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Original Article

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Effect of Tranexamic Acid Infusion to Reduce Intraoperative Blood Loss in Large Meningioma: A Prospective Randomized Control Study (Preliminary Report)

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ABSTRACT

OBJECTIVE Resection of intracranial meningioma has been related to significant blood loss. Intravenous tranexamic acid (TXA) has been shown to successfully attenuated blood loss and transfusion in various surgical procedures. However, the evidence has been limited in the surgical management of brain tumors. This study aims to evaluate the efficacy of intravenous TXA in reducing intraoperative blood loss and the need for blood transfusion during the surgical resection of intracranial meningiomas.

METHODS We conducted a prospective, randomized double-blind controlled study aiming for a sample size of 44 patients. In this preliminary report, twenty-five patients aged 18-60 years with large intracranial meningioma undergoing elective meningioma resection were enrolled and randomized to receive either TXA or a placebo. "Large meningioma" was defined as a radiographic finding of a tumor with a diameter > 5 cm in at least 2 dimensions. The TXA group was administered TXA at 20 mg/kg over 20 minutes, prior to the operation, followed by an infusion of 1 mg/kg/hr until the end of the operation. The primary outcome measure was volume of intraoperative blood loss. Continuous variables were analyzed with Student's t-test or the Mann-Whitney U-test depending upon the distribution of the data. Fisher's exact test was used to compare categorical variables.

RESULTS Twenty-five patients were randomized with 12 in the TXA group and 13 in the placebo group. Baseline characteristics of the patients in the two groups were similar. The median intraoperative blood loss volume was 1,925 mL (IQR=1,575) in the TXA group and 1,500 mL (IQR=1,700) in the placebo group (p = 0.904). The median of intraoperative packed red cells (PRC) transfusion volume was 801.5 mL (IQR=825.5) in the TXA group and 493 mL (IQR=856) in the placebo group (p = 0.883). There was no significant difference in blood transfusion volumes between the groups in first 24 hours after surgery (p = 0.581). The incidence of thromboembolic events was similar in the two groups (p = 1.0). No postoperative seizures occurred in either group during the study.

CONCLUSIONS TXA did not reduce intraoperative blood loss, the intraoperative transfusion requirement, and the transfusion requirements during the first 24 hours after surgery in patients who underwent large intracranial meningioma resection.

KEYWORDS tranexamic acid; meningioma; blood loss; blood transfusion

INTRODUCTION

Meningioma is the most common primary central nervous system (CNS) tumor, accounting for one-third of primary brain tumors. Its histology is usually benign and presents with intracranial, extra-axial, and dural attachment lesions. Meningioma has been found in 53.3% of all CNS non-malignant tumors (1-3). Neurological symptoms develop in only 8.1% of patients due to the tumor's slow-growing nature which allows adequate time for cerebral auto-regulation and cerebral compensation. For that reason, most patients presenting to the neurosurgeon have a large meningioma (3, 4). Meningioma contains more tissue plasminogen activator (tPA) than normal brain tissue which causes hyperfibrinolysis during resection of the meningioma resulting from release of tPA into the blood circulatory system. The degree of hemostatic disturbance from tPA is directly associated with the volume of the meningioma and the extent of the resection (5-7).

Surgical removal of meningioma is associated with a large volume of blood loss which causes hemodynamic instability and usually requires allogeneic blood transfusion. Massive blood transfusion, however, increases morbidity and mortality due to prolonged use of a ventilator, a longer postoperative Intensive Care Unit (ICU) stay and hospital stay, a higher incidence of 30-day major complications, and coagulation disturbance (8, 9). Minimizing bleeding during meningioma resection is primarily in the surgeons' hands and their expertise. Various strategies have been developed to decrease intra-operative blood loss and transfusion requirements, e.g., preoperative embolization of the arterial supply of the tumor, preoperative autologous blood transfusion, preoperative erythropoietin administration, acute normovolemic hemodilution, and a blood cell saver. Those methods are currently practiced, but they are not routine (10) and none of those strategies are considered a standard technique.

