

ORIGINAL ARTICLE

Perioperative Tranexamic Acid and Intraoperative Blood Loss in Convexity and Spheno-Orbital Meningioma Resection: A Double-Blind Randomized Placebo-Controlled Trial

Dwiandi Susilo^{1*}¹ Department of Neurosurgery, Dr. Mohammad Hoesin General Hospital, Palembang, Indonesia

ARTICLE INFO

Article history:

Received: September 29, 2025

Revised: October 15, 2025

Accepted: October 28, 2025

Available: November 6, 2025

Published: November 8, 2025

Keywords:

Blood loss, surgical; Craniotomy; Meningioma;

Randomized controlled trial; Tranexamic acid

Corresponding author:

Dwiandi Susilo

Email:

Deand1rs@gmail.com

DOI:

<https://doi.org/10.37275/sjs.v8i2.167>

Access licence:

Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International License (CC BY-NC-SA 4.0).

Copyright:

© 2025 The Authors. Authors retain copyright and grant the journal the right of first publication. Published by HM Publisher.

ABSTRACT

Background: Resection of convexity and spheno-orbital meningiomas can cause substantial bleeding. Trials of tranexamic acid (TXA) in meningioma surgery disagree, and indexed evidence from Indonesia, where most patients are women with skull-base tumors, is lacking.

Objective: To determine whether perioperative TXA reduces intraoperative blood loss during resection of convexity and spheno-orbital meningiomas.

Methods: In this single-center, double-blind, placebo-controlled trial at a tertiary hospital in Palembang (January–December 2024), 30 adults were randomized to TXA (15 mg/kg bolus, then 1 mg/kg/h to dural closure) or saline. The primary outcome was intraoperative blood loss. Location-adjusted and baseline-adjusted estimates were evaluated over all datasets compatible with the group summaries.

Results: All 30 patients, all women, were analyzed. Blood loss was 765.0 mL (SD 94.4) with TXA and 1010.0 mL (SD 131.2) with placebo (difference –245.0 mL; 95% CI –330.5 to –159.5; $p < 0.001$), and the reduction persisted in every location-adjusted configuration (–322.1 to –167.9 mL). Twenty-four-hour D-dimer was lower with TXA (850 vs 1620 ng/mL; $p < 0.001$), and hemoglobin fell less (–0.97 vs –2.36 g/dL; $p = 0.010$; Holm-adjusted $p = 0.055$). Transfusion was required in 73.3% vs 86.7% (risk difference –13.3 points; 95% CI –40.4 to 15.8). No thromboembolic event occurred (0/15 per arm; risk difference 95% CI –20.4 to 20.4 points).

Conclusion: Perioperative TXA reduced blood loss and suppressed fibrinolysis during convexity and spheno-orbital meningioma resection; the smaller hemoglobin fall was supportive. The trial was too small to establish effects on transfusion or thromboembolic safety, which require multicenter trials.

1. Introduction

Meningioma is the most frequent primary intracranial tumor, accounting for 41.7% of all primary brain and other central nervous system tumors in the 2017–2021 population-based report from the United States, and it is considerably more common in women¹. In a national French series of 30,223 histologically confirmed meningiomas, women made up 74.1% of patients and WHO grade 1 tumors 83.9% of cases². A female predominance is also reported in an Indonesian surgical series: among 66 patients with spheno-orbital meningiomas treated at Cipto Mangunkusumo Hospital, 93.9% were women, with a mean age of 44.7 years³. Exposure to selected progestogens is one plausible contributor: a French national case-control study and a US cohort study reported associations between progestogen exposure, particularly depot medroxyprogesterone acetate, and meningioma^{4,5}. Among Indonesian women with meningioma, hormonal contraception was associated with spheno-orbital location (odds ratio [OR] 2.57)⁶. These reports highlight the relevance of women and spheno-orbital tumors to the Indonesian surgical population.

Bleeding is a central technical problem in this surgery. Larger maximal diameter, intratumoral flow voids and skull-base location independently predicted an estimated blood loss of 500 mL or more in a recent case-control study (adjusted ORs 1.58 per cm, 5.68 and 3.35)⁷, and a preoperative vascularity index predicted blood loss independently of tumor volume⁸. Bone involvement adds a further source: meningiomas with hyperostosis lose more blood and take longer to resect⁹, and invasive growth with bone erosion or hyperostosis was the strongest imaging predictor of blood loss in a Central Asian

series¹⁰. Spheno-orbital tumors combine these features, because their resection requires frontotemporal craniotomy, orbito-optic osteotomy and drilling of hyperostotic sphenoid bone¹¹, and proptosis and periorbital edema scale with the intraosseous tumor volume¹². Blood loss in turn drives transfusion, which is associated with worse outcomes. In 40,883 tumor craniotomies in the American College of Surgeons National Surgical Quality Improvement Program (NSQIP), female sex (OR 1.41), preoperative anemia (OR 2.84) and a meningioma indication (OR 1.28) independently predicted transfusion¹³; in a German meningioma series, transfusion was driven by tumor size and blood loss and was associated with shorter survival¹⁴; and in 8,159 brain-tumor craniotomies each 10% postoperative fall in hemoglobin increased the odds of 30-day death by 46%¹⁵. In low-resource settings the burden is larger: at an Ethiopian tertiary hospital, mean estimated blood loss during elective brain-tumor craniotomy exceeded one liter and 37% of patients were transfused¹⁶.

Surgical trauma to the dura, bone and tumor bed releases tissue plasminogen activator, which converts plasminogen to plasmin; plasmin degrades fibrin, dissolves newly formed clots and sustains diffuse oozing from the operative field. Tranexamic acid (TXA), a synthetic lysine analogue, occupies the lysine-binding sites of plasminogen and blocks both its binding to fibrin and its activation. In children undergoing craniofacial surgery, TXA increased postoperative clot firmness and resistance to plasminogen-activator-induced lysis¹⁷, and in arthroplasty a higher dose lowered D-dimer and fibrin degradation products while further reducing blood loss¹⁸. The safety of TXA has been examined in very large trials. In 9,535 patients undergoing

noncardiac surgery, TXA reduced the composite bleeding outcome (hazard ratio [HR] 0.76) without a demonstrable increase in cardiovascular events (HR 1.02)¹⁹; standard-dose TXA did not increase vascular occlusive events in more than 12,000 patients with traumatic brain injury²⁰; and a meta-analysis of 216 trials and 125,550 patients found thromboembolic events in 2.1% of patients given TXA and 2.0% of controls²¹. Two concerns persist in neurosurgery. TXA has been independently associated with convulsive seizures after open-heart surgery²², although a randomized comparison of high- and low-dose infusions in cardiac surgery found no significant difference in seizures²³, and a 4 g 24-hour infusion in gastrointestinal bleeding nearly doubled venous thromboembolism without reducing deaths²⁴; and patients undergoing tumor craniotomy already carry a substantial baseline thrombotic risk.

Evidence in meningioma surgery is mixed. Placebo-controlled trials that gave a loading dose followed by an infusion until the end of surgery reported reductions in blood loss of 294 mL in India²⁵, 251 mL in Tunisia²⁶ and 534 mL in a 30-patient Indian trial²⁷, and four meta-analyses have pooled reductions of 263 to 316 mL^{28–31}. However, the most recent pooled estimate carries extreme heterogeneity ($I^2 = 99\%$)³¹, and a large Beijing trial that gave a single 20 mg/kg bolus to 600 patients found no reduction in blood loss³². Most trials pooled tumors of all locations, so the effect in bone-involving spheno-orbital tumors remains uncertain. Safety evidence is also thin: the six meningioma trials in one meta-analysis included 381 patients and recorded no venous thromboembolism in either arm²⁹, yet cohort studies report postoperative venous thromboembolism in 6–10% of patients after meningioma or skull-base surgery^{33–35}.

The question is particularly relevant in Indonesia. Anemia is common in Indonesian women, with a high proportion of microcytic anemia attributable to iron deficiency and thalassaemia³⁶, so many patients start surgery with little hemoglobin reserve. Blood services in low- and middle-income countries depend on voluntary and replacement donors and frequently charge for components³⁷, and a regional Asia-Pacific donor study that included Indonesia found older donors underrepresented in every participating region³⁸. Consultant neurosurgeon density averages 1.13 per 100,000 people in upper-middle-income countries such as Indonesia, against more than 2 per 100,000 in high-income countries³⁹, so long operations on hypervascular tumors compete for scarce theatre time, anesthesia staff and blood. The only earlier Indonesian randomized trial of TXA in meningioma surgery was published in a national anesthesia journal⁴⁰, and no trial has addressed convexity and spheno-orbital tumors specifically or reported the fibrinolytic response at Dr. Mohammad Hoesin General Hospital, the tertiary referral center for South Sumatra.

This double-blind, randomized, placebo-controlled trial therefore tested the hypothesis that a perioperative regimen of TXA — a 15 mg/kg loading dose followed by 1 mg/kg/h until dural closure — reduces intraoperative blood loss compared with placebo in adults undergoing elective resection of convexity or spheno-orbital meningiomas. Secondary aims were to estimate the effects on transfusion, perioperative hemoglobin and hematocrit, coagulation and fibrinolysis markers, and 30-day thromboembolic and other adverse events; to test whether the primary result was robust to the imbalance in tumor location between arms; and to place the result in the context of the published trials.

2. Methods

Trial design

This was a single-center, prospective, randomized, double-blind, placebo-controlled, parallel-group superiority trial with 1:1 allocation, reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) 2010 statement. The trial compared a perioperative intravenous regimen of tranexamic acid (TXA) with a matching saline placebo in adults undergoing elective craniotomy for convexity or spheno-orbital meningioma.

Ethical approval

The trial was conducted in accordance with the Declaration of Helsinki and the International Council for Harmonisation Good Clinical Practice guideline. The protocol and the informed-consent form were reviewed and approved by CMHC Indonesia (approval number CMHC/EC/IRB/2024/8556) in 2024, before the first patient was enrolled. Every participant, or a legally authorized representative, gave written informed consent before any study-related procedure.

Setting and participants

The trial was conducted at the Department of Neurosurgery, Dr. Mohammad Hoesin General Hospital, Palembang, South Sumatra, Indonesia, the Ministry of Health tertiary referral hospital for the province, between January and December 2024. All adults scheduled for elective meningioma resection during this period were screened consecutively. Patients were eligible if they were 18–65 years old, had a convexity or spheno-orbital meningioma diagnosed on contrast-enhanced magnetic resonance imaging (MRI) or, when MRI was contraindicated, contrast-enhanced computed tomography (CT), and were scheduled for elective primary craniotomy and tumor resection.

Patients were excluded if they had any of the following: known hypersensitivity to TXA; serum creatinine above 1.5 mg/dL or an estimated glomerular filtration rate below 60 mL/min/1.73 m²; Child–Pugh class B or C hepatic dysfunction; a personal history of arterial or venous thromboembolism (deep-vein thrombosis, pulmonary embolism, ischemic stroke or myocardial infarction); an unprovoked thromboembolic event in a first-degree relative before the age of 50 years; known inherited or acquired thrombophilia; active coagulopathy (platelet count below 100,000/μL or international normalized ratio [INR] above 1.5); use of anticoagulant or antiplatelet drugs within 7 days of surgery; preoperative tumor embolization; pregnancy or lactation; or inability to give informed consent. All patients enrolled during the study period were women; sex was not an eligibility criterion.

Randomization, allocation concealment and blinding

An independent statistician who had no role in recruitment, clinical care or outcome assessment generated a block randomization sequence with randomly varying block sizes of four and six in R version 4.2.1 (R Foundation for Statistical Computing, Vienna, Austria). The sequence was held by the central hospital pharmacy. After a patient had given consent, the clinical research coordinator contacted the pharmacy, where a pharmacist who was not otherwise involved in the trial consulted the sequence and prepared the study drug in identical, opaque 100 mL infusion bags labeled only with the patient's study number and a batch number. Patients, neurosurgeons, anesthesiologists, operating-room staff and all personnel who collected data or assessed outcomes were therefore unaware of the allocation. Emergency unblinding through the head of pharmacy was permitted only for a suspected life-threatening adverse event attributable to the

study drug, such as anaphylaxis or massive thromboembolism; no unblinding was required.

Interventions

Patients allocated to TXA received intravenous TXA (Kalex®, Kalbe Farma, Indonesia) as a loading dose of 15 mg/kg actual body weight diluted in 100 mL of 0.9% saline and infused over 10 minutes, starting approximately 30 minutes before skin incision, followed by a continuous infusion of 1 mg/kg/h until the operating surgeon confirmed final dural closure. Patients allocated to placebo received 100 mL of 0.9% saline over 10 minutes followed by a saline infusion at the same rate and for the same duration, delivered in an identical bag.

