



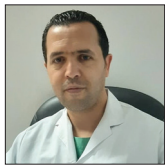
Original Article

# Intraoperative tranexamic acid use in patients undergoing excision of intracranial meningioma: Randomized, placebo-controlled trial

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Received : 19 February 2021

Accepted : 01 May 2021

Published : 14 June 2021

DOI

10.25259/SNI\_177\_2021

Quick Response Code:



## ABSTRACT

**Background:** Intracranial meningioma resection is associated with substantial intraoperative bleeding. Intraoperative tranexamic acid (TXA) use can reduce bleeding in a variety of surgical procedures. The objective of this study was to evaluate the effects of TXA treatment on blood loss and transfusion requirements in patient undergoing resection of intracranial meningioma.

**Methods:** We conducted a prospective, randomized double-blind clinical study. The patient scheduled to undergo excision of intracranial meningioma were randomly assigned to receive intraoperatively either intravenous TXA or placebo. Patients in the TXA group received intravenous bolus of 20 mg/kg over 20 min followed by an infusion of 1 mg/kg/h up to surgical wound closure. Efficacy was evaluated based on total blood loss and transfusion requirements. Postoperatively, thrombotic complications, convulsive seizure, and hematoma formation were noted.

**Results:** Ninety-one patients were enrolled and randomized: 45 received TXA (TXA group) and 46 received placebo (group placebo). Total blood loss was significantly decreased in TXA group compared to placebo (283 ml vs. 576 ml;  $P < 0.001$ ). Transfusion requirements were comparable in the two groups ( $P = 0.95$ ). The incidence of thrombotic complications, convulsive seizure, and hematoma formation was similar in the two groups.

**Conclusion:** TXA significantly reduces intraoperative blood loss, but did not significantly reduced transfusion requirements in adults undergoing resection of intracranial meningioma.

**Keywords:** Blood loss, Blood transfusion, Intracranial meningioma, Intraoperative, Tranexamic acid

## INTRODUCTION

Intracranial meningioma accounts for 20–30% of brain tumors.<sup>[24]</sup> They are benign tumors whose removal significantly improves the quality of life after surgery.<sup>[22,24]</sup> The surgical procedure is often associated with a high amount of blood loss, because these tumors induce local tissue plasminogen activator and cause fibrinolysis.<sup>[26]</sup> Intraoperative blood loss may be major leading to hemodynamic instability and requiring the use of massive blood transfusions, often associated with an increase in postoperative morbidity and mortality. A strategy aimed at reducing the importance of intraoperative blood loss and the use of transfusion of labile blood products is, therefore, essential.

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Tranexamic acid (TXA) is a synthetic derivative of amino acid lysine that reversibly blocks plasminogen conversion to plasmin and inhibiting fibrin clot dissolution.<sup>[26]</sup> Its effectiveness in reducing perioperative bleed and transfusion requirements has been proven in a variety of surgical procedures.<sup>[6,13,16]</sup> However, in neurosurgery, the literature is poor in studies proving the interest of this antifibrinolytic, especially during surgery for intracranial meningioma.

The primary objective of this study was to evaluate the effects of TXA treatment on blood loss and transfusion requirements in patient undergoing resection of intracranial meningioma. The second objective was to evaluate the effects of TXA on perioperative complications and neurological outcome.

## METHODS

### Study design

This was a single-center, prospective, double-blind, placebo-controlled, randomized study conducted between April 2017 and December 2018 at the Department of Neurosurgery, Traumatology and Severe Burns Center, Tunisia.

### Sample size calculation

Sample size calculation was based on our hypothesis that TXA reduces total blood loss compared with placebo. Average blood loss during intracranial meningioma surgery in the previous studies ranged from 340 mL to 1100 mL.<sup>[3]</sup> Considering 25% reduction in blood loss according to the study by Hooda *et al.*,<sup>[12]</sup> the required number of patients is 88 for a type I error of 5% and 80% power. We will recruit a total of 110 patients.

### Study population

This protocol was approved by the Ethical and Scientific Committee of Traumatology and Severe Burns Center, Tunisia (ESCTSBC/2017/R02). After obtaining written informed consent, 110 consecutive American Society of Anesthesiology Grade I and II patients, in the age group of 18 and 70 years, of either sex undergoing resection of intracranial meningioma were enrolled for the study. The exclusion criteria were as follows: patients who refused to participate in the study, history of allergy to TXA, previous thromboembolic episode, previous seizures, preexisting renal or hepatic disorders, abnormal coagulation parameters (abnormal prothrombin time [PT] or platelet counts), clinical history of bleeding diathesis, current treatment with oral anticoagulant or antiplatelet agents, and pregnant or lactating mothers. In addition, patients planned for preoperative embolization were also not enrolled. All patients were operated by a neurosurgeon with at least 5 years of

experience. Demographic data and tumor size were noted. Preoperative laboratory values (baseline value of hemoglobin [Hb], PT, platelets count and fibrinogen) were noted.