Tranexamic acid (TXA), an anti-fibrinolytic agent, binds to lysine receptors on plasmin and blocks the binding of plasmin to fibrin, inhibiting fibrinolysis (11). TXA has been shown to reduce perioperative blood loss and transfusion in various surgical procedures. In the neurosurgical field, large sample size trial of TXA have been limited to traumatic brain injury (TBI) and subarachnoid hemorrhage patients (12, 13). There is only very limited evidence of TXA being used in a craniotomy to remove a brain tumor. To fill this knowledge gap, we studied the effect of TXA in large meningioma surgery because of TXA's inhibitory effect on the fibrinolysis pathway.

The primary purpose of this study is to determine efficacy of TXA in reducing intraoperative blood loss. Secondary objectives are to assess the efficacy of TXA in attenuation of intraoperative and 24 hours post-surgery blood transfusion requirements. Adverse effects of TXA, focusing on thromboembolic events and convulsions, are also recorded.

METHODS

Study design

This was a single-center, prospective, double-blind, placebo-controlled, randomized study conducted between August 2020 and January 2022 at the Maharaj Nakorn Chiang Mai Hospital, Thailand.

Methodology

The Research Ethics Committee No.2 of the Faculty of Medicine, Chiang Mai University, authorized the study protocol (ANE-2563-07307). This permission allows the execution of human research in full accordance with the study protocol. The ClinicalTrials.gov ID was NCT04386642. After obtaining ethics committee approval and written informed consent from patients, twenty-five individuals aged 18 to 60 years who were diagnosed with intracranial meningioma with a radiographic finding of a tumor diameter > 5 cm in at least 2 dimensions were included (14-16). All the patients were scheduled for elective craniotomy to remove the tumor. The exclusion criteria were patients who refused to participate in this study, patients with recurrent tumors, an intracranial tissue biopsy, a history of TXA allergy, pregnancy, a history of significant thromboembolic episodes, or significant renal dysfunction (GFR ≤ 50 mL/min).

Sample size calculation

The sample size was calculated based on a previous study of TXA effects to reduce blood loss during intracranial meningioma removal (14). The average blood loss in large meningioma remov-

al in our institution is 800 mL. The mean loss in the experimental group was 500 mL. The sample size, calculated using continuous outcome for the superiority trial, was 44 patients (22 patients per group). This sample size had a power of 90%, a significance level of 5%, and standard deviation of outcome of 300. Due time limitations, we were not able to achieve the expected number participants. For that reason, this study presents the preliminary results of 25 patients.

Randomization and blinding

We used a computer-generated permuted block of 4 randomization. The random assignments were concealed in opaque, sealed envelopes. The envelopes were sent to the central pharmaceutical unit for preparation of the study drugs. The pharmacist opened the concealed envelopes and prepared the drug in clear 50 mL syringes. Patients in the TXA group received a TXA 20 mg/kg loading over 20 minutes before the skin incision, followed by a maintenance infusion of 1 mg/kg/hr until the end of operation (17, 18). The patients randomized to a placebo group received 0.9% normal saline. All the patients, attending anesthesiologists, neurosurgeons, data collectors and outcome assessors were blinded to the randomization. This blinding process was reliable as the research drug and placebo were prepared by a pharmacist who was not involved in the study. The investigational drug and the placebo were contained in a 50 mL clear syringe as a transparent solution.

Surgical procedure

The standard treatment for large meningioma is surgical removal. Surgical approaches are determined by the tumor's size, location, and vascular supply. This research focused exclusively on tumors situated within the supratentorial compartment. Total resection is the objective for neurosurgeons; however, this must be balanced against factors such as blood loss, brain edema, injury to adjacent normal brain tissue, and the patient's overall condition. A craniotomy for the removal of a large meningioma typically requires over six hours of surgical intervention and is associated with considerable blood loss.