Anesthetic and surgical management

All patients received a standardized general anesthetic managed by a consultant anesthesiologist. Anesthesia was induced with fentanyl 1–3 µg/kg, propofol 2–3 mg/kg and rocuronium 1.2 mg/kg and maintained with sevoflurane at 1.0–1.5 minimum alveolar concentration in a 50:50 oxygen–air mixture, with intermittent fentanyl boluses as required. Every patient had an arterial line for invasive blood-pressure monitoring and a central venous catheter for pressure monitoring and fluid administration, and mean arterial pressure was kept within 20% of the patient's baseline value. Operations were performed by one of three consultant neurosurgeons, each with more than 10 years of experience in neurosurgical oncology, who chose the approach (for example pterional or frontotemporal) according to tumor location and size. The surgical goal was maximal safe resection, aiming for Simpson grade I or II removal where anatomically and functionally feasible. Red blood cells were transfused when hemoglobin fell below 7 g/dL, or at a higher hemoglobin concentration when hemodynamic instability or end-organ ischaemia was attributed to anemia.

Outcomes and measurements

The primary outcome was total intraoperative blood loss (mL) from skin incision to completion of skin closure. A dedicated research nurse who was unaware of the allocation measured blood loss with a standardized composite method. For the gravimetric component, all gauzes and sponges were collected and weighed on a single digital scale calibrated daily (AND EJ-6100); the recorded dry weight was subtracted and the net weight (g) was converted to blood volume by dividing by the specific gravity of blood (1.06 g/mL). For the volumetric component, the volume of irrigation fluid (0.9% saline), tallied prospectively by the scrub nurse on a separate counter, was subtracted from the total suction-canister volume. Total blood loss was the sum of the two components.

Secondary efficacy outcomes were the proportion of patients who received any allogeneic packed red blood cell (PRBC) transfusion intraoperatively or within 24 hours, the volume of PRBC transfused in that window, the absolute change in hemoglobin (g/dL) and hematocrit (percentage points) from the preoperative value to 24 hours after surgery, the duration of surgery (minutes) and the length of hospital stay (days). Exploratory laboratory outcomes were prothrombin time expressed as the INR, activated partial thromboplastin time (aPTT), fibrinogen and D-dimer measured before surgery and 24 hours after surgery.

The primary safety outcome was a composite of symptomatic, objectively confirmed thromboembolic events within 30 days of surgery: deep-vein thrombosis confirmed by compression Doppler ultrasonography, pulmonary embolism confirmed by CT pulmonary angiography, ischemic stroke confirmed by diffusion-weighted MRI, and myocardial infarction confirmed by electrocardiographic changes with a rise in cardiac troponin.

Postoperative seizures and surgical-site infections were also recorded. All patients were followed for 30 days after surgery.

Sample size

An audit of the 50 most recent craniotomies for meningioma at the hospital showed a mean intraoperative blood loss of about 1,000 mL with a standard deviation (SD) of 150 mL. The minimal clinically important difference (MCID) was set at a 200 mL reduction, about 20% of the expected loss. With a two-sided α of 0.05 and 90% power, a two-sample t-test required 13 patients per group (80% power would have required 10 per group). To allow for withdrawals and protocol deviations, 15 patients per group (30 in total) were enrolled.

Statistical analysis

All analyses followed the intention-to-treat principle, with every randomized patient analyzed in the allocated group; there were no missing outcome data. Continuous variables were inspected with the Shapiro–Wilk test and normal Q–Q plots and are summarized as mean (SD). Between-group differences in continuous outcomes are reported as the difference in means (TXA minus placebo) with a 95% confidence interval (CI) from the two-sample t-test; Welch's unequal-variance test was run as a sensitivity analysis. Standardized effects are reported as Hedges' g with exact 95% CIs from the noncentral t distribution, and, for the primary outcome, as an approximate probability of superiority (the probability that a randomly chosen TXA patient lost less blood than a randomly chosen placebo patient, which assumes normally distributed blood loss). Binary outcomes were compared with Fisher's exact test and summarized as relative risks (log-method CI) and risk differences (Newcombe hybrid score CI). Proportions carry Wilson score intervals, or exact Clopper–Pearson intervals when no events occurred. Following CONSORT, baseline characteristics were compared with standardized differences (Cohen's d for continuous and Cohen's h for categorical variables) rather than significance tests. PRBC volume was compared among transfused patients; because this comparison is conditional on a post-randomization event, it is descriptive and not protected by randomization.

Tumor location, a prognostic factor for bleeding, was more frequent in one arm than the other, so the primary outcome was also examined in a sensitivity analysis adjusted for location by analysis of covariance (ANCOVA). Because blood loss was not cross-classified by tumor location in the analysis dataset, this sensitivity analysis was carried out over the space of datasets consistent with the observed group summaries. Within each arm, the variance of blood loss bounds how far the mean of convexity tumors can differ from that of spheno-orbital tumors; the location-adjusted treatment effect, its 95% CI and p value were computed for every combination of these within-arm differences on a 401×401 grid, together with the location-specific (convexity and spheno-orbital) treatment effects and their Welch tests. The location-specific tests assumed an equal within-location SD inside each arm. Because configurations at the edge of the admissible space imply zero within-location variance, the location-specific results are also reported at the reference configuration with no location effect within arms. An estimate whose whole attainable range lay on one side of zero was regarded as robust, and one whose range crossed zero as not identifiable from the data. The same approach was used to adjust the 24-hour hemoglobin, hematocrit and D-dimer values for their baseline values by ANCOVA, varying the unknown within-arm correlation between baseline and change (or baseline and 24-hour value) from -0.99 to 0.99 .

To express the clinical relevance of the primary result, the posterior probability that the true reduction exceeded 0, 100

and 200 mL (the MCID) was calculated with a normal approximation to the likelihood under four priors: a non-informative prior; a skeptical prior centered on no effect with a 5% prior probability of exceeding the MCID (SD 121.6 mL); an evidence-based prior equal to the pooled estimate of the most recent meta-analysis of meningioma trials (mean -270.3 mL, SD 77.8 mL)³¹; and a pessimistic prior centered on no effect with an SD of 60 mL, which places 95% prior probability on effects smaller than about 120 mL and serves as a deliberately pessimistic sensitivity scenario alongside the mixed published trial evidence³². The posterior used a normal approximation with the standard error derived from the t-based confidence interval; a t likelihood with 28 degrees of freedom changed the reported probabilities by less than 0.01. Consistency of the present estimate with the pooled estimate was assessed with a z test for the difference between two independent estimates; because the pooled interval does not reflect between-study heterogeneity, this test indicates consistency only. For the safety outcomes, the probability of observing no thromboembolic event among 30 patients was calculated across plausible true event rates, and the sample sizes required for definitive transfusion and thromboembolism endpoints were estimated with the arcsine approximation (80% power, two-sided $\alpha = 0.05$).

Descriptive statistics were produced with SPSS Statistics version 28.0 (IBM Corp., Armonk, NY, USA); the effect-size

intervals, sensitivity (identification) analyses, Bayesian calculations and figures were produced with Python 3.14 (SciPy 1.18, statsmodels 0.15, Matplotlib 3.10). All tests were two-sided with $\alpha = 0.05$, and p values are reported to three decimal places. The primary outcome was the single confirmatory comparison. For the family of six secondary efficacy outcomes listed above (proportion transfused, PRBC volume, hemoglobin change, hematocrit change, duration of surgery and length of stay), Holm-adjusted p values are also reported; exploratory laboratory outcomes were not adjusted and are interpreted as supportive.

3. Results

Participant flow and baseline characteristics

Between January and December 2024, 38 patients scheduled for meningioma resection were assessed for eligibility (Figure 1). Five (13.2%; 95% CI 5.8–27.3) met an exclusion criterion — renal insufficiency in two, a history of pulmonary embolism in one, aspirin use in one and preoperative embolization in one — and three declined to take part, so 30 of the 33 eligible patients (90.9%; 95% CI 76.4–96.9) were randomized, 15 to each arm. Every patient received the allocated infusion, underwent the planned resection and completed 30-day follow-up; no allocation was unblinded, and all 30 were analyzed in the group to which they had been assigned.

Table 1. Baseline demographic, clinical, laboratory and tumor characteristics of the randomized patients.

Characteristic	Tranexamic acid (n = 15)	Placebo (n = 15)	Standardized difference
Female sex, n (%)	15 (100.0)	15 (100.0)	0.00
Age, years, mean (SD)	45.5 (4.5)	44.9 (4.6)	0.13
Body-mass index, kg/m ² , mean (SD)	26.1 (3.2)	25.8 (3.5)	0.09
Hemoglobin, g/dL, mean (SD)	11.9 (1.7)	12.6 (2.2)	−0.36
Hematocrit, %, mean (SD)	35.7 (5.1)	37.8 (6.6)	−0.36
Platelets, $\times 10^3/\mu\text{L}$, mean (SD)	265.0 (74.5)	300.7 (67.9)	−0.50
INR, mean (SD)	1.02 (0.11)	0.96 (0.12)	0.52
aPTT, s, mean (SD)	28.5 (2.1)	29.1 (2.5)	−0.26
Fibrinogen, mg/dL, mean (SD)	355 (55)	348 (62)	0.12
D-dimer, ng/mL, mean (SD)	280 (95)	265 (105)	0.15
Tumor location, n (%)			0.69 ^a
Convexity	9 (60.0)	4 (26.7)	
Spheno-orbital	6 (40.0)	11 (73.3)	
Tumor volume, cm ³ , mean (SD)	96.5 (47.8)	102.4 (43.0)	−0.13
WHO grade, n (%)			0.00 ^a
Grade 1	13 (86.7)	13 (86.7)	
Grade 2 (atypical)	2 (13.3)	2 (13.3)	

Standardized differences are Cohen's *d* (tranexamic acid minus placebo, pooled SD) for continuous variables and ^aCohen's *h* for proportions; values above 0.10 in absolute terms indicate imbalance. In keeping with CONSORT, baseline differences were not tested for statistical significance. aPTT, activated partial thromboplastin time; INR, international normalized ratio; SD, standard deviation; WHO, World Health Organization.

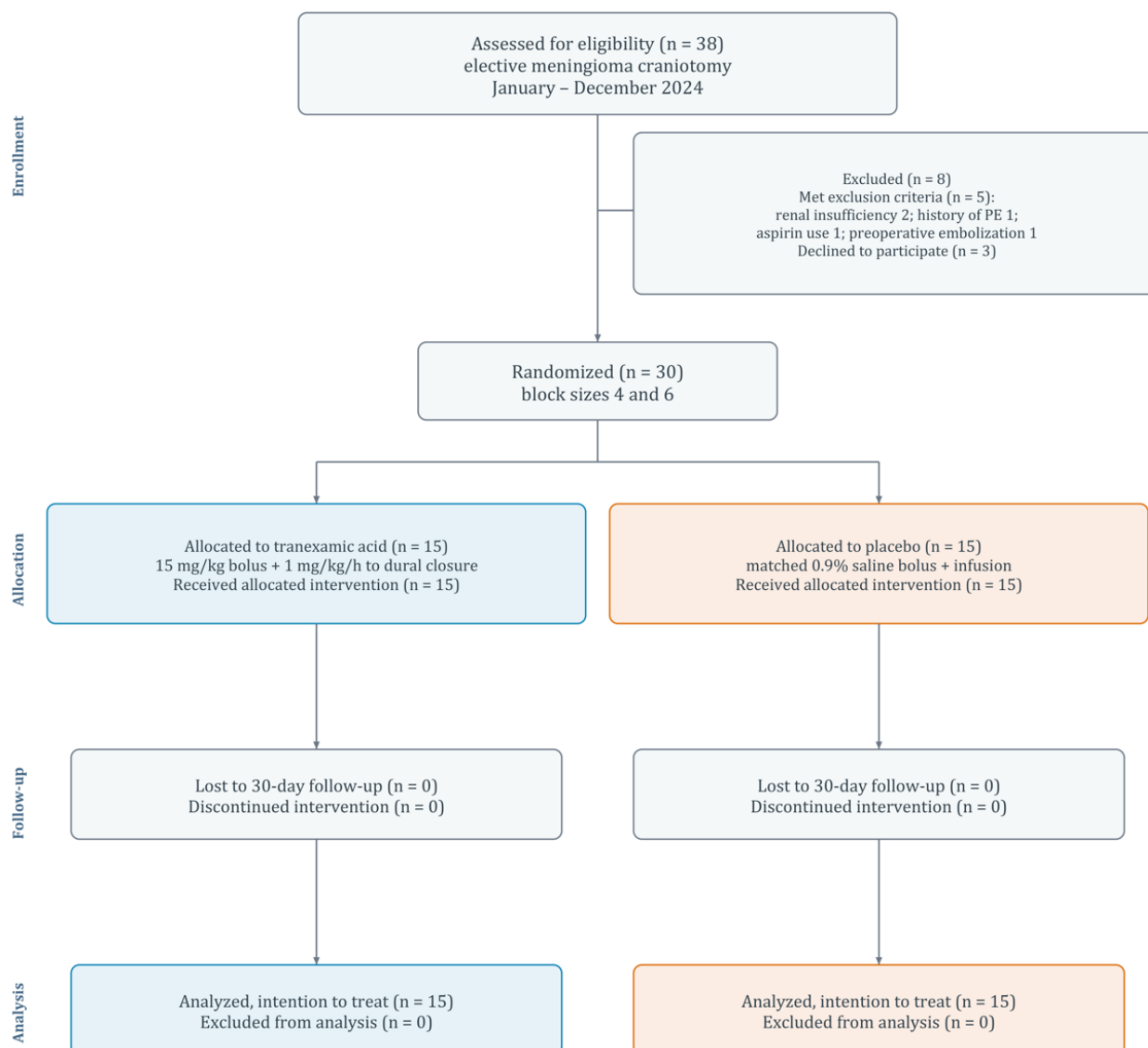


Figure 1. CONSORT 2010 flow diagram of participants through the trial. All 30 randomized patients received the allocated infusion, completed 30-day follow-up and were analyzed in the group to which they were allocated.

