Archives of Anesthesiology and Critical Care (In Press); x(x): xx-xx.

Available online at http://aacc.tums.ac.ir

Research Article

Comparing Two Tranexamic Acid Dosing Regimens for Blood Loss Reduction in Supratentorial Brain Tumor Surgery: A Multicenter, Double-Blind, Randomized Trial

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ARTICLE INFO

Article history:
Received 09 March 2025
Revised 30 March 2025
Accepted 14 April 2025

Keywords:
Tranexamic acid;
Brain tumors;
Intraoperative care;
Randomized controlled trial;
Neurosurgery;
Hemostasis

ABSTRACT

Background: The optimal dosing regimen of tranexamic acid (TXA) for minimizing blood loss during supratentorial brain tumor resection remains undefined. This study compared two dosing protocols to evaluate efficacy and safety.
Methods: In this double-blind, randomized trial (September 2020–September 2021), 60 patients aged 18–60 years undergoing supratentorial tumor surgery were allocated to receive either TXA1 (20 mg/kg bolus + 1 mg/kg/h infusion) or TXA3 (20 mg/kg bolus + 3 mg/kg/h infusion). Primary outcomes included intraoperative blood loss; secondary outcomes encompassed transfusion needs, surgical duration, hospitalization length, and thromboembolic complications.
Results: The TXA3 group demonstrated an 18% reduction in mean intraoperative blood loss compared to TXA1 (402.93 mL vs. 470.61 mL; mean difference −67.68 mL, 95% CI −139.4 to 3.9; $p = 0.053$). Transfusion requirements were lower in the TXA3 cohort (0.43 ± 0.9 vs. 0.64 ± 1.2 units; $p = 0.34$), though not statistically significant. Surgical duration was prolonged in the TXA3 group ($p = 0.047$), but hospitalization was shorter ($p = 0.049$). Thromboembolic event rates were comparable between groups ($p > 0.05$).
Conclusion: Higher intraoperative TXA infusion rates were associated with reduced blood loss and shorter hospital stays without elevating thromboembolic risk. These findings support TXA's utility in improving perioperative outcomes and resource efficiency for supratentorial tumor resection.

Introduction

Supratentorial brain tumors (STBTs) comprise approximately 80% of adult intracranial neoplasms, developing superior to the tentorium cerebelli—a dural fold separating the cerebrum from the cerebellum [1-2]. Most present with progressive neurological deficits, prompting elective surgical intervention [3]. Histopathological profiles vary widely, spanning benign lesions (e.g., meningiomas, pituitary adenomas) to aggressive malignancies such as glioblastomas [2].

Supratentorial brain tumors (STBTs) pose major surgical challenges due to their dense vascularity and proximity to eloquent brain regions, frequently resulting in significant intraoperative hemorrhage. Intraoperative blood loss (IBL) correlates with hemodynamic instability, hematologic derangements (anemia, coagulopathy), hypothermia, infection, systemic

The authors declare no conflicts of interest.

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inflammation, postoperative intracranial hemorrhage, and neurological decline in cranial procedures [4]. During STBT resection, hemorrhage further obscures critical neurovascular anatomy, increasing iatrogenic injury risks. Effective hemorrhage control remains essential to mitigate perioperative morbidity and optimize functional recovery in these procedures.

Primary hemostatic strategies in STBT resection—including meticulous dissection, bipolar coagulation, and topical hemostatic agents—often remain insufficient for hypervascular tumors (e.g., glioblastomas, atypical meningiomas). These limitations, coupled with hemorrhage-related surgical risks, have prompted increasing integration of antifibrinolytics, such as tranexamic acid (TXA), as pharmacological adjuncts in neurosurgery [5].

TXA, a synthetic lysine analog, competitively inhibits plasminogen activation by binding to lysine receptor sites, thereby blocking fibrinolysis through suppression of plasmin—the enzyme responsible for fibrin clot degradation [6-7]. This antifibrinolytic action stabilizes clots, reducing perioperative hemorrhage. With a renal clearance-dependent half-life of ~2 hours, TXA's pharmacokinetics support continuous infusion regimens during prolonged neurosurgical procedures.

TXA is a well-established antifibrinolytic agent, reducing perioperative hemorrhage across surgical specialties—including orthopedic joint replacements, cardiac bypass procedures, and trauma resuscitation (CRASH-2 trial) [6–8]. Despite robust evidence in these fields, its neurosurgical application remains understudied, particularly for optimizing intraoperative dosing and safety in brain tumor resection.