Anesthetic protocols

A standard anesthetic protocol was followed with all the patients. At the operating theatre, patients received total intravenous anesthesia (TIVA) with propofol infusion via target-controlled infusion (TCI) following the Schneider pharmacokinetic model. Propofol TCI was set at an effect site concentration (Ce) of 4-6 mcg/mL. Fentanyl 2 mcg/kg and Cis-atracurium 0.15 mg/kg were administered during the induction period. Anesthesia was maintained by propofol TCI titration to the Bi-Spectral Index (BIS) value of 40-60. Ventilation was controlled with an air-oxygen mixture (FiO_2 0.4-0.5) with 2 L/min fresh gas flow. An arterial line and central venous line (if needed) were cannulated after induction of anesthesia. The blinded study drug was loaded at 0.5 mL/kg 20 mins prior to skin incision followed by 0.025 mL/kg/hr (1 mg/kg/hr) continuously infused to the end of operation. Propofol TCI tailed off when closing the dura mater was started. In-operating-theater extubation was discussed with the surgeons, and considered the patient's preoperative condition as well as anesthetic and surgical aspects. When to turn off the propofol infusion and whether to switch to a volatile anesthetic was determined by the attending anesthesiologist. Fentanyl was intermittently supplemented (25-50 mcg) during the surgery as needed.

Intraoperative fluid management was guided by pulse pressure variation (PPV). For the patients who had a central venous catheterization, PPV could be augmented by central venous pressure as a guided fluid administration. Arterial waveform analysis showing a PPV greater than 13% suggests the blood pressure is likely responsive to volume administration, classifying the patient as a volume responder. Serial arterial blood gas (ABG) analysis was done to assess the acid-base status, oxygenation, ventilation, hemoglobin (Hb) and hematocrit (Hct) and blood glucose. The types and volume of blood transfusion were decided by an anesthesiologist based on significant hemodynamic changes and the degree of anemia. The perioperative transfusion triggers in our institute are Hct < 30% for packed RBCs, INR > 1.5 for fresh frozen plasma (FFP) and platelet counts < 100,000/mm^3 for platelet transfusion. The volume of transfused packed RBCs, FFP and platelets were recorded. The visual estimation of intraoperative blood loss was done by estimating the amount of blood in surgical sponges and the

operative field, then subtracting the amount of irrigation fluid used from the total volume blood and fluid in the scaled suction canisters.

Following surgery, the patients were admitted to the neurosurgical ICU. Intubation and ventilation assistance was continued for variable periods depending on intraoperative events and the patient's neurological condition. The patients were transferred to a normal ward when their neurological status and hemodynamic were stable. Postoperative imaging is not routinely done in our institution. The radiologist was consulted urgently if the patient developed a new neurological deficit, pupils had either unequal responsiveness or total unresponsiveness to light or a worsening Glasgow Coma Scale (GCS) score. The systemic causes of the problems were then evaluated and corrected.

Statistical analysis

Statistical analysis was performed using Stata statistical software version 16.1 (Statacorp LLc, College Station, TX, USA). The distribution of data was assessed using the Kolmogorov-Smirnov and Shapiro-Wilk tests. The Mann-Whitney U-test and Student's t-test were used to analyze continuous variables depending on the distribution of the data. Normally distributed continuous variables are expressed as mean ± SD. Non-parametric variables are expressed as median (range). The Chi-square test and Fisher's exact test were used to compare categorical variables. Intention-to-treat analysis was used for the primary analysis. A p-value < 0.05 indicated statistical significance.

Ethic approval

The Research Ethics Committee No.2 of the Faculty of Medicine, Maharaj Nakorn Chiang Mai Hospital, Chiang Mai University (ANE-2563-07307) approved the study. Clinical trial registration: ClinicalTrials.gov Identifier: NCT04386642

RESULTS

In this preliminary study, twenty-five patients were enrolled. Twelve patients were randomized to the TXA group and thirteen patients were randomized to the placebo group. There were no dropouts or withdrawals. However, two patients in the placebo group received TXA during the operation due to life-threatening uncontrolled hemorrhage. The dosage of TXA administered to those two patients was 500 mg and 1,000 mg, respectively, which was significantly lower than that received by patients in the treatment group. We classified the two patients as belonging to the placebo group and included them in the intention-to-treat analysis. The consort diagram is shown in Figure 1.