Baseline characteristics are shown in Table 1. All 30 patients were women, with a mean age of 45.5 (SD 4.5) years in the TXA arm and 44.9 (SD 4.6) years in the placebo arm. Age, body-mass index, tumor volume, fibrinogen, D-dimer and WHO grade were well balanced (absolute standardized differences 0.00–0.15). Preoperative hemoglobin (11.9 vs 12.6 g/dL; $d = -0.36$), hematocrit (35.7% vs 37.8%; $d = -0.36$) and platelet count (265.0 vs $300.7 \times 10^3/\mu\text{L}$; $d = -0.50$) were lower, and the INR slightly higher (1.02 vs 0.96; $d = 0.52$), in the TXA arm. The largest imbalance concerned tumor location: convexity tumors made up 60.0% (9/15; 95% CI 35.7–80.2) of the TXA arm but 26.7% (4/15; 95% CI 10.9–52.0) of the placebo arm (Cohen's $h = 0.69$), and sphenoid-orbital tumors correspondingly 40.0% and 73.3%. Two patients in each arm (13.3%) had WHO grade 2 (atypical) tumors.

Primary outcome

Mean intraoperative blood loss was 765.0 mL (SD 94.4) with TXA and 1010.0 mL (SD 131.2) with placebo (Table 2 and Figure 2), a difference of -245.0 mL (95% CI -330.5 to -159.5 ; $p < 0.001$) or a relative reduction of 24.3%. Welch's test gave the same conclusion (95% CI -330.9 to -159.1 ; $p < 0.001$). The standardized difference was large (Hedges' $g = -2.09$; 95% CI -2.98 to -1.20), corresponding to an approximate probability of superiority of 0.935 under the assumption of normally distributed blood loss. The 95% CI included the MCID of -200 mL, so the trial alone could not establish that the true reduction exceeded the prespecified clinically important threshold. Although operations in the TXA arm were on average 29.4 minutes longer, the ratio of group means corresponded to 117 mL of blood lost per hour of surgery with TXA and 166 mL per hour with placebo; these are descriptive ratios of group means rather than patient-level rates.

Table 2. Primary and secondary efficacy outcomes.

Outcome	Tranexamic acid (n = 15)	Placebo (n = 15)	Difference (95% CI)	p	Hedges' g (95% CI)
Primary outcome					
Intraoperative blood loss, mL, mean (SD)	765.0 (94.4)	1010.0 (131.2)	–245.0 (–330.5 to –159.5)	<0.001	–2.09 (–2.98 to –1.20)
Secondary outcomes					
Patients transfused with PRBC, n (%)	11 (73.3)	13 (86.7)	RD –13.3 points (–40.4 to 15.8); RR 0.85 (0.59 to 1.22)	0.651 ^b	—
PRBC volume in transfused patients, mL, mean (SD) ^a	398.3 (88.6) [n = 11]	506.0 (94.6) [n = 13]	–107.7 (–185.8 to –29.6)	0.009	–1.13 (–2.00 to –0.27)
Hemoglobin change, baseline to 24 h, g/dL, mean (SD)	–0.97 (1.20)	–2.36 (1.55)	1.39 (0.35 to 2.43)	0.010	0.98 (0.23 to 1.71)
Hematocrit change, baseline to 24 h, % points, mean (SD)	–2.9 (3.6)	–7.1 (4.7)	4.2 (1.1 to 7.3)	0.010	0.98 (0.23 to 1.71)
Duration of surgery, min, mean (SD)	393.7 (75.6)	364.3 (93.4)	29.4 (–34.2 to 93.0)	0.351	0.34 (–0.37 to 1.04)
Length of hospital stay, days, mean (SD)	6.8 (1.5)	7.3 (2.0)	–0.5 (–1.8 to 0.8)	0.445	–0.28 (–0.97 to 0.43)

Differences are tranexamic acid minus placebo; continuous outcomes were compared with the two-sample t-test (Welch's test gave p values identical to the third decimal except where stated in the text).^a Packed red blood cells transfused intraoperatively and within 24 h, summarized among transfused patients; because this comparison is conditional on a post-randomization event, it is descriptive.^b Fisher's exact test. CI, confidence interval; PRBC, packed red blood cells; RD, risk difference (Newcombe hybrid score interval); RR, relative risk (log method); SD, standard deviation. Holm-adjusted p values across the six secondary outcomes: PRBC volume, hemoglobin change and hematocrit change 0.055 each; proportion transfused, duration of surgery and length of stay 1.000.

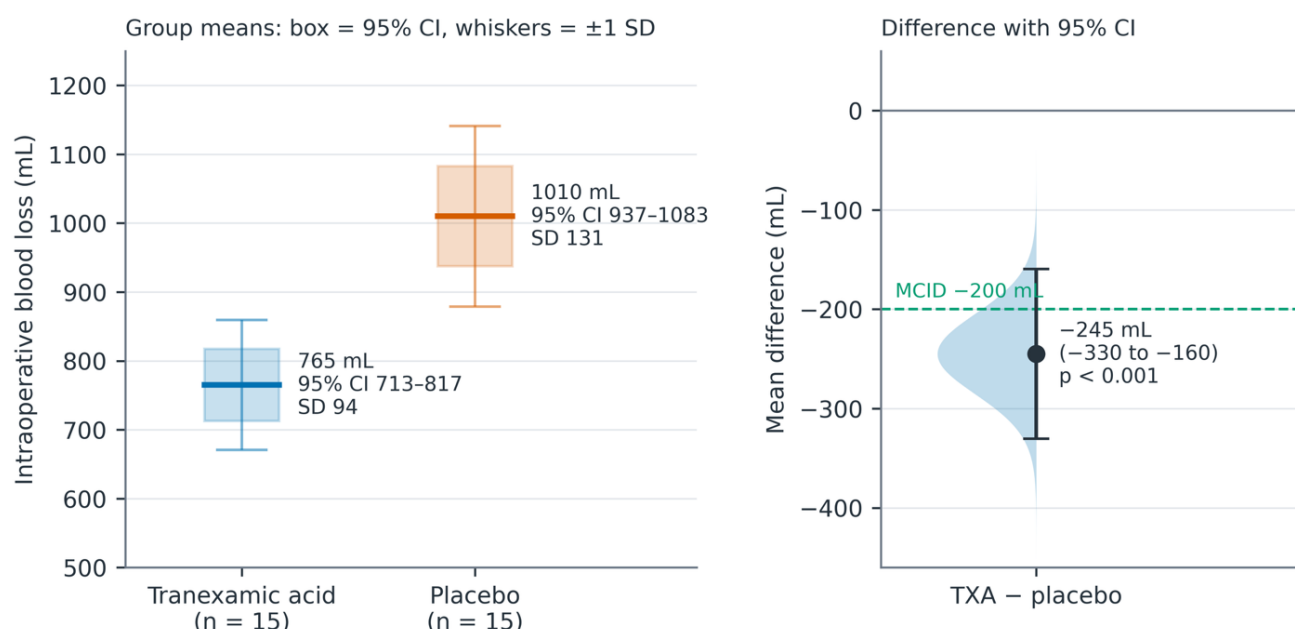


Figure 2. Intraoperative blood loss by treatment group. Left: group mean (thick line), 95% confidence interval (shaded box) and ±1 standard deviation (whiskers). Right: mean difference (tranexamic acid minus placebo) with its 95% confidence interval and the corresponding t distribution; the dashed line marks the prespecified minimal clinically important difference of –200 mL.

The standardized differences for all continuous outcomes are summarized in Figure 3. Intervals excluded zero for blood loss, PRBC volume among transfused patients, the change in

hemoglobin and hematocrit, and the 24-hour D-dimer concentration, and included zero for fibrinogen, INR, aPTT, duration of surgery and length of stay.

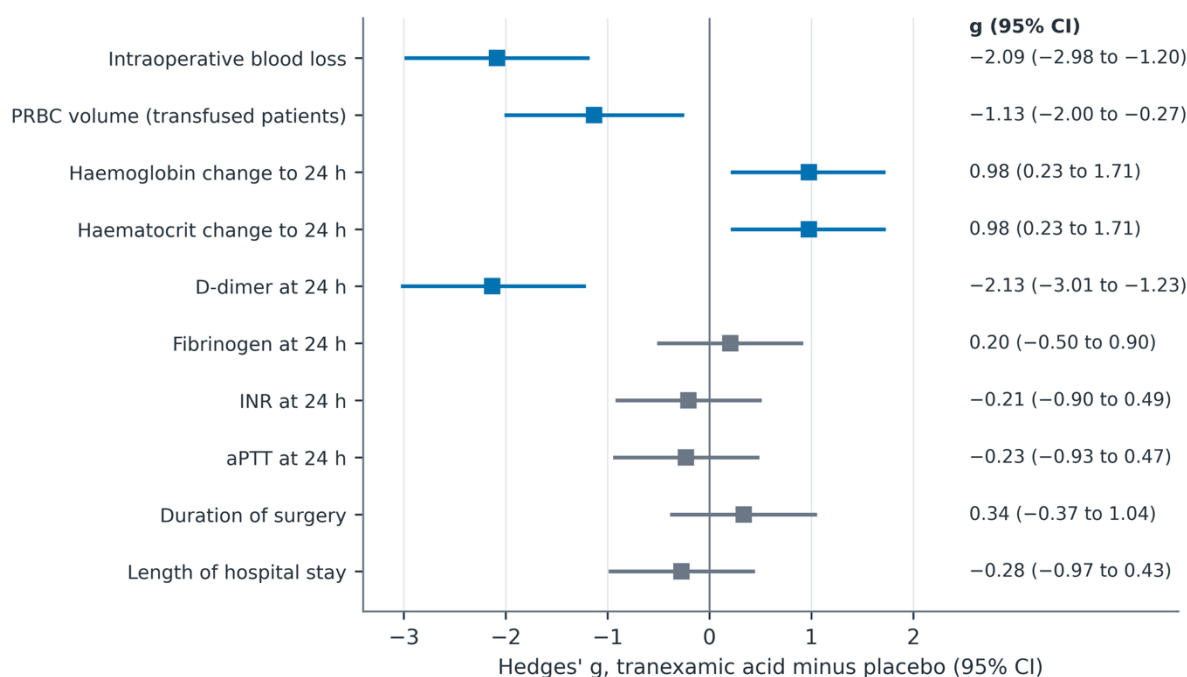


Figure 3. Standardized between-group differences (Hedges' g, tranexamic acid minus placebo) with exact 95% confidence intervals from the noncentral t distribution. Blue estimates have intervals excluding zero. Negative values indicate lower values in the tranexamic acid arm; for hemoglobin and hematocrit change, positive values indicate a smaller fall.

Sensitivity analysis for tumor location

Given the observed SDs, the mean blood loss of convexity and spheno-orbital tumors could differ by at most 186 mL within the TXA arm and 287 mL within the placebo arm. Across every combination of within-arm differences compatible with these limits, the location-adjusted treatment effect ranged from -322.1 to -167.9 mL, the upper 95% confidence limit never rose above -123.4 mL, and p remained below 0.001 throughout (Table 3 and Figure 4). The ANCOVA estimate of -238.5 mL corresponds to spheno-orbital tumors losing about 19.5 mL more blood than convexity tumors within each arm; at that point the 95% CI was -330.8 to -146.2 mL ($p < 0.001$). The reduction with TXA was therefore robust to the location imbalance under every admissible configuration of the data.

The location-specific analyses were less conclusive. Among the 17 patients with spheno-orbital tumors (6 TXA, 11 placebo), the attainable treatment effect ranged from -433 to -57 mL and was statistically significant across the entire admissible space, a result that includes edge configurations with no within-location variance; at the reference configuration with no location effect within arms, the spheno-orbital difference was -245 mL (95% CI -368 to -122; $p < 0.001$). Among the 13 patients with convexity tumors (9 TXA, 4 placebo), it ranged from -530 to +40 mL and reached significance in 67% of the space (-245 mL; 95% CI -447 to -43; $p = 0.027$ at the no-location-effect configuration). The difference between the two location-specific effects (the location-by-treatment interaction) could lie anywhere between -473 and +473 mL; the data therefore cannot identify whether TXA is more or less effective in convexity than in spheno-orbital tumors.

Table 3. Sensitivity and identification analyses.