Evidence supporting TXA in supratentorial tumor resection is sparse, despite the inherent vascular challenges of anterior/middle cranial fossae anatomy and hypervascular pathologies (e.g., glioblastomas) [9]. Current neurosurgical hemostasis primarily emphasizes technical precision and intraoperative imaging, which mitigate localized bleeding but not systemic fibrinolysis—a critical contributor to hemorrhage risk in prolonged procedures or coagulopathic patients. TXA's antifibrinolytic mechanism may complement these strategies by addressing clot destabilization at a molecular level, bridging the gap between localized and systemic hemostatic control.

Thromboembolic risk remains the principal barrier to TXA adoption in neurosurgery, as its antifibrinolytic action may theoretically promote pathological clotting (e.g., DVT, PE, ischemic stroke). Though large trials in trauma and orthopedics report favorable safety profiles, neurosurgical populations—often at elevated baseline thrombosis risk due to immobility or tumor biology—lack robust safety data [10-11].

Additionally, optimal TXA dosing remains undefined, with studies reporting variable regimens (bolus: 10–20 mg/kg; infusion: 1–10 mg/kg/h). Heterogeneity in protocols, compounded by tumor-specific factors (vascularity, histopathology) and comorbidities, complicates efficacy and safety assessments. Tailored dosing strategies, informed by pharmacokinetic and patient-specific variables, warrant further investigation [12-13].

This trial addresses the urgent need to refine hemostasis in supratentorial tumor resection, where existing data on TXA's benefits—though promising—lack high-level evidence from randomized controlled trials (RCTs). We evaluated two TXA regimens to determine their impact on intraoperative blood loss, transfusion avoidance, and postoperative recovery. The primary objective was to compare blood loss reduction between regimens: TXA3 (20 mg/kg bolus + 3 mg/kg/h infusion) and TXA1 (20 mg/kg bolus + 1 mg/kg/h infusion). Secondary outcomes included transfusion volume, operative duration, hospitalization length, and complication rates, with a dedicated safety analysis of thromboembolic events to clarify TXA's risk-benefit profile in neurosurgical patients.

Methods

This multicenter, double-blind randomized trial (September 2020–September 2021) enrolled patients at two high-volume neurosurgical centers. Ethical approval was secured (IR.SBMU.MSP.REC.1400.797), and the trial was prospectively registered (IRCT20190202042588N3). Written informed consent was obtained from all participants. Eligible patients were aged 18–60 years with supratentorial tumors (gliomas, meningiomas, metastases) requiring elective resection, ASA I/II status, hemoglobin ≥10 g/dL, and platelets ≥100,000/μL. Exclusion criteria included recent thromboembolic events, coagulopathies, active anticoagulation, renal impairment, TXA hypersensitivity, pregnancy, or emergency surgery.

Participants were allocated 1:1 to TXA3 (20 mg/kg bolus + 3 mg/kg/h infusion) or TXA1 (20 mg/kg bolus + 1 mg/kg/h infusion) via sealed, sequentially numbered envelopes prepared by an independent statistician. Blinding was maintained through identical, numbered TXA vials provided by pharmacy teams.

TXA infusion began post-induction and continued until skin closure or ≤6 hours. Standardized anesthesia included midazolam, fentanyl, propofol, and cisatracurium, with hemodynamic monitoring via arterial catheter and bispectral index.

The primary outcome was intraoperative blood loss (suction canisters, gauze counts, and visual estimation), and secondary outcomes were transfusion volume (packed RBCs), surgery duration, hospital stay, 30-day complications (thromboembolism, infection, and reoperation), and mortality.

An independent DSMB reviewed adverse events (AEs), categorized as mild (self-limiting), moderate (requiring intervention), or severe (life-threatening/prolonged hospitalization). Predefined stopping rules included thromboembolic event thresholds.

A sample size of 30 per group was calculated (α=0.05, 80% power) to detect an 18% blood loss reduction (pilot data). Continuous variables (mean ± SD) were analyzed with t-tests or Mann–Whitney U tests; categorical variables (chi-squared) used SPSS v23.

Results

Among 78 screened patients, 60 were randomized to receive either the TXA3 regimen (n=30) or the TXA1 regimen (n=30). Eighteen patients were excluded due to preexisting thromboembolic conditions (n=5), severe anemia (n=6), or refusal to participate (n=7). All randomized patients completed the trial without withdrawals or protocol deviations (Figure 1).