The demographic characteristics and preoperative laboratory parameters of patients were comparable between the two groups (Table 1). The tumor volume was calculated by multiplication of three dimensions divided by 2.

$$(ABC)/2$$

A, B and C are the dimensions of the tumor measured by a radiologist using a recent CT / MRI brain (19).

The tumor volume of the two groups was similar: 100.58±35.63 cm^3 in the TXA group and 95.98±34.96 cm^3 in the placebo group, p = 0.747. Tumor location, duration of surgery, extension of

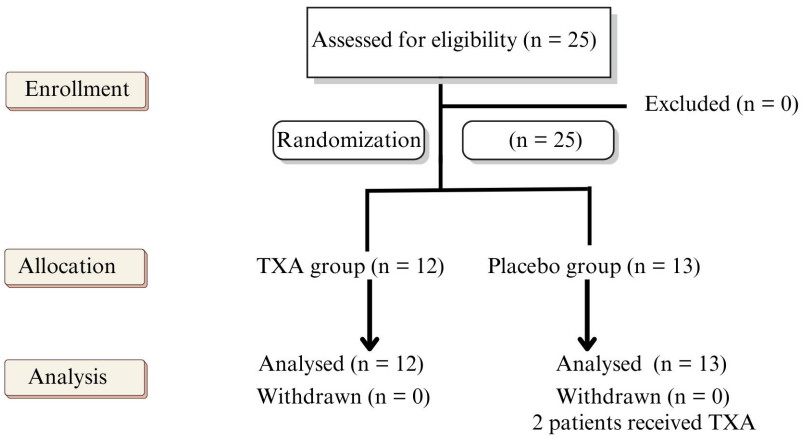

Figure 1. Consort diagram

Table 1. Demographic characteristics

Variables	TXA group (n=12)	Placebo group (n=13)	*p*-value
Age (years)	50.83±8.38	52.69±7.63	0.567
Male/female	1 [8.3%]/11 [91.6%]	5 [38.4%]/8 [61.5%]	0.160
BMI (kg/m^2)	24.79±5.37	24.44±4.89	0.867
Glasgow Coma Scale (GCS) score	15 (0.5)	15 (0.0)	0.659
Tumor volume (cm^3)	100.58±35.63	95.98±34.96	0.747
Pre-op hemoglobin (g/dL)	13.74±1.87	13.41±1.40	0.626
Pre-op platelet (cells/cu.mm.)	257,000±39,886	24,8384±54,386	0.658
Pre-op INR	0.98±0.04	1.01±0.06	0.197
Pre-op PTT ratio	0.85±0.12	0.82±0.12	0.553

Values are expressed as mean ± SD, median (IQR), number [%]
BMI, body mass index; INR, International Normalised Ratio; PTT partial thromboplastin time; TXA, tranexamic acid

Table 2. Demographic characteristics

Variables	TXA group (n=12)	Placebo group (n=13)	*p*-value
Duration of surgery (minutes)	541.2±146.4	493.4±113.7	0.369
Extent of resection (complete/partial)	4 [33.3%]/8 [66.6%]	5 [38.4]/8 [61.54]	1.000
Intraoperative crystalloid (mL)	2,525 (1,050)	2,150 (1,372)	0.2641
Intraoperative colloid (mL)	950 (750)	500 (1,000)	0.560
Intraoperative urine output (mL)	1,287±664	1,059±472	0.164
Intraoperative blood loss (mL) (median and IQR)	1,925 (1,575)	1,500 (1,700)	0.904
Intraoperative transfusion			
Packed red cells (mL)	801.5 (825.5)	493.0 (856.0)	0.883
Fresh frozen plasma (mL)	247 (548.5)	337 (1,017.0)	0.594
Platelets (mL)	0 (122.5)	0 (330.0)	0.302

Values are expressed as mean ± SD, median (IQR), number [%]
TXA, tranexamic acid

resection and anesthetic drug consumption were not different between groups. The amount of resuscitation fluid between groups was also alike (Tables 1 and 2).

