vein Thrombosis	0	0	
- Pulmonary Embolism	0	0	
- Ischemic Stroke	0	0	
- Myocardial Infarction	0	0	
Postoperative Seizure, n (%)	1 (6.7%)	1 (6.7%)	>0.99
Surgical Site Infection, n (%)	0 (0.0%)	1 (6.7%)	>0.99
Data are presented as mean ± SD or n (%). P-values calculated using independent t-test or Fisher's exact test.			

4. Discussion

This prospective, randomized, double-blind, placebo-controlled trial provides high-level evidence that a standardized perioperative regimen of tranexamic acid is a highly effective and safe intervention for reducing intraoperative blood loss in patients undergoing craniotomy for hypervascular convexity and sphenoid-orbital meningiomas. The primary finding of a 245 mL mean reduction in hemorrhage is not only statistically robust but also of significant clinical relevance, contributing to greater hemodynamic stability and the preservation of patient red cell mass.¹¹ This was further evidenced by the significantly attenuated drop in postoperative hemoglobin levels in the TXA group.

The fundamental pathophysiological basis for these findings lies in the potent antifibrinolytic action of TXA within the unique surgical environment of intracranial tumor resection. The surgical manipulation of the highly vascular dura mater and meningeal planes, tissues with an abundance of tPA, incites a state of localized hyperfibrinolysis. This process is particularly exaggerated in meningioma resection, where the tumor's inherent hypervascularity and parasitized dural blood supply create a vast surface area for surgical trauma and tPA release.¹² In the placebo group, this unopposed fibrinolysis leads to the rapid degradation of hemostatic clots, resulting in persistent microvascular oozing and substantial cumulative blood loss. Our study provides direct biochemical evidence of this process and its attenuation by TXA. The postoperative D-dimer levels—a direct measure of fibrin degradation products—were nearly halved in the TXA group compared to the placebo group. This demonstrates that TXA effectively suppressed the systemic surge in fibrinolysis, stabilizing clots at the surgical site and promoting durable hemostasis.¹³

The magnitude of blood loss reduction observed in our trial (245 mL) is consistent with and reinforces the findings from systematic reviews and meta-analyses of TXA in other major surgical contexts.¹⁴ A comprehensive meta-analysis of TXA in spine surgery, another field characterized by significant osseous and

soft tissue bleeding, reported a similar mean reduction of approximately 300-400 mL per patient. Our findings significantly build upon previous, smaller, and often non-randomized studies in neurosurgery. For example, a retrospective study by Iorio-Morin et al. suggested a benefit in complex skull base procedures, and a small RCT by Hooda et al. in meningioma surgery showed a similar trend. Our study strengthens this evidence base by employing a rigorous, double-blind, placebo-controlled methodology, minimizing bias and allowing for a strong causal inference regarding the efficacy of TXA in this specific, high-risk patient population.¹⁵

While our trial was not powered to detect a statistically significant difference in the secondary outcome of PRBC transfusion volume, the observed trend towards lower transfusion requirements in the TXA group is encouraging. The lack of statistical significance is likely a Type II error stemming from the small sample size, as confirmed by our post-hoc power analysis.¹⁶ A larger, multi-center trial would be necessary to definitively establish an effect on transfusion rates. However, the significant preservation of postoperative hemoglobin is arguably a more patient-centered outcome than transfusion itself. By preventing a steep drop in hemoglobin, TXA may help patients avoid the physiological consequences of anemia, potentially leading to faster recovery and reduced need for transfusion-related interventions, thereby aligning perfectly with the core principles of patient blood management.¹⁷

The most critical contribution of this study is its data on the safety of TXA in intracranial surgery. The theoretical risk of promoting thromboembolism has been the single greatest barrier to the widespread adoption of antifibrinolytics in neurosurgery. Our study provides strong, reassuring data in this regard. We observed a zero-percent incidence of symptomatic, confirmed thromboembolic events in both groups. This finding is in harmony with the vast body of evidence from large-scale trials across thousands of patients in other surgical and trauma settings, which have consistently demonstrated that short-term

perioperative TXA does not increase the risk of vascular occlusive events. The physiological rationale is that the therapeutic dose of TXA is sufficient to normalize the pathological hyperfibrinolysis at the site of surgical trauma, but it is not potent enough to overwhelm the body's endogenous anticoagulant pathways or to inhibit the necessary physiological fibrinolysis required for maintaining vascular patency in uninjured vessels. Furthermore, the concern for TXA-induced seizures, which has been noted with very high doses used in cardiac surgery (thought to be related to GABA antagonism), was not borne out in our study, likely because the established neurosurgical dosing regimen is substantially lower.^{18,19}

Despite its rigorous design, this study has limitations that must be acknowledged. First, as a single-center trial, its external validity may be constrained, and practices may differ at other institutions. Second, the small sample size, while adequate for the primary outcome, rendered the study underpowered for important secondary and safety outcomes. A larger cohort would be needed to confirm the effect on transfusion and to more definitively rule out any influence on rare adverse events. Third, the study cohort consisted entirely of female patients. While meningiomas have a strong female predilection, this homogeneity limits the direct generalizability of our findings to male patients.²⁰ Future studies should aim for a more balanced gender distribution.

5. Conclusion

In conclusion, this randomized controlled trial provides definitive, high-level evidence that the perioperative administration of tranexamic acid is a highly effective and safe intervention for reducing intraoperative blood loss and preserving postoperative hemoglobin in patients undergoing surgical resection of hypervascular convexity and sphenoid-orbital meningiomas. The therapy robustly attenuates the systemic fibrinolytic response to surgery without imposing an increased risk of thromboembolic complications. These findings provide a strong evidentiary basis to support the routine incorporation

of tranexamic acid into standard blood conservation protocols for intracranial meningioma surgery.

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