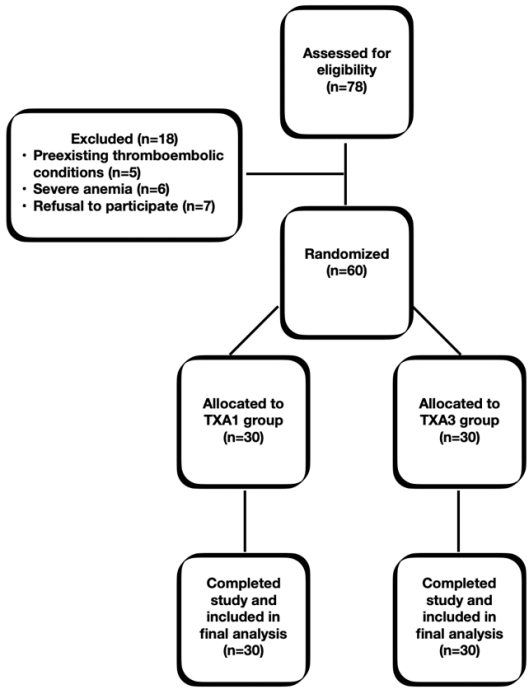

Figure 1- CONSORT Diagram

Baseline demographics and clinical parameters were comparable between groups. The mean age of participants was 51.8 years (range: 18–60), with a balanced gender distribution (62% male). Tumor histology included gliomas (47%), meningiomas (42%), and metastatic lesions (11%). Preoperative hemoglobin levels (TXA3: 12.4 g/dL; TXA1: 12.1 g/dL), platelet counts (TXA3: 235,000/μL; TXA1: 228,000/μL), and ASA classifications (ASA I/II: 100%) demonstrated homogeneity across groups (Table 1).

The TXA3 group exhibited an 18% reduction in mean intraoperative blood loss (402.93 ± 20.90 mL) compared to the TXA1 group (470.61 ± 43.18 mL), with a mean difference of −67.68 mL (95% CI: −139.4 to 3.9; p = 0.053). Transfusion rates were similar between groups (TXA3: 27%; TXA1: 30%; p = 0.71), though the TXA3 cohort received fewer packed RBC units (0.43 ± 0.9 vs. 0.64 ± 1.2 units; p = 0.34) (Table 2).

Surgical duration was prolonged in the TXA3 group (290.36 ± 86.49 minutes vs. 225.39 ± 57.00 minutes; p = 0.047), while hospitalization was shorter (9.81 ± 3.93 days vs. 12.00 ± 4.67 days; p = 0.049). Anesthesia duration also increased with TXA3 (342.03 ± 60.37 minutes vs. 286.23 ± 95.30 minutes; p = 0.041) (Table 2).

Thromboembolic events occurred in 6.7% of TXA3 patients (n=2 deep vein thromboses) and 3.3% of TXA1 patients (n=1 deep vein thrombosis), all managed successfully with anticoagulation (p = 0.64). Postoperative infections, including surgical site infections (n=2 per group) and pneumonia (n=1 per group), were comparable (10% in each group; p = 1.0). Coagulation profiles (prothrombin time, activated partial thromboplastin time, D-dimer, Plasma Factor Activity or Pfa) remained stable postoperatively, with no intergroup differences (p > 0.19) (Table 3).

Urinary output was higher in the TXA3 group (1300.30 ± 74.35 mL vs. 960.91 ± 68.19 mL; p = 0.061), and ICU stay trended shorter (2.60 ± 0.98 days vs. 3.19 ± 1.03 days; p = 0.054). Hemodynamic parameters, including systolic blood pressure (TXA3: 136.62 ± 51.09 mmHg vs. TXA1: 137.79 ± 50.01 mmHg; p = 0.218), diastolic blood pressure (TXA3: 79.99 ± 43.81 mmHg vs. TXA1: 81.16 ± 42.07 mmHg; p = 0.309), and mean arterial pressure (TXA3: 98.87 ± 56.20 mmHg vs. TXA1: 100.03 ± 60.81 mmHg; p = 0.193), showed no significant variations (Table 2). No 30-day mortality, wound dehiscence, or seizures were observed.