The median intraoperative blood loss in TXA group was 1,925 (IQR=1,575) mL and in the placebo group was 1,500 (IQR=1,700) mL with no statistically significant difference between groups (p = 0.904) (Figure 2). The median intraoperative volume of packed RBCs was 801.5 (IQR=825.5) in the TXA group and 493 (IQR=856) in the placebo group (p = 0.883). There were no statistically significant differences in intraoperative blood transfusion volumes of packed RBCs, fresh frozen plasma or platelets (Table 2). The volume of blood transfused (mL) is a more precise measurement than the quantity of blood units as blood may occasionally be transfused in half-bag increments while patients are being transported to the ICU following the completion of surgery. The outcome remained unchanged when calculated in terms of blood units rather than blood volume in milliliters. Furthermore, there were no statistically significant differences in blood transfusion volumes in

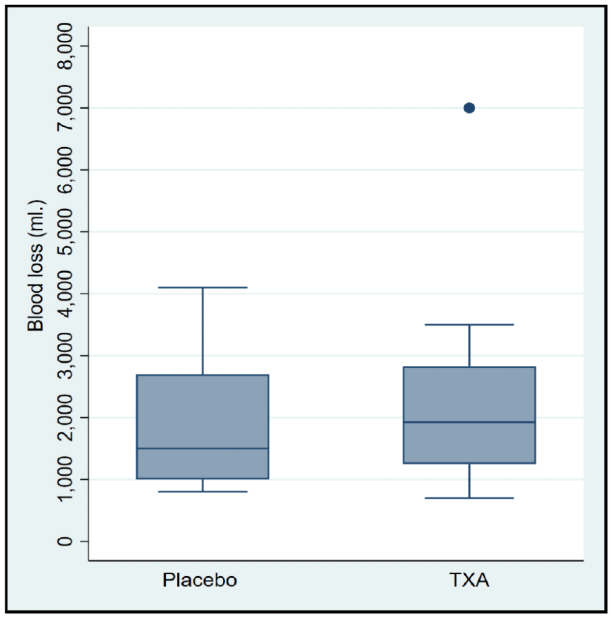

Figure 2. Volume of intraoperative blood loss (Primary outcome)

Table 3. Postoperative data

Variables	TXA group (n=12)	Placebo group (n=13)	*p*-value
Average volume of blood components received in the first 24 h of surgery			
Packed red cells (mL)	399	546	0.581
Fresh frozen plasma (mL)	0	0	0.797
Platelets (mL)	135	0	0.530
Number of patients who developed adverse events			
Thromboembolic events	1 (8.33%)	2 (15.38%)	1.000
Postoperative seizure	0.00	0.00	1.000

TXA, tranexamic acid

the first 24 hours after surgery in terms of packed RBCs, FFP or platelets (Table 3). There were no significant differences in the incidence of thromboembolic events and postoperative seizures between the two groups (Table 3).

DISCUSSION

Inarguably, surgical removal of intracranial meningioma is usually associated with massive hemorrhage and often requires a large volume of allogeneic blood transfusion. Factors correlated with significant blood loss in meningioma resection include large tumor size, tumors invading the sphenoid wing, a rich vascular supply, adjacent to the vessels, and accidental tearing of vessels (17). The larger the amount of meningioma resected the more tPA is released into the blood circulation. The tPA causes hyperfibrinolysis and interferes with clot formation. Massive blood transfusion further amplifies consumptive coagulopathy. Additionally, even a judicious volume of crystalloid solution causes dilutional coagulopathy. Some colloid solutions affect the coagulation pathway. TXA has been shown to reduce perioperative blood loss and transfusion in various surgical procedures, but there is only limited evidence for brain tumor removal, particularly meningioma surgery.