Analysis	Unknown quantity explored	Attainable estimate (TXA – placebo)	Largest p value	Conclusion
Location-adjusted blood loss (ANCOVA)	Within-arm convexity – spheno-orbital mean difference: up to ± 186 mL (TXA) and ± 287 mL (placebo)	-322.1 to -167.9 mL; at the ANCOVA estimate of -238.5 mL, 95% CI -330.8 to -146.2	<0.001	Robust: reduction holds in every admissible dataset
Spheno-orbital subgroup (6 vs 11)	As above	-433 to -57 mL	<0.05 in 100% of the space	Direction robust
Convexity subgroup (9 vs 4)	As above	-530 to +40 mL	<0.05 in 67% of the space	Not identifiable
Location $\times$ treatment interaction	As above	-473 to +473 mL	—	Not identifiable
Hemoglobin at 24 h adjusted for baseline	Within-arm correlation of baseline with change (-0.99 to 0.99)	0.90 to 1.88 g/dL; lowest 95% lower limit 0.21	0.020	Robust
Hematocrit at 24 h adjusted for baseline	As above	2.7 to 5.7 points; lowest 95% lower limit 0.6	0.020	Robust
D-dimer at 24 h adjusted for baseline	Within-arm correlation of baseline with 24-h value (-0.99 to 0.99)	-820 to -720 ng/mL	<0.001	Robust

Each analysis evaluates the estimate at every value of the unknown quantity that is compatible with the observed group sizes, means and standard deviations (401×401 grid for tumor location; 199×199 grid for baseline correlations). 'Largest p value' is the least favorable result across that space; subgroup rows give the share of the space in which the location-specific Welch test reached $p < 0.05$. ANCOVA, analysis of covariance; TXA, tranexamic acid.

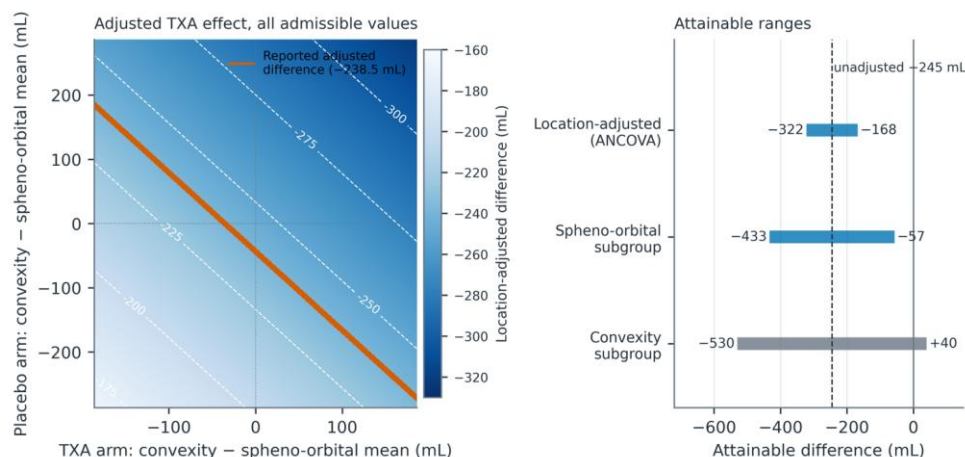


Figure 4. Location-adjusted effect of tranexamic acid on intraoperative blood loss across every within-arm association between tumor location and blood loss compatible with the observed group standard deviations. Left: the adjusted difference (ANCOVA) as a function of the convexity-minus-spheno-orbital mean difference in each arm; the orange line marks the combinations that reproduce the adjusted estimate of -238.5 mL. Right: attainable ranges of the location-adjusted difference and of the location-specific differences; blue bars lie entirely below zero.

Transfusion, hemoglobin and hematocrit

PRBC transfusion was required in 11 of 15 patients given TXA (73.3%; 95% CI 48.0–89.1) and 13 of 15 given placebo (86.7%; 95% CI 62.1–96.3), a risk difference of -13.3 percentage points (95% CI -40.4 to 15.8) and a relative risk of 0.85 (95% CI 0.59 – 1.22 ; $p = 0.651$) (Table 2). Among transfused patients, the mean PRBC volume was 398.3 mL (SD 88.6) with TXA and 506.0 mL (SD 94.6) with placebo, a difference of -107.7 mL (95% CI -185.8 to -29.6 ; $p = 0.009$; Hedges' $g = -1.13$); this comparison is conditional on transfusion and therefore descriptive.

Hemoglobin fell by a mean of 0.97 g/dL (SD 1.20) with TXA and 2.36 g/dL (SD 1.55) with placebo between the preoperative measurement and 24 hours after surgery, a difference of 1.39 g/dL in favor of TXA (95% CI 0.35 to 2.43 ; $p = 0.010$; $g = 0.98$). Hematocrit fell by 2.9 (SD 3.6) and 7.1 (SD 4.7) percentage points, a difference of 4.2 points (95% CI 1.07 to 7.33 ; $p = 0.010$) (Figure 5). After Holm adjustment across the six secondary

outcomes, the adjusted p values for the changes in hemoglobin and hematocrit and for PRBC volume were each 0.055 , and those for the proportion transfused, duration of surgery and length of stay were 1.000 . Because the TXA arm started with a 0.7 g/dL lower hemoglobin, the 24-hour values were also adjusted for baseline (Figure 6 and Table 3). Across the full range of within-arm correlations between baseline and change, the baseline-adjusted difference in 24-hour hemoglobin ranged from 0.90 to 1.88 g/dL with $p \leq 0.020$ throughout, and that in hematocrit from 2.72 to 5.68 points with $p \leq 0.020$; when baseline and change were uncorrelated, the adjusted hemoglobin difference was 1.39 g/dL (95% CI 0.31 to 2.47 ; $p = 0.013$).

Mean duration of surgery was 393.7 minutes (SD 75.6) with TXA and 364.3 minutes (SD 93.4) with placebo (difference 29.4 minutes; 95% CI -34.2 to 93.0 ; $p = 0.351$), and mean length of stay was 6.8 (SD 1.5) and 7.3 (SD 2.0) days (difference -0.5 days; 95% CI -1.8 to 0.8 ; $p = 0.445$).

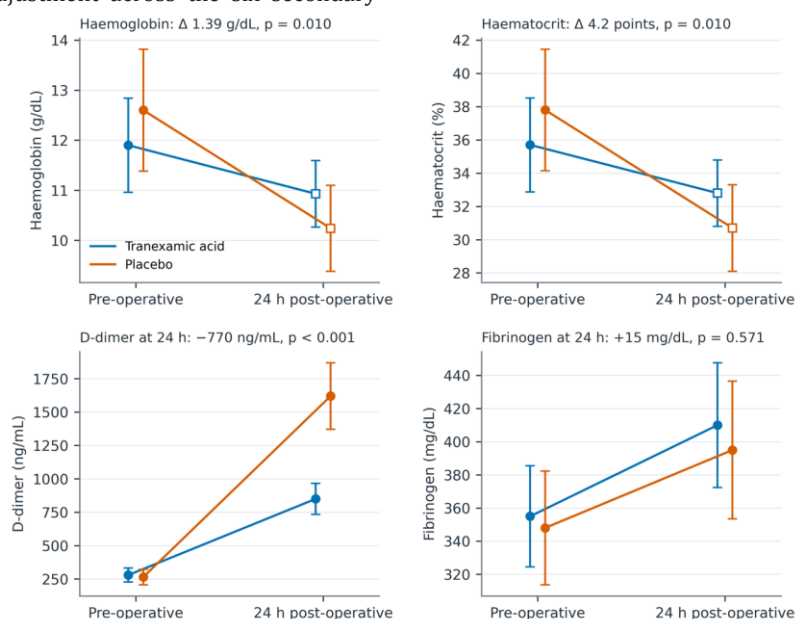


Figure 5. Perioperative hematological and coagulation markers. Points show group means with 95% confidence intervals at baseline and 24 h after surgery. For hemoglobin and hematocrit, the 24-h value is the baseline mean plus the mean change, and its interval is the 95% confidence interval of the mean change. Panel titles give the between-group difference at 24 h (D-dimer, fibrinogen) or in change from baseline (hemoglobin, hematocrit).

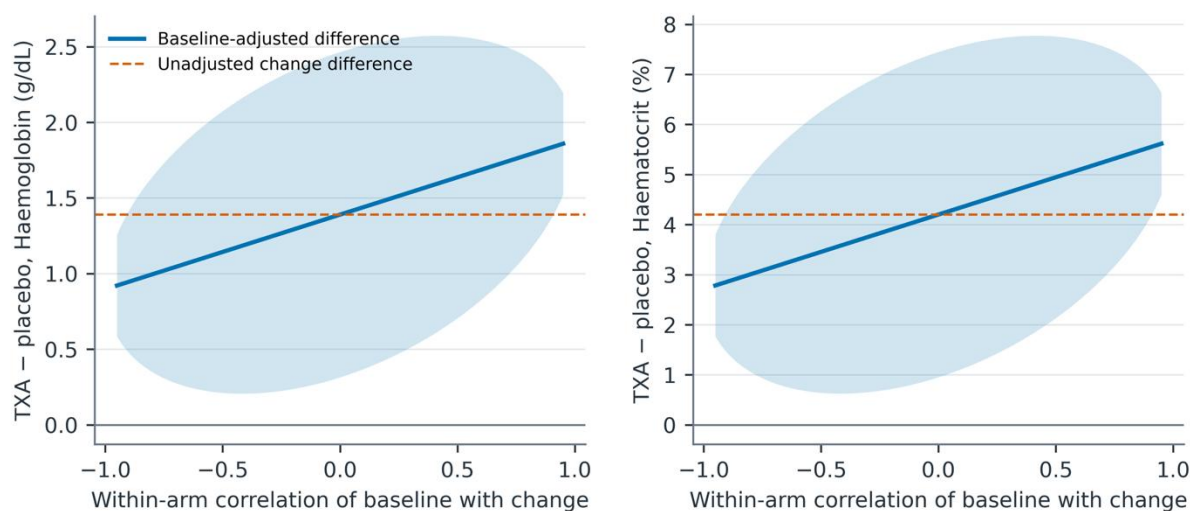


Figure 6. Baseline-adjusted differences in hemoglobin and hematocrit at 24 h (ANCOVA of the 24-h value on the baseline value) across the full range of within-arm correlations between baseline value and change. The shaded band is the 95% confidence interval; the dashed line is the unadjusted difference in change.

Coagulation and fibrinolysis

D-dimer rose from 280 to 850 ng/mL (a 3.0-fold increase in group means) with TXA and from 265 to 1,620 ng/mL (6.1-fold) with placebo (Table 4 and Figure 5). At 24 hours the D-dimer concentration was 770 ng/mL lower with TXA (95% CI 507.4 to 1032.6 lower; $p < 0.001$; $g = -2.13$), and the ratio of group means was 0.52. Adjustment for baseline D-dimer gave differences

between -820 and -720 ng/mL across all admissible baseline–24-hour correlations, with $p < 0.001$ throughout. Fibrinogen increased in both arms, from 355 to 410 mg/dL with TXA and from 348 to 395 mg/dL with placebo, and did not differ at 24 hours (difference 15 mg/dL; 95% CI -38.5 to 68.5 ; $p = 0.571$). The 24-hour INR (1.05 vs 1.08; $p = 0.563$) and aPTT (29.8 vs 30.5 seconds; $p = 0.522$) were also similar.

Table 4. Coagulation and fibrinolysis markers at 24 hours and adverse events within 30 days.

Outcome	Tranexamic acid (n = 15)	Placebo (n = 15)	Difference (95% CI)	p
Laboratory values at 24 h, mean (SD)				
INR	1.05 (0.13)	1.08 (0.15)	-0.03 (-0.13 to 0.07)	0.563
aPTT, s	29.8 (2.8)	30.5 (3.1)	-0.7 (-2.9 to 1.5)	0.522
Fibrinogen, mg/dL	410 (68)	395 (75)	15 (-39 to 69)	0.571
D-dimer, ng/mL	850 (210)	1620 (450)	-770 (-1033 to -507)	<0.001
Adverse events within 30 days, n (%; 95% CI)			Risk difference, % points (95% CI)	
Thromboembolic composite ^a	0 (0.0; 0.0–21.8)	0 (0.0; 0.0–21.8)	0.0 (-20.4 to 20.4)	1.000
Deep-vein thrombosis / pulmonary embolism	0 / 0	0 / 0	—	—
Ischemic stroke / myocardial infarction	0 / 0	0 / 0	—	—
Postoperative seizure	1 (6.7; 1.2–29.8)	1 (6.7; 1.2–29.8)	0.0 (-23.8 to 23.8)	1.000
Superficial surgical-site infection	0 (0.0; 0.0–20.4)	1 (6.7; 1.2–29.8)	-6.7 (-29.8 to 14.4)	1.000

Laboratory differences are tranexamic acid minus placebo (two-sample t-test). Event proportions carry exact Clopper–Pearson intervals for zero counts and Wilson intervals otherwise; risk differences carry Newcombe hybrid score intervals; p values for events are from Fisher's exact test.^a Symptomatic deep-vein thrombosis (compression ultrasonography), pulmonary embolism (CT pulmonary angiography), ischemic stroke (diffusion-weighted MRI) or myocardial infarction (ECG and troponin). aPTT, activated partial thromboplastin time; INR, international normalized ratio; SD, standard deviation.