### Randomization and treatment groups

The patients were randomized to receive TXA group or normal saline (placebo group) using a computer-generated random sequence. The choice of TXA dose was based on study by Hooda *et al.*<sup>[12]</sup> Anesthetists and surgeons were not aware of the treatment given to each patient. All solutions were prepared in a 50 ml syringe by an anesthesiologist who participates in the study but are not involved in the patient's perioperative management. For TXA group, 2000 mg of TXA was diluted to 50 ml with normal saline (40 mg/ml) and the same volume (50 ml) of normal saline was taken for placebo group.

TXA group: Bolus dose of 20 mg/kg (0.5 ml/kg) was administered for 20 min before the surgical incision followed by perfusion of 1 mg/kg/hup to surgical wound closure at completion of surgery.

Placebo group: A saline placebo was administered according to the same TXA group infusion protocol.

### Anesthetic management

On admission to the operating room, the patients were placed in the supine position and monitored by cardiac electrical activity, noninvasive blood pressure measurement, and pulse oximetry, with the placement of a peripheral venous catheter at the upper limb. A BIS monitor has been installed if the location of the tumor is not frontal. After verifying the vital constants of the patient, the anesthetic induction was done with remifentanyl (0.5 µg/kg over 3 min), propofol (2.5 mg/kg) and cisatracurium (0.15 mg/kg). After intubation, mechanical ventilation was adjusted to have the end-tidal carbon dioxide (EtCO<sub>2</sub>) between 30 and 35 mmHg. Anesthesia was maintained with remifentanyl (0.1–0.4 µg/kg/min), propofol (4 mg/kg/h), and cisatracurium (0.12 mg/kg/h). Intraoperative sedation monitoring is performed by the BIS with intraoperative objectives between 40 and 60. Invasive monitoring of blood pressure was performed by a radial catheter. A subclavian central venous catheter was placed. The temperature was controlled within a range of 36–37°C. Duration of surgery and anesthesia was noted. The record of HR, MAP, SpO<sub>2</sub>, urine output, and temperature was done every hour.

### Measurements of blood loss, fluid therapy, and transfusion strategy

Intraoperatively, the estimation of blood loss is done by the principal investigator and the surgeon without being aware of the treatment given to the patient. Blood loss was determined from the surgical suction bottle (after subtracting the amount of

irrigation fluid), soaked sponges, cotton pledges, and the volume of blood in surgical drapes. This measure was done every hour.

Postoperative blood loss corresponded blood volume collected by suction drains at 48 h. Total bleeding was the sum of intra- and postoperative blood loss.

Fluid therapy consisted of administration isotonic crystalloids and colloids guided by monitoring mean arterial pressure and urine output.

Perioperative, transfusion trigger for red blood cells was an Hb concentration <8 g/dl. Fresh frozen plasma was transfused at PT < 60% and platelet concentrate was transfused at platelet count <100,000/mm<sup>3</sup>.

### Postoperative care

All the patients were transferred to the neurosurgical intensive care unit. After monitoring, laboratory investigations were performed (Hb, electrolytes, PT, fibrinogen, and platelet amount) and the decision of extubate or elective ventilation was based on the assessment of the consultant anesthesiologist. Cerebral computed tomography was performed to evaluate tumor resection and hematoma formation. Side effects, such as thrombotic complications or convulsive seizure, were noted during hospitalization and a month later. The Extended Glasgow Outcome Scale (GOSE) was evaluated at the time of discharge of patient from the hospital and was categorized as good recovery (GOSE 7–8), moderate disability (GOSE 5–6), and severe disability (GOSE 1–4). The duration of ICU and hospital stay was recorded.

### Primary outcome

The primary outcome was set as the rate of intraoperative hemorrhage. The amount of estimated intraoperative blood loss (in ml), the amount of transfusion (in ml), and postoperative level of hemoglobin (in g/dl) were recorded.

### Statistical analysis

Statistical analysis was performed with SPSS statistical software version 25. The Kolmogorov–Smirnov statistic was used for testing normality for continuous variables. Continuous variables were expressed as mean SD and compared using Student's *t*-test or the Mann–Whitney U-test for nonnormal distribution variables. Categorical variables were compared using the Chi-square or Fisher's test. All statistical analyses were carried out at 5% level of significance and *P* < 0.05 was considered as statistically significant.

## RESULTS

In total, 110 patients were evaluated during the period of study; 91 defined inclusion criteria, were retained in the final

sample, and randomized into two groups to receive either TXA or saline (45 in TXA group and 46 in placebo group) [Figure 1].

### Demographics

Demographic, anesthesia, and surgery characteristics are summarized in [Table 1]. There were 48 female patients and 42 male patients presented in the study (*P* = 0.53). The mean age was 48.2 ± 9.1 years in placebo group versus 49.5 ± 8.7 years in TXA group (*P* = 0.49). Tumor size, duration of surgery and anesthesia, and the amount of fluids were comparable in the two groups. The operated intracranial meningiomas were