In our preliminary report of 25 patients, there was no significant difference in intraoperative blood loss between the two groups. The median intraoperative blood loss was 1,925 mL (IQR=1,575) in the TXA group and 1,500 mL (IQR=1,700) in the placebo group. There have been few studies of using TXA in patients undergoing excision intracranial meningioma. Those studies, which administered the same dose of TXA as in our study, reported that TXA could significantly reduce intraoperative blood loss during elective craniotomy for excision of intracranial meningioma by 27.00% (17), 46.43% (20) and 24.60% (21). Total intraoperative blood loss in our study was much higher in the placebo group (median 1,500 mL) than in studies by Hooda et al. (mean 1,124), Ravi et al. (mean 1,150 mL), Rebai et al. (mean 495 mL) (17, 20, 21). The reason for the differences might be due to differences in the size of the meningiomas. In our study, we enrolled patients with a tumor diameter > 5 cm in at least 2 dimensions, which is larger than in the previous studies. Ravi et al. recruited patient with tumor diameter > 5 cm in at least 1 dimension, while Hooda et al. and Rebai et al. recruited patients with meningioma regardless of the size of the tumor (17, 20-21). The tumor volume in our study is greater than those reported in previous studies. In the present study, the mean tumor volume was 100.58 cm^3 in the TXA group and 95.98 cm^3 in the placebo group. The Ravi et al. study reported a mean tumor volume of 63.79 cm^3 in the TXA group and 43.36 cm^3 in the placebo group (20). As mention earlier, a larger tumor can initiate a greater hemostatic disturbance by releasing greater amounts of tPA.

In the secondary outcomes, there was no significant difference in the transfusion requirement during the intraoperative period and the first 24 hours after surgery between the groups which is consistent with previous studies (17, 21-23). As is well known, TXA induces fibrinolytic suppression and promotes clot stabilization. Thus, the main theoretical risk of TXA is thromboembolic events. In our study, the incidence of thromboembolic events was similar between the groups which is consistent with previous studies. The other potential side effect of concern from TXA is seizure. In the setting of intracranial surgery, postoperative convulsion may result from the meningioma itself, from the surgical lesion, and may

possibly be TXA-induced. A previous systematic review showed that a newly-developed seizure after resection of meningioma occurred in 1.4% of patients and that it can significantly increase mortality (21). The incidence of TXA-associated seizures has been reported to be directly correlated with high doses of TXA (22). To reduce the risk of seizures, we chose to use an intermediate dose of TXA in the amount of 20 mg/kg loading 20 minutes before the skin incision and followed by a maintenance infusion of 1 mg/kg/h until the end of the operation. No postoperative seizures were observed in the present study. Our findings support what was reported in a CRASH-3 study which included 12,737 TBI patients. That study reported the incidence of thromboembolic events and seizures associated with the use of TXA were not higher in TBI patients (12).

This study had several limitations. This preliminary report, which involves a limited number of subjects, may lack sufficient statistical power to demonstrate a potential benefit of TXA, if such a benefit exists. Therefore, obtaining data from a larger sample as originally calculated may be required. Second, estimating blood loss by the visual method is subjective and can vary among the attending anesthesiologists. Based on the observed non-significant differences in outcomes between the two groups, the results of the present study indicate a reversal of prior evidence suggesting that TXA reduces blood loss during meningioma surgery. The authors chose to present the results of the study as preliminary findings.

CONCLUSIONS

As shown in this preliminary report, administration of TXA did not attenuate intraoperative blood loss during surgical removal of meningioma nor did it decrease transfusion requirements either intraoperatively or during the first 24 hours after surgery. The incidence of thromboembolic events in this study was similar between the two groups. No postoperative seizures occurred in our study. In future studies, obtaining the calculated desired sample size may be needed.

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CONFLICTS OF INTEREST

The authors have no conflicts of interest to report.

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