Safety

No patient in either arm had a symptomatic thromboembolic event within 30 days: there was no deep-vein thrombosis, pulmonary embolism, ischemic stroke or myocardial infarction (Table 4). With no events among 15 patients per arm, the upper 95% confidence limit of the thromboembolic risk was 21.8% in each arm and 11.6% for the trial as a whole, and the risk difference between arms was 0.0 percentage points with a 95% CI of -20.4 to 20.4 points (Table 5 and Figure 7). If the true 30-day risk were 3.0%, as reported after tumor craniotomy at the Mayo Clinic⁴¹, a trial of 30 patients would observe no events 40% of the time; at 6.0%, the symptomatic rate after

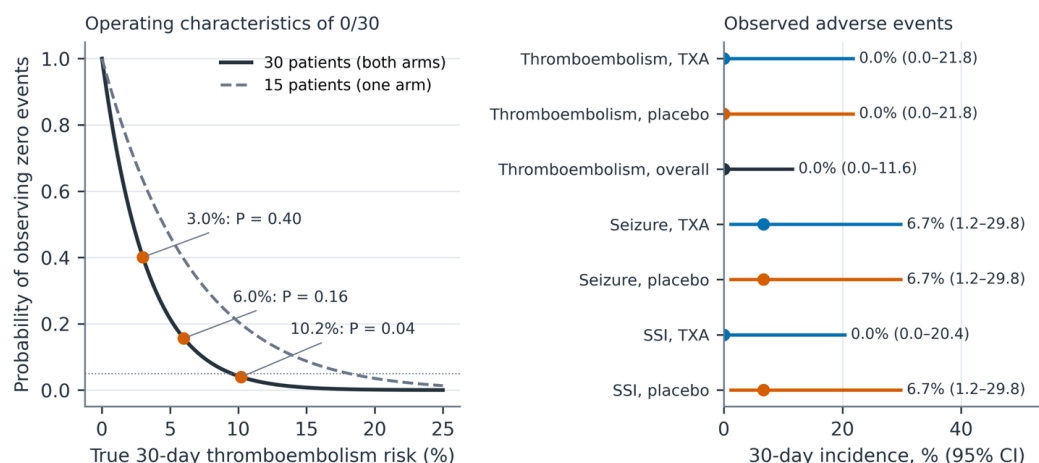
meningioma resection at Brigham and Women's Hospital³³, it would still do so 16% of the time.

One patient in each arm had a postoperative seizure (6.7%; 95% CI 1.2–29.8), which was controlled with standard anticonvulsant therapy (risk difference 0.0 points; 95% CI -23.8 to 23.8). One superficial surgical-site infection occurred in the placebo arm and resolved with oral antibiotics (risk difference -6.7 points; 95% CI -29.8 to 14.4). Detecting a doubling of thromboembolic risk from 3% to 6% would require about 729 patients per arm, and excluding an absolute increase of three percentage points about 508 per arm; a definitive comparison of the proportion transfused would require about 138 per arm (Table 5).

Table 5. What the trial can and cannot exclude, and sample sizes required for definitive secondary and safety endpoints.

End point	Observed	95% CI / bound	Sample size required (80% power, two-sided $\alpha = 0.05$)
Thromboembolism, per arm	0/15 in each arm	Upper bound 21.8% per arm; risk difference –20.4 to 20.4 points	≈729 per arm to detect a doubling from 3% to 6%; ≈508 per arm to exclude an absolute increase of 3 points
Thromboembolism, all patients	0/30	Upper bound 11.6% (rule of three: 10%)	—
Any PRBC transfusion	73.3% vs 86.7%	RD –40.4 to 15.8 points	≈138 per arm
Seizure	1/15 vs 1/15	RD –23.8 to 23.8 points	—
Intraoperative blood loss (MCID 200 mL, SD 150 mL)	–245 mL	–330.5 to –159.5 mL	9.9 per arm (80% power); 12.9 per arm (90% power)

All sample sizes are approximate. Sample sizes for proportions use the arcsine (Cohen's *h*) approximation; the non-inferiority figure uses a normal approximation with a 3% event rate in both arms. CI, confidence interval; MCID, minimal clinically important difference; PRBC, packed red blood cells; RD, risk difference.

**Figure 7.** Precision of the safety data. Left: probability of observing no thromboembolic event among 30 (solid) or 15 (dashed) patients as a function of the true 30-day risk; points mark published venous thromboembolism rates after tumor craniotomy (3.0% and 10.2%) and the symptomatic rate after meningioma resection (6.0%). Right: observed 30-day adverse-event incidence with exact (Clopper-Pearson, zero counts) or Wilson 95% confidence intervals.

Comparison with earlier trials and clinical relevance

The reduction in blood loss in this trial (–245 mL) lay within the range reported by earlier placebo-controlled meningioma trials that used a loading dose followed by an infusion (–251 to –534 mL)^{25–27} and close to the pooled estimates of four meta-analyses (–263 to –316 mL)^{28–31} (Table 6 and Figure 8). The difference between the present estimate and the most recent pooled estimate was 25 mL ($z = 0.29$; $p = 0.775$); because the pooled interval does not include between-study heterogeneity, this indicates consistency rather than agreement. By contrast, a large Beijing trial that gave a single 20 mg/kg dose to 600 patients found no reduction in blood loss³².

Under a non-informative prior, the probability that TXA reduced blood loss at all exceeded 0.999, the probability of a reduction of more than 100 mL was 1.000, and the probability of a reduction larger than the MCID of 200 mL was 0.86 (Figure 9). With a skeptical prior the posterior mean was –219 mL (95% credible interval –297 to –142) and the probability of exceeding the MCID 0.69; with the evidence-based prior the corresponding values were –251 mL (–323 to –179) and 0.92. Under the pessimistic prior anchored on the two large null trials, the posterior mean shrank to –165 mL (–232 to –98): a reduction remained almost certain (probability 0.97 of exceeding 100 mL), but the probability of exceeding the MCID fell to 0.15.

Table 6. Present trial in the context of earlier placebo-controlled trials and meta-analyses of tranexamic acid in meningioma surgery

Study	Setting / design	Regimen	Blood-loss difference, mL (95% CI)	Transfusion and safety
Hooda et al. 2017 ²⁵	India; RCT, n = 60	20 mg/kg + 1 mg/kg/h	–294 (–559 to –29) ^a	Fewer transfusions (NS); better surgical hemostasis
Ravi et al. 2021 ²⁷	India; RCT, n = 30	20 mg/kg + 1 mg/kg/h	–534 (–837 to –231)	Transfused 0/15 vs 6/15; no seizure or thromboembolism to 24 h
Rebai et al. 2021 ²⁶	Tunisia; RCT, n = 91	20 mg/kg + 1 mg/kg/h	–251 (–282 to –220) ^b	Transfusion similar; thrombotic events similar
Peng/Li et al. 2024 ³²	China; non-inferiority RCT, n = 600	20 mg/kg single dose	No significant difference ^c	Seizures 4.3% vs 3.7% (non-inferior)
Present trial	Indonesia; RCT, n = 30, convexity/spheno-orbital	15 mg/kg + 1 mg/kg/h	–245 (–330 to –160)	Transfused 73.3% vs 86.7%; no thromboembolism
Meta-analysis 2023 ²⁸	4 studies, n = 281	Mixed	–316 (–533 to –99)	Transfusion OR 0.52
Meta-analysis 2024 ²⁹	6 RCTs, n = 381	20 mg/kg + 1 mg/kg/h	–282 (–368 to –197)	Transfusion OR 0.26; no VTE in either arm
Meta-analysis 2024 ³⁰	7 RCTs, n = 981	Mixed	–263 (–398 to –128)	RBC transfusion OR 0.47; seizures OR 1.06
Meta-analysis 2025 ³¹	6 RCTs, n = 881	Mixed	–270 (–423 to –118); $I^2 = 99\%$	Transfusion RR 0.60

Differences are tranexamic acid minus placebo, as reported in the cited abstracts or, for the 2021 trials, computed from the published group means and SDs.^a Interval derived from the reported means and $p = 0.03$.^b Intraoperative loss (244 ± 68 vs 495 ± 81 mL); total including drain loss –293 mL.^c Blood loss was a secondary outcome; no summary values are given in the abstract. NS, not significant; OR, odds ratio; RBC, red blood cells; RCT, randomized controlled trial; RR, relative risk; VTE, venous thromboembolism.

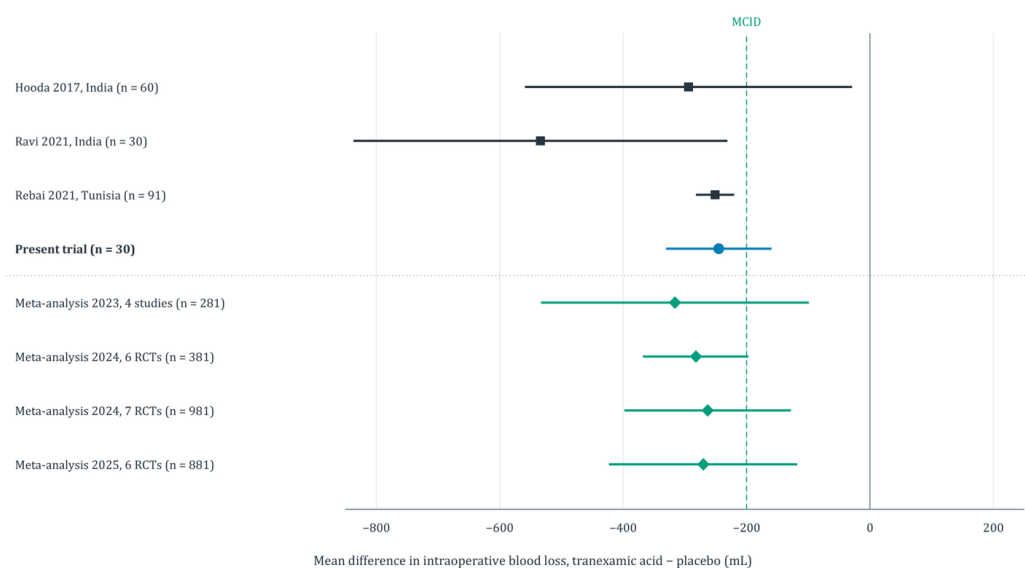


Figure 8. Mean difference in intraoperative blood loss (tranexamic acid minus placebo) in the present trial compared with selected earlier placebo-controlled meningioma trials and meta-analyses available by 20 September 2025. Horizontal lines show the recorded 95% confidence intervals. The present-trial estimate and interval are unchanged.

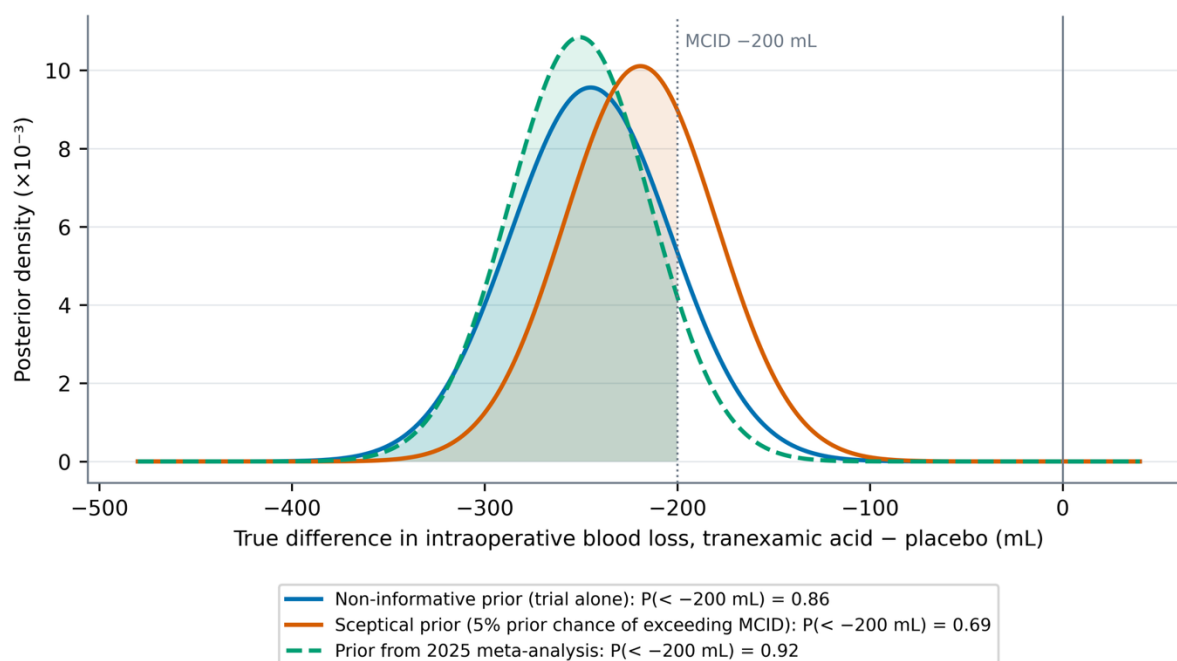


Figure 9. Probability distributions of the true effect of tranexamic acid on intraoperative blood loss under a non-informative prior (present trial alone), a skeptical prior centered on no effect with a 5% prior probability of exceeding the minimal clinically important difference (MCID), and an evidence-based prior centered on the 2025 meta-analysis estimate. Shaded areas below -200 mL indicate the posterior probability that the reduction exceeds the MCID.