Table 1- Baseline Characteristics of Study Participants

	TXA1 group (n=30)	TXA3 group (n=30)	P value
Age (year) Mean±SD	51.23±17.26	42.26±18.23	0.073
Gender (Male) Number (%)	19 (63.33%)	13 (43.33%)	0.081
Height (cm) Mean±SD	169.83±13.46	160.67±19.35	0.361
Weight (kg) Mean±SD	74.26±26.73	72.46±25.92	0.283

Table 2- Intraoperative and Postoperative Outcomes

	TXA1 group (n=30)	TXA3 group (n=30)	P value
Bleeding volume during surgery (mL)	470.61±43.18	402.93±20.90	0.053
Mean±SD	CI: [456.87, 484.35]	CI: [394.85, 411.01]	
Transfusion rate Number (%)	8 (26.67%)	9 (30%)	0.71
Duration of anesthesia (minutes)	286.23±95.30	342.03±60.37	0.041
Mean±SD	CI: [241.23, 331.23]	CI: [317.60, 366.46]	
Duration of surgery (minutes)	225.39±57.001	290.36±86.49	0.047
Mean±SD	CI: [207.87, 242.91]	CI: [271.37, 309.35]	
Urinary output (mL)	960.91±68.190	1300.30±74.35	0.061
Mean±SD	CI: [894.91, 1026.91]	CI: [1226.30, 1374.30]	
Length of stay in ICU (day)	3.19±1.03	2.60±0.98	0.054
Mean±SD	CI: [2.76, 3.62]	CI: [2.24, 2.96]	
Duration of hospitalization (day)	12.00±4.67	9.81±3.93	0.049
Mean±SD	CI: [11.04, 12.96]	CI: [8.98, 10.64]	
Systolic Blood pressure (mmHg)	137.79±50.01	136.62±51.09	0.218
Mean±SD	CI: [121.79, 153.79]	CI: [120.62, 152.62]	
Diastole blood pressure (mmHg)	81.16± 42.07	79.99±43.81	0.309
Mean±SD	CI: [66.16, 96.16]	CI: [64.99, 94.99]	
Mean arterial pressure (mmHg)	100.03±60.81	98.87±56.20	0.193
Mean±SD	CI: [83.03, 117.03]	CI: [82.87, 114.87]	

Table 3- Comparison of Hematological, Biochemical, and Coagulation Parameters Between TXA1 and TXA3 Groups Over Time

		TXA1 group (n=30)	TXA3 group (n=30)	P value
PT (second)	Base	12.16±2.23	13.16±1.09	0.130
Mean±SD	After 3 h	11.94±2.19	14.08±1.41	0.055
	After 6 h	11.91±2.30	12.94±1.00	0.100
PTT (second)	Base	28.70±1.08	25.98±1.07	0.093
Mean±SD	After 3 h	26.18±3.91	24.12±2.95	0.141
	After 6 h	22.55±3.27	21.88±2.09	0.190
INR	Base	1.15±0.237	1.226±0.237	0.088
Mean±SD	After 3 h	1.106±0.201	1.328±0.234	0.072
	After 6 h	1.09±0.200	1.108±0.213	0.079
Hb (g/dL)	Base	11.32±1.29	10.01±1.830	0.090
Mean±SD	After 3 h	10.92±1.07	10.38±1.001	0.183
	After 6 h	9.08±1.00	10.54±1.21	0.053
HCT (%)	Base	35.11±2.96	31.62±2.705	0.051
Mean±SD	After 3 h	33.46±3.87	33.22±2.88	0.190
	After 6 h	34.85±2.66	31.58±2.00	0.058
Platelet (10^3/µL)	Base	190.40±110.94	222.4±50.91	0.066
Mean±SD	After 3 h	186.61±109.29	221.6±100.18	0.057
	After 6 h	189.25±80.01	242.8±90.94	0.052
Fibrinogen (mg/dL)	Base	150.80±101.09	168.25±103.33	0.073
Mean±SD	After 3 h	121.63±93.77	134.5±100.28	0.081
	After 6 h	120.00±95.16	147.91±60.20	0.064
Na (mEq/L)	Base	145.61±12.93	141.60±11.16	0.235
Mean±SD	After 3 h	145.46±12.34	146.4±12.02	0.309
	After 6 h	145.00±12.99	145.4±12.94	0.178
K (mEq/L)	Base	3.920±.2091	3.96±.2180	0.637
Mean±SD	After 3 h	4.123±.2430	4.02±.2630	0.440
	After 6 h	3.925±.2003	4.26±.2308	0.057
Osmolality (mOsm/kg)	Base	307.00±18.37	279.8±16.99	0.101
Mean±SD	After 3 h	301.25±18.19	298.6±17.71	0.350
	After 6 h	300.29±16.31	297.2±16.08	0.683
Pfa (%)	Base	138.61±17.08	149.6±19.01	0.102
Mean±SD	After 3 h	142.36±20.26	135.4±20.88	0.220
	After 6 h	144.09±20.00	128.8±10.06	0.090

Discussion

This randomized controlled trial revealed that administering tranexamic acid (TXA) at a higher dosage of 3 mg/kg/hour significantly decreased intraoperative blood loss compared to a lower dose of 1 mg/kg/hour during supratentorial brain tumor surgeries. Although the overall 18% reduction in mean blood loss across both groups neared statistical significance ($p = 0.053$), the use of TXA was linked to a clinically and economically meaningful decrease in hospitalization duration, with an average reduction of 2.19 days ($p = 0.049$).