4. Discussion

Principal findings

In this double-blind trial at Dr. Mohammad Hoesin General Hospital, Palembang, a perioperative regimen of TXA reduced intraoperative blood loss by 245 mL, about one quarter of the loss with placebo, during resection of convexity and sphenoorbital meningiomas. The reduction was large in standardized terms and remained significant at every combination of within-arm location effects compatible with the data, so the imbalance in tumor location between arms cannot explain it. TXA also roughly halved the 24-hour D-dimer concentration, without changing fibrinogen, INR or aPTT, and the fall in hemoglobin was 1.39 g/dL smaller, a secondary finding that persisted after adjustment for baseline hemoglobin but was of borderline

significance after adjustment for multiple secondary outcomes (Holm-adjusted $p = 0.055$). The proportion of patients transfused was 13 percentage points lower with TXA, but the interval was wide and compatible with no effect. No thromboembolic event occurred in either arm, although with 15 patients per arm the trial could not exclude an absolute increase in risk of up to 20 percentage points.

Comparison with earlier trials

The absolute reduction was close to the pooled estimates of four meta-analyses (-263 to -316 mL)^{28–31} and was consistent with the most recent of them ($p = 0.775$, a test that does not account for between-study heterogeneity). It also lay within the range of the three earlier placebo-controlled trials that, like the present trial, combined a loading dose with an infusion continued to the

end of surgery: Hooda et al. reported 830 versus 1,124 mL (a 26% reduction) in 60 Indian patients²⁵, Rebai et al. 244 versus 495 mL of intraoperative loss (51%) in 91 Tunisian patients²⁶, and Ravi et al. 616 versus 1,150 mL (46%) in 30 Indian patients²⁷. The relative reduction of 24% in Palembang is therefore at the conservative end of this range. The standardized effect (Hedges' $g = -2.09$) appears large, but standardized effects depend on how homogeneous blood loss is within each arm: the group SDs reported by Rebai et al. imply a standardized difference of about 3.4, and those of Ravi et al. about 1.3. Absolute and relative reductions are the more transportable quantities, and in both respects the present result resembles the earlier infusion trials. Small trials nevertheless tend to overestimate treatment effects, and the relative reductions of 46–51% in the two smaller earlier trials illustrate this risk; a 30-patient trial is subject to the same bias, which is why the Bayesian analysis below examines the result under skeptical and pessimistic priors.

The large Beijing trial found no reduction in blood loss³². It gave a single 20 mg/kg bolus after induction, with no maintenance infusion, to 600 patients undergoing supratentorial meningioma resection; its primary outcome was seizures, and blood loss was a secondary, estimated outcome³². Differences in dosing and outcome measurement may help explain variation between studies. We hypothesize that a single bolus may not maintain antifibrinolytic exposure throughout prolonged operations. In pediatric craniostomy surgery, a low-dose infusion regimen maintained plasma concentrations near 30 $\mu\text{g/mL}$ and was non-inferior to a high-dose regimen for blood loss⁴². Blood-loss measurement is also a source of uncertainty: a systematic review found bias and limitations in commonly used visual, gravimetric and calculated estimation methods⁴³, and published formulas failed to approximate radio-labeled blood-volume measurements in spinal fusion⁴⁴. A dedicated, blinded research nurse measured blood loss gravimetrically and volumetrically in the present trial, which reduces measurement error but makes absolute volumes only partly comparable with those of trials that relied on estimates or formulas. Differences in maintained TXA exposure, measurement methods and case mix may contribute to between-study heterogeneity.

The Bayesian analysis makes the strength of evidence explicit. On its own, the trial makes some reduction in blood loss virtually certain and a reduction of more than 100 mL highly probable, but the probability that the true reduction exceeds the 200 mL threshold judged clinically important was 0.86 — high but short of conclusive. A skeptic who believed beforehand that large effects were unlikely would still conclude that the probability exceeds two-thirds (0.69), and combining the trial with the earlier meta-analysis raises it to 0.92. Only under the deliberately pessimistic prior would the analysis suggest that the effect is probably smaller than 200 mL (probability of exceeding it 0.15), and even that reader would accept that a reduction of more than 100 mL is very likely. The practical conclusion — that the regimen reduces bleeding in this population, while the size of the benefit varies across settings — is therefore robust to reasonable prior beliefs.

Tumor location and the speno-orbital subgroup

Spheno-orbital tumors made up 73.3% of the placebo arm but only 40.0% of the TXA arm. Because these tumors involve the sphenoid wing and orbit, and because hyperostosis and bone invasion are among the strongest predictors of blood loss^{9,10}, the imbalance could in principle have exaggerated the treatment effect. The sensitivity analysis rules this out: with the within-arm variance as the only constraint, the location-adjusted effect

could range only between -322.1 and -167.9 mL, with every configuration significant. The location-adjusted estimate of -238.5 mL implies that spheno-orbital tumors bled only about 19.5 mL more than convexity tumors within each arm, a modest difference that may reflect the fact that convexity tumors in this series were large (mean volume about 100 cm^3) and drew on dural and pial supply. Within the spheno-orbital stratum, the reduction with TXA was present in every admissible configuration (-433 to -57 mL), which is clinically relevant because these operations combine tumor removal with extensive drilling of hyperostotic bone, a setting in which, we hypothesize, fibrinolysis of clot on cancellous bone surfaces contributes to oozing. This stratum result includes edge configurations of the admissible space; at the reference configuration with no location effect, the reduction was 245 mL (95% CI 122 to 368 mL), and both the stratum finding and its proposed mechanism should be regarded as hypothesis-generating until tested in a location-stratified trial. In the convexity stratum, with only four placebo patients, the effect could not be identified, and neither could the interaction between location and treatment. Future trials should stratify randomization by location, because the arms in a 30-patient trial can easily become unbalanced on a binary prognostic factor.

Transfusion and hemoglobin

Transfusion was frequent in both arms (73.3% and 86.7%), much more frequent than the 3.65% of tumor craniotomies in NSQIP¹³ or the 16.1% of primary meningioma resections in a German series¹⁴, and closer to the 37% reported in an Ethiopian tertiary hospital¹⁶. Several features of the cohort explain this. The tumors were large, most were skull-based, and operations lasted more than six hours. Mean preoperative hemoglobin was below 13 g/dL in both arms, consistent with the high prevalence of anemia among Indonesian women³⁶, and preoperative anemia is the strongest modifiable predictor of transfusion in tumor craniotomy¹³. The transfusion trigger also allowed transfusion above 7 g/dL when the anesthesiologist judged that anemia caused hemodynamic instability, which is common during rapid bleeding from the skull base; the 24-hour hemoglobin values also include transfused red cells. With transfusion rates this high, a 13-point absolute reduction is plausible — it is close to the relative risk of 0.60 pooled across meningioma trials³¹ — but about 138 patients per arm would be needed to confirm it. Among transfused patients, those given TXA received about 108 mL less red cells, roughly one-third of a typical unit.

If confirmed, the smaller fall in hemoglobin would be clinically relevant in its own right. A fall of 1.4 g/dL less with TXA corresponds approximately to the increment expected from one unit of red cells in an adult, and postoperative hemoglobin drift after brain-tumor craniotomy is associated in a dose-dependent manner with 30-day mortality¹⁵; preoperative anemia and low hematocrit carry similar associations^{45,46}. The optimal transfusion threshold after brain surgery is itself uncertain. A liberal threshold improved neurological outcome after acute brain injury in the TRAIN trial⁴⁷, whereas the HEMOTION trial in traumatic brain injury found no significant benefit⁴⁸; in either case, preventing the fall in hemoglobin is preferable to correcting it with allogeneic blood. Transfusion may confound the comparison of hemoglobin change, but the direction of any bias favors the null: fewer patients in the TXA arm were transfused and they received smaller volumes, so transfusion would have narrowed rather than widened the difference in hemoglobin change between arms. The result is nevertheless a secondary outcome of borderline significance after Holm

adjustment ($p = 0.055$), and its main support is its persistence across every baseline-adjusted configuration.

Coagulation and fibrinolysis

The laboratory pattern is consistent with the mechanism of TXA (Figure 10). D-dimer, a product of plasmin-mediated degradation of cross-linked fibrin, rose sixfold with placebo but only threefold with TXA, whereas fibrinogen, INR and aPTT were similar between arms at 24 hours. TXA therefore attenuated fibrinolysis without measurably altering coagulation factor levels, which agrees with the increased clot firmness and resistance to lysis, without procoagulant changes in conventional tests, seen in children given TXA during craniofacial surgery¹⁷, and with the dose-dependent fall in D-dimer and fibrin degradation products after arthroplasty¹⁸. Ravi et al. also measured coagulation and fibrinolysis markers in

meningioma surgery and reported an improved profile with TXA²⁷. The rise in fibrinogen in both arms is the expected acute-phase response to surgery. One practical consequence deserves attention. Postoperative D-dimer screening is used to detect venous thrombosis after brain-tumor surgery: a cut-off of 3.3 $\mu\text{g/mL}$ on the third postoperative day had a sensitivity of only 0.64 in one Japanese series, which led the authors to recommend a lower threshold of 1.5 $\mu\text{g/mL}$ ⁴⁹, and routine D-dimer screening raised the detected incidence of thrombosis from 1.7% to 22.6% in a German cohort⁵⁰. Because TXA halved the 24-hour D-dimer concentration, we hypothesize that thresholds derived in untreated patients may miss thrombosis in patients given TXA; this extrapolation from 24-hour values to third-day screening thresholds should be tested before such thresholds are applied to patients given TXA.

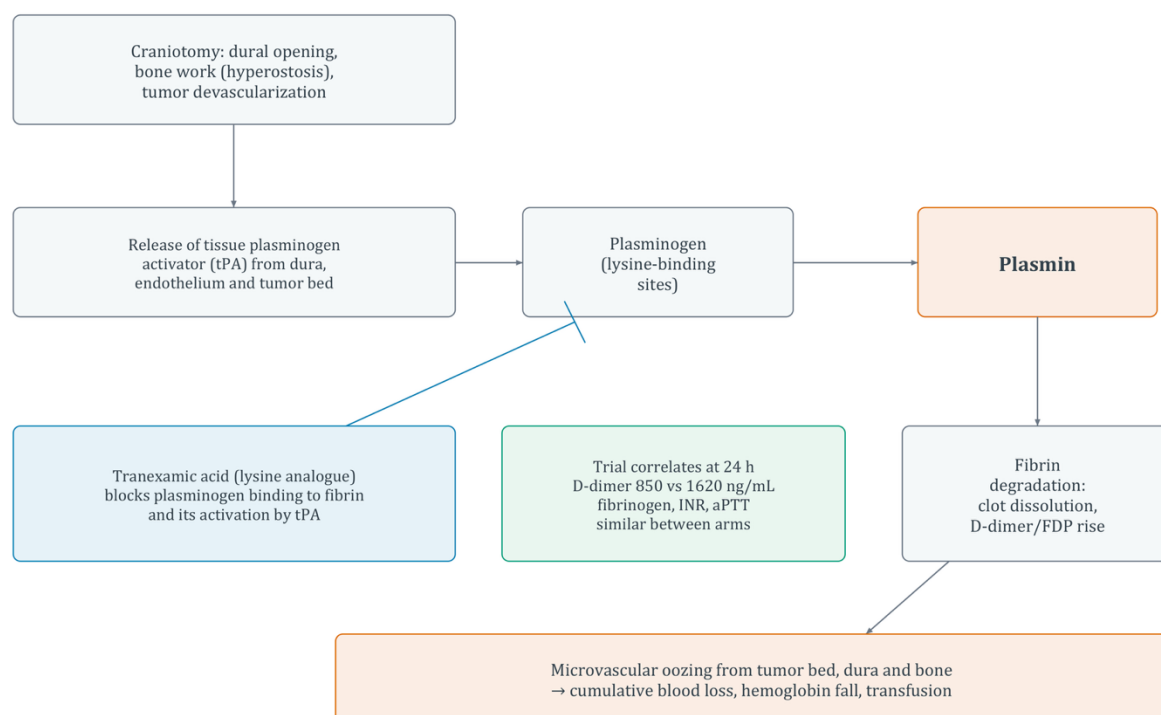


Figure 10. Proposed mechanism of tranexamic acid in meningioma surgery. Surgical trauma to the dura, bone and tumor bed releases tissue plasminogen activator; plasmin degrades fibrin and generates D-dimer, sustaining microvascular oozing. Tranexamic acid occupies the lysine-binding sites of plasminogen, preventing its binding to fibrin and its activation. The trial's 24-h laboratory correlates are shown in the green box.

Safety

No thromboembolic event occurred in either arm, but the trial was not designed to establish safety. With 15 patients per arm, the upper 95% confidence limit for the thromboembolic risk was 21.8% in each arm, and the risk difference could lie anywhere between -20.4 and $+20.4$ percentage points. Reported rates of venous thromboembolism after meningioma or tumor craniotomy range from 3.0% at the Mayo Clinic⁴¹ through 5.7% in Serbia⁵¹, 6.0% symptomatic and 8.7% total at Brigham and Women's Hospital³³, 8.4% deep-vein thrombosis among 9,067 Beijing patients³⁵ and 9.6% with routine Doppler surveillance after skull-base surgery³⁴, to 10.2% in a Thai cohort⁵². At a true risk of 3%, a trial of 30 patients would observe no events 40% of the time, and at 6% it would still do so 16% of the time. The absence of events in this trial is therefore uninformative about the comparative risk and reflects the small sample, the restriction to symptomatic events, the exclusion of patients with previous thrombosis and the relatively young age of the cohort. Moreover, most postoperative deep-vein

thromboses after meningioma resection occur after discharge, at a median of 12.5 days⁵³, which underlines the importance of complete 30-day follow-up, achieved here for every patient.

The reassurance on thrombotic safety must therefore come from larger trials. In POISE-3, TXA did not increase the composite of cardiovascular events¹⁹; a meta-analysis of 216 trials found no association between intravenous TXA and thromboembolism, and its meta-regression found no association between dose and venous events²¹; prehospital TXA in severe trauma did not increase vascular events⁵⁴; and the six meningioma trials pooled by Nguyen et al. recorded no venous thromboembolism in either arm²⁹. The exception is the very high 4 g 24-hour regimen of HALT-IT, which increased venous events in gastrointestinal bleeding²⁴; the present regimen delivers about 1.3 g to a 60 kg patient during a six-hour operation, well below that exposure. Seizures occurred in one patient in each arm (6.7%), similar to the 5.8% incidence of early postoperative seizures after supratentorial meningioma surgery⁵⁵ and below the 10.9% rate of new postoperative

seizures in the Japanese national registry⁵⁶. Seizures attributed to TXA have been described mainly after open-heart surgery²²; even there, a randomized comparison of high- and low-dose infusions found no significant difference in seizures²³, TXA given after cardiopulmonary bypass was not associated with seizures in 6,298 patients⁵⁷, and in 600 patients undergoing meningioma resection a 20 mg/kg dose was non-inferior to placebo for seizures (4.3% vs 3.7%)³². The single superficial surgical-site infection, in the placebo arm, is consistent with the 5.5% incidence reported after elective craniotomy⁵⁸.

Clinical and local implications

For neurosurgical practice, the results, together with earlier trials and meta-analyses, support the use of a maintained TXA regimen — a loading dose followed by an infusion until dural closure — in elective resection of large convexity and sphenoorbital meningiomas in patients without thrombotic risk factors, as part of a broader patient blood management strategy that includes detection and correction of preoperative anemia. Preoperative embolization, the main alternative strategy for hypervascular meningiomas, has given inconsistent results: a matched multicenter study reported smaller falls in hemoglobin after embolization (0.9 vs 2.8 g/dL)⁵⁹, whereas a propensity-matched series of 66 giant meningiomas found no difference in blood loss or transfusion⁶⁰, and embolization did not reduce blood loss in a vascularity-index cohort⁸. TXA is a locally manufactured generic drug that requires no additional procedure, so it is better suited than embolization to routine use in Indonesian referral hospitals. Embolized patients were excluded from this trial, and the combination of the two strategies has not been studied.

In the Indonesian context, the value of blood conservation is amplified by three factors. First, most patients are women in their forties, a group with a high background prevalence of iron-deficiency anemia and thalassaemia trait³⁶, so preoperative hemoglobin reserves are often limited. Second, blood components in low- and middle-income health systems are supplied through donor systems that depend on voluntary and replacement donors and frequently on payment for components³⁷, and a regional Asia-Pacific donor study that included Indonesia found older donors under-represented in every participating region³⁸; every unit saved relieves pressure on a scarce resource. Third, neurosurgical capacity remains well below that of high-income countries³⁹, and faster hemostasis may shorten long operations, although this trial did not show a difference in operating time. The strong female predominance also has a scientific implication: the association between progestogen-containing contraceptives and meningioma, in particular sphenoorbital meningioma^{4–6}, suggests that hormonal history should be recorded in future Indonesian trials as a descriptor of the population.

Research agenda

Several specific studies follow from these results. A multicenter Indonesian trial of about 140 patients per arm, stratified by tumor location and center, would have 80% power to detect a 13-point reduction in the proportion transfused, the most patient-relevant efficacy endpoint. Thrombotic safety cannot be settled by single trials of this size: detecting a doubling of venous thromboembolism from 3% to 6% would require about 729 patients per arm, so safety should instead be addressed by pooling individual patient data across trials or by a prospective registry with systematic Doppler ultrasonography at 7 and 30 days, because screening substantially increases detection^{34,50}. A dose-comparison trial — a single bolus versus a bolus with infusion, and 15 versus 20 mg/kg — would resolve the apparent

conflict between the infusion trials and the large bolus trial³², ideally with measurement of plasma TXA concentrations. Trials should agree on a common, blinded method of measuring blood loss and report the transfusion volume per randomized patient, hemoglobin at fixed time points, Simpson grade and the surgeon. Finally, because D-dimer-based screening for venous thrombosis may be miscalibrated after TXA, the diagnostic accuracy of postoperative D-dimer in TXA-treated patients deserves a dedicated study⁴⁹.

Strengths and limitations

The trial has several strengths. Allocation was concealed by an independent pharmacy with identical opaque infusion bags, and patients, surgeons, anesthesiologists and the nurse who measured blood loss were unaware of the allocation. There were no crossovers, losses to follow-up or missing outcome data, and every patient was followed for 30 days. The primary outcome was measured with a standardized composite gravimetric and volumetric method rather than clinical estimation. The analyses report effect sizes with intervals for every outcome, test the robustness of the primary result to the location imbalance across every compatible configuration of the data, and express both the clinical relevance and the uncertainty of the findings in explicit probabilistic terms.

The limitations are equally important. This was a small, single-center trial, and its results may not transfer to centers with different surgical techniques or case mixes. All participants were women; although this reflects the female predominance of meningioma in Indonesia, the effect in men is untested. The trial was powered only for the primary outcome and cannot establish effects on transfusion or thromboembolic safety, and only symptomatic thromboembolic events were captured. Tumor location was unbalanced between arms, and blood loss was not cross-classified by tumor location in the analysis dataset, so the location-adjusted and location-specific effects were evaluated across the range of values compatible with the group summaries rather than estimated directly; the location-specific effect in convexity tumors and the location-by-treatment interaction could not be identified. PRBC volume was summarized among transfused patients, so the volume per randomized patient is not available. Hemoglobin change may be influenced by transfusion and fluid administration, which were not recorded in detail, although the bias would favor the null. Extent of resection, the operating surgeon and intraoperative fluid volumes were not reported by arm, and the hemoglobin, hematocrit and PRBC-volume results were of borderline significance after Holm adjustment (adjusted $p = 0.055$). Blood absorbed by drapes and gowns was not captured, which would underestimate losses similarly in both arms, and the success of blinding was not formally assessed, although a drier operative field might have been perceptible to the surgeons.

5. Conclusion

In women undergoing elective resection of convexity and sphenoorbital meningiomas at a tertiary referral hospital in Indonesia, a perioperative regimen of tranexamic acid — 15 mg/kg followed by 1 mg/kg/h until dural closure — reduced intraoperative blood loss by 245 mL (95% CI 160 to 330 mL), and the reduction was robust to the imbalance in tumor location between arms. The regimen also halved the postoperative D-dimer response without altering fibrinogen or clotting times, consistent with its antifibrinolytic mechanism, and was associated with a 1.4 g/dL smaller fall in hemoglobin, a secondary finding of borderline significance after multiplicity adjustment. Together with earlier trials and meta-analyses, these findings support a maintained TXA infusion as part of

patient blood management for large convexity and sphenoorbital meningiomas in patients without thrombotic risk factors. Effects on transfusion and thromboembolic safety remain uncertain and should be established in a multicenter Indonesian trial of about 140 patients per arm stratified by tumor location, complemented by pooled or registry data with systematic ultrasound surveillance for venous thrombosis.

6. Declarations

Ethics Approval and Consent to Participate

The trial was conducted in accordance with the Declaration of Helsinki and the International Council for Harmonisation Good Clinical Practice guideline. The protocol and the informed-consent form were reviewed and approved by CMHC Research Center Indonesia (approval number 2024/8556), before the first patient was enrolled. Every participant, or a legally authorized representative, gave written informed consent before any study-related procedure.

Consent for Publication

Not applicable. The article reports only aggregate data; no individual patient data, images or other identifying information are included.

Availability of Data and Materials

All summary data analyzed in this article are reported in the tables. The de-identified patient-level dataset is held by the corresponding author and is available on reasonable request, subject to approval by the ethics committee.

Artificial Intelligence Use Statement

None. No generative artificial intelligence were used in preparation of this manuscript.

Author Contribution Statement

DS: Conceptualization, Methodology, Investigation, Data curation, Formal analysis, Visualization, Writing – original draft, and Writing – review & editing. The author approved final version of manuscript.

Funding

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Conflict of Interest

The author declares no competing interests.

Acknowledgements

The author thanks the patients who took part, the hospital pharmacists who prepared and labeled the study infusions, the research nurse who measured blood loss, and the anesthesia and operating-room teams of the Department of Neurosurgery.

7. References

- Price M, Ballard C, Benedetti J, et al. CBTUS Statistical Report: Primary Brain and Other Central Nervous System Tumors Diagnosed in the United States in 2017–2021. *Neuro Oncol.* 2024;26(Suppl 6):vi1–vi85. doi: 10.1093/neuonc/noae145
- Depond CC, Zouaoui S, Darlix A, et al. Descriptive epidemiology of 30,223 histopathologically confirmed meningiomas in France: 2006–2015. *Acta Neurochir (Wien).* 2024;166(1):214. doi: 10.1007/s00701-024-06093-z
- Aman RA, Santoso F, Amelia R, et al. Clinicopathology Profile and Post-Microsurgical Outcome of Sphenoorbital Meningioma: Single Institution Experience. *Gulf J Oncolog.* 2025;1(47):49–53. PMID: 40464434
- Roland N, Neumann A, Hoisnard L, et al. Use of progestogens and the risk of intracranial meningioma: national case-control study. *BMJ.* 2024;384:e078078. doi: 10.1136/bmj-2023-078078
- Xiao T, Kumar P, Lobbous M, et al. Depot Medroxyprogesterone Acetate and Risk of Meningioma in the US. *JAMA Neurol.* 2025;82(11):1094–102. doi: 10.1001/jamaneurol.2025.3011
- Malueka RG, Hartanto RA, Setyawan NH, et al. Association of Hormonal Contraception with Meningioma Location in Indonesian Patients. *Asian Pac J Cancer Prev.* 2022;23(3):1047–51. doi: 10.31557/APJCP.2022.23.3.1047
- Jarmula J, Murayi R, Gordillo A, et al. Preoperative Radiographic Features Independently Predict High Blood Loss During Intracranial Meningioma Resection: A Case-Control Study. *World Neurosurg.* 2024;192:e210–e216. doi: 10.1016/j.wneu.2024.09.068
- Ghodrat F, Mekonnen M, Mahgerefteh N, et al. Preoperative meningioma vascularity index is associated with significantly increased intraoperative blood loss and greater risk of subtotal resection. *J Neurooncol.* 2023;161(3):583–91. doi: 10.1007/s11060-023-04259-w
- McDonald MF, Khan AB, Chang A, et al. Integrated Clinical Genetic Analysis of Meningiomas Causing Bony Hyperostosis Shows More Severe Clinical Course and Overexpression of Secreted Pro-Osteogenic Factors. *Neurosurgery.* 2025;97(4):842–52. doi: 10.1227/neu.0000000000003465
- Eshkuvvatov G, Asadullayev U, Yakubov J, et al. Prediction of Intraoperative Blood Loss during Surgery of Brain Meningiomas. *Asian J Neurosurg.* 2024;19(4):666–71. doi: 10.1055/s-0044-1788682
- Kiyofuji S, Casabella AM, Graffeo CS, et al. Sphenoorbital meningioma: a unique skull base tumor. Surgical technique and results. *J Neurosurg.* 2020;133(4):1044–51. doi: 10.3171/2019.6.JNS191158
- Zohdy YM, Jacob F, Agam M, et al. Volumetric Analysis of Sphenoorbital Meningiomas: Prognostic Correlation and a Compartmentalized Approach. *Neurosurgery.* 2024;94(4):736–44. doi: 10.1227/neu.0000000000002724
- Aziz N, Waqar U, Bukhari MM, et al. Blood transfusions in craniotomy for tumor resection: Incidence, risk factors, and outcomes. *J Clin Neurosci.* 2025;132:111009. doi: 10.1016/j.jocn.2024.111009
- Neef V, König S, Monden D, et al. Clinical Outcome and Risk Factors of Red Blood Cell Transfusion in Patients Undergoing Elective Primary Meningioma Resection. *Cancers (Basel).* 2021;13(14):3601. doi: 10.3390/cancers13143601
- Zhang Y, Jia L, Tian Y, et al. Association of Postoperative Drift in Hemoglobin With Mortality After Brain Tumor Craniotomy. *Neurosurgery.* 2023;93(1):168–75. doi: 10.1227/neu.0000000000002396
- Abate Shiferaw A, Negash AY, Tirsit A, et al. Perioperative Care and Outcomes of Patients with Brain Tumors Undergoing Elective Craniotomy: Experience from an Ethiopian Tertiary-Care Hospital. *World Neurosurg.* 2024;181:e434–e446. doi: 10.1016/j.wneu.2023.10.077
- Fenger-Eriksen C, Lindholm AD, Krogh L, et al. Effect of Tranexamic Acid on Coagulation and Fibrin Clot Properties in Children Undergoing Craniofacial Surgery. *Thromb Haemost.* 2020;120(3):392–9. doi: 10.1055/s-0039-3402762
- Lei YT, Xie JW, Huang Q, et al. The antifibrinolytic and anti-inflammatory effects of a high initial-dose tranexamic acid in total knee arthroplasty: a randomized controlled trial. *Int Orthop.* 2020;44(3):477–86. doi: 10.1007/s00264-019-04469-w
- Devereaux PJ, Marcucci M, Painter TW, et al. Tranexamic Acid in Patients Undergoing Noncardiac Surgery. *N Engl J Med.* 2022;386(21):1986–97. doi: 10.1056/NEJMoa2201171
- CRASH-3 trial collaborators. Effects of tranexamic acid on death, disability, vascular occlusive events and other morbidities in patients with acute traumatic brain injury (CRASH-3): a randomised, placebo-controlled trial. *Lancet.* 2019;394(10210):1713–23. doi: 10.1016/S0140-6736(19)32233-0
- Taeuber I, Weibel S, Herrmann E, et al. Association of Intravenous Tranexamic Acid With Thromboembolic Events and Mortality: A Systematic Review, Meta-analysis, and Meta-regression. *JAMA Surg.* 2021;156(6):e210884. doi: 10.1001/jamasurg.2021.0884
- Hulde N, Zittermann A, Deutsch MA, et al. Associations of preoperative stroke and tranexamic acid administration with convulsive seizures in valvular open-heart surgery. *J Anesth.* 2021;35(3):451–4. doi: 10.1007/s00540-021-02924-w
- Shi J, Zhou C, Pan W, et al. Effect of High- vs Low-Dose Tranexamic Acid Infusion on Need for Red Blood Cell Transfusion and Adverse Events in Patients Undergoing Cardiac Surgery: The OPTIMAL Randomized Clinical Trial. *JAMA.* 2022;328(4):336–47. doi: 10.1001/jama.2022.10725