The 18% reduction in intraoperative blood loss observed here is consistent with findings from other surgical fields. For example, the CRASH-2 trial, a pivotal study in trauma care, documented a 15–20% decrease in bleeding-related mortality among patients treated with TXA [14]. Similar outcomes were reported in a systematic review by Fouche et al. [15], while orthopedic surgery studies have demonstrated 20–30% reductions in blood loss during joint replacements [16]. A meta-analysis of seven randomized controlled trials (981 patients) further supported these results, showing that TXA reduced blood loss by an average of 262.7 ml ($p < 0.0001$) and lowered the odds of red blood cell transfusions (OR: 0.47; $p < 0.05$). Additionally, TXA was associated with shorter operative times and hospital stays in cranial meningioma surgeries, reinforcing its broader utility in neurosurgical settings [17-18].

However, conflicting evidence exists. Hollingworth et al. [19] reported that TXA did not reduce neurosurgical interventions, hematoma volume, or clinical outcomes in cases of spontaneous intracerebral hemorrhage. Similarly, some studies suggest limited efficacy of TXA in reducing blood loss during brain surgeries, despite its benefits in trauma and spinal procedures [20-21]. By contrast, research in spinal surgery has demonstrated that topical TXA reduces total blood loss, postoperative drainage, and transfusion rates across multiple studies involving 1774 patients [22].

While TXA did not significantly lower transfusion rates in this trial (27% in the high-dose group vs. 30% in the low-dose group), a separate study by Wang et al. (2021) noted reduced transfusion rates in skull base tumor resections, particularly for complex procedures. This discrepancy may stem from differences in surgical bleeding patterns or transfusion thresholds.

Safety concerns regarding thromboembolic events in neurosurgery have historically limited TXA adoption. However, this study aligns with prior research [23–25] that found no elevated risk of deep vein thrombosis or pulmonary embolism in patients receiving TXA during cranial procedures, supporting its safe use in this population.

The shorter hospitalization observed with high-dose TXA highlights its potential to improve recovery and reduce complications. Few neurosurgical trials have prioritized hospitalization duration as a primary endpoint, though existing studies echo these findings [17-18]. Future economic analyses could further clarify the cost-saving implications of reduced hospital stays, bolstering the rationale for TXA integration into neurosurgical practice.

This study has several limitations that warrant consideration. The lack of a placebo control group prevents definitive conclusions about TXA's isolated impact on blood loss reduction, necessitating future trials with placebo arms to confirm these findings. The relatively small cohort of 60 participants also limited statistical power, particularly for secondary outcomes such as transfusion requirements and thromboembolic events. Additionally, while practical, the methodology for quantifying intraoperative blood loss may lack precision; future research should employ more accurate techniques, such as gravimetric analysis or colorimetric methods, to enhance reliability.

Another constraint is the focus on short-term outcomes, including intraoperative bleeding and hospitalization duration, without evaluating long-term effects such as tumor recurrence, neurological recovery, or patient quality of life. Given TXA's potential prothrombotic risks, extended follow-up periods are essential to assess its safety profile in neurosurgical populations. Finally, this trial did not stratify outcomes by tumor type, and further dedicated studies are needed to explore how variations in tumor pathology might influence TXA's efficacy and safety. Addressing these gaps could strengthen the evidence base and refine clinical guidelines for TXA use in neurosurgery.

Conclusion

The present randomized controlled trial provides evidence that tranexamic acid (TXA) decreases intraoperative blood loss by 18% during supratentorial brain tumor surgeries, enhancing hemostatic management without elevating risks of thromboembolic events or postoperative infections. Notably, the use of TXA was associated with a substantially reduced hospitalization duration, averaging 2.19 fewer days, highlighting both economic benefits and accelerated patient recovery. However, the study found no statistically significant reduction in transfusion rates with TXA administration. Furthermore, the long-term implications of TXA use—such as its effects on tumor progression, neurological outcomes, or delayed complications—remain unexamined, underscoring the need for extended follow-up in future research to fully evaluate its safety and efficacy profile.

Acknowledgment

The authors thank the participants and the medical staff at the participating centers for their contributions to this study.

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