24. HALT-IT Trial Collaborators. Effects of a high-dose 24-h infusion of tranexamic acid on death and thromboembolic events in patients with acute gastrointestinal bleeding (HALT-IT): an international randomised, double-blind, placebo-controlled trial. *Lancet*. 2020;395(10241):1927-36. doi: 10.1016/S0140-6736(20)30848-5
25. Hooda B, Chouhan RS, Rath GP, et al. Effect of tranexamic acid on intraoperative blood loss and transfusion requirements in patients undergoing excision of intracranial meningioma. *J Clin Neurosci*. 2017;41:132-8. doi: 10.1016/j.jocn.2017.02.053
26. Rebai L, Mahfoudhi N, Fitouhi N, et al. Intraoperative tranexamic acid use in patients undergoing excision of intracranial meningioma: Randomized, placebo-controlled trial. *Surg Neurol Int*. 2021;12:289. doi: 10.25259/SNI_177_2021
27. Ravi GK, Panda N, Ahluwalia J, et al. Effect of tranexamic acid on blood loss, coagulation profile, and quality of surgical field in intracranial meningioma resection: A prospective randomized, double-blind, placebo-controlled study. *Surg Neurol Int*. 2021;12:272. doi: 10.25259/SNI_296_2021
28. Clynch AL, Gillespie CS, Richardson GE, et al. Tranexamic acid use in meningioma surgery - A systematic review and meta-analysis. *J Clin Neurosci*. 2023;110:53-60. doi: 10.1016/j.jocn.2023.01.012
29. Nguyen A, Brown NJ, Gendreau J, et al. The association of thromboembolic complications and the use of tranexamic acid during resection of intracranial meningiomas: systematic review and meta-analysis of randomized controlled trials. *J Neurosurg*. 2024;140(4):1008-18. doi: 10.3171/2023.7.JNS23849
30. Vychopen M, Arlt F, Güresir E, et al. Intraoperative tranexamic acid administration in cranial meningioma surgery: a meta-analysis of prospective randomized, double-blinded, and placebo-controlled trials. *Front Oncol*. 2024;14:1464671. doi: 10.3389/fonc.2024.1464671
31. de Carvalho Barros L, Avancini C, Gonçalves PE, et al. Efficacy, safety and dose patterns of tranexamic acid in meningioma surgery: a systematic review and updated meta-analysis of randomized controlled trials. *Neurosurg Rev*. 2025;48(1):23. doi: 10.1007/s10143-025-03180-2
32. Li S, Liu M, Yang J, et al. Intravenous tranexamic acid for intracerebral meningioma resections: A randomized, parallel-group, non-inferiority trial. *J Clin Anesth*. 2024;92:111285. doi: 10.1016/j.jclinane.2023.111285
33. Rizzo SM, Tavakol S, Bi WL, et al. Meningioma resection and venous thromboembolism incidence, management, and outcomes. *Res Pract Thromb Haemost*. 2023;7(2):100121. doi: 10.1016/j.rpth.2023.100121
34. Abunimer AM, Lak AM, Calvachi P, et al. Early Detection and Management of Venous Thrombosis in Skull Base Surgery: Role of Routine Doppler Ultrasound Monitoring. *Neurosurgery*. 2022;91(1):115-22. doi: 10.1227/neu.0000000000001936
35. Kong Y, Jin B, Zhang Y, et al. Risk factors for postoperative thrombotic complications after meningioma resection: a retrospective single-center study in China. *Front Neurol*. 2025;16:1579384. doi: 10.3389/fneur.2025.1579384
36. Priliani L, Harahap AR, Satyagraha AW, et al. Mapping anemia prevalence across Indonesia. *Asia Pac J Clin Nutr*. 2025;34(3):430-9. doi: 10.6133/apjcn.202506_34(3).0017
37. Patidar GK, Thachil J, Dhimani Y, et al. Management of blood transfusion services in low-resource countries. *Vox Sang*. 2022;117(12):1375-83. doi: 10.1111/vox.13373
38. Fung YL, Lee CK, Kwon SY, et al. The contribution and potential of older blood donors in Asia Pacific regions. *Transfus Med*. 2022;32(1):71-6. doi: 10.1111/tme.12845
39. Gupta S, Gal ZT, Athni TS, et al. Mapping the global neurosurgery workforce. Part 1: Consultant neurosurgeon density. *J Neurosurg*. 2024;141(1):1-9. doi: 10.3171/2023.9.JNS231615
40. Sutanto S, Yulianti Bisri D, Bisri T. [The effect of intravenous tranexamic acid on intraoperative bleeding and transfusion requirements in meningioma surgery]. *Jurnal Neuroanestesi Indonesia*. 2019;8(1):8-16. In Indonesian. doi: 10.24244/jni.vol8i1.200
41. Rinaldo L, Brown DA, Bhargav AG, et al. Venous thromboembolic events in patients undergoing craniotomy for tumor resection: incidence, predictors, and review of literature. *J Neurosurg*. 2020;132(1):10-21. doi: 10.3171/2018.7.JNS181175
42. Goobie SM, Staffa SJ, Meara JG, et al. High-dose versus low-dose tranexamic acid for paediatric craniostomy surgery: a double-blind randomised controlled non-inferiority trial. *Br J Anaesth*. 2020;125(3):336-45. doi: 10.1016/j.bja.2020.05.054
43. Gerdessen L, Meybohm P, Choorapoikayil S, et al. Comparison of common perioperative blood loss estimation techniques: a systematic review and meta-analysis. *J Clin Monit Comput*. 2021;35(2):245-58. doi: 10.1007/s10877-020-00579-8
44. Fletcher ND, Gilbertson LE, Bruce RW, et al. Blood loss estimation during posterior spinal fusion for adolescent idiopathic scoliosis. *Spine Deform*. 2022;10(3):581-8. doi: 10.1007/s43390-021-00440-1
45. Liu Y, Li L, Hu H, et al. Association between preoperative hematocrit and postoperative 30-day mortality in adult patients with tumor craniotomy. *Front Neurol*. 2023;14:1059401. doi: 10.3389/fneur.2023.1059401
46. Xiao Y, Cheng X, Jia L, et al. Preoperative hematocrit levels and postoperative mortality in patients undergoing craniotomy for brain tumors. *Front Oncol*. 2023;13:1246220. doi: 10.3389/fonc.2023.1246220
47. Taccone FS, Rynkowski CB, Møller K, et al. Restrictive vs Liberal Transfusion Strategy in Patients With Acute Brain Injury: The TRAIN Randomized Clinical Trial. *JAMA*. 2024;332(19):1623-33. doi: 10.1001/jama.2024.20424
48. Turgeon AF, Fergusson DA, Clayton L, et al. Liberal or Restrictive Transfusion Strategy in Patients with Traumatic Brain Injury. *N Engl J Med*. 2024;391(8):722-35. doi: 10.1056/NEJMoa2404360
49. Okamoto E, Ishikawa E, Kino H, et al. Perioperative Deep Vein Thrombosis and D-dimer Measurement in Patients with Brain Tumor. *Neurol Med Chir (Tokyo)*. 2022;62(4):186-94. doi: 10.2176/jns-nmc.2021-0339
50. Zimmer K, Scheer M, Scheller C, et al. Influence of postoperative D-dimer evaluation and intraoperative use of intermittent pneumatic vein compression (IPC) on detection and development of perioperative venous thromboembolism in brain tumor surgery. *Acta Neurochir (Wien)*. 2024;166(1):480. doi: 10.1007/s00701-024-06379-2
51. Lasica N, Djilvesi D, Papic V, et al. Venous thromboembolic and hemorrhagic events after meningioma surgery: A single-center retrospective cohort study of risk factors. *PLoS One*. 2022;17(8):e0273189. doi: 10.1371/journal.pone.0273189
52. Kaewborisutsakul A, Tunthanathip T, Yuwakosol P, et al. Incidence and Risk Factors for Venous Thromboembolism Following Craniotomy for Intracranial Tumors: A Cohort Study. *Asian J Neurosurg*. 2020;15(1):31-8. doi: 10.4103/ajns.AJNS_351_19
53. Stonnington H, Shahbandi A, Bcharah G, et al. Timing and Morbidity of Intracranial Meningioma Resection Complications. *World Neurosurg*. 2024;183:e293-e303. doi: 10.1016/j.wneu.2023.12.084
54. PATCH-Trauma Investigators and the ANZICS Clinical Trials Group, Gruen RL, Mitra B, et al. Prehospital Tranexamic Acid for Severe Trauma. *N Engl J Med*. 2023;389(2):127-36. doi: 10.1056/NEJMoa2215457
55. Cai Q, Wu Y, Wang S, et al. Preoperative antiepileptic drug prophylaxis for early postoperative seizures in supratentorial meningioma: a single-center experience. *J Neurooncol*. 2022;158(1):59-67. doi: 10.1007/s11060-022-04009-4
56. Oya S, Ikawa F, Ichihara N, et al. Nation-wide Brain Tumor Registry-based Study of Intracranial Meningioma in Japan: Analysis of Surgery-related Risks. *Neurol Med Chir (Tokyo)*. 2021;61(2):98-106. doi: 10.2176/nmc.2020-0304
57. Chen C, Liu J, Du L. Tranexamic acid after cardiopulmonary bypass does not increase risk of postoperative seizures: a retrospective study. *Gen Thorac Cardiovasc Surg*. 2022;70(4):337-46. doi: 10.1007/s11748-021-01709-y
58. Ribeiro BB, Pereira RD, Vaz R, et al. Nonemergent craniotomy surgical site infection: a retrospective cohort study. *Porto Biomed J*. 2022;7(2):e152. doi: 10.1097/j.pbj.0000000000000152
59. Al-Mufti F, Gandhi CD, Couldwell WT, et al. Preoperative meningioma embolization reduces perioperative blood loss: a multi-center retrospective matched case-control study. *Br J Neurosurg*. 2023;37(1):67-70. doi: 10.1080/02688697.2021.1979191
60. Yin Y, Li Y, Jiang Z, et al. Clinical Outcomes and Complications of Preoperative Embolization for Intracranial Giant Meningioma Tumorectomy: A Retrospective, Observational, Matched Cohort Study. *Front Oncol*. 2022;12:852327. doi: 10.3389/fonc.2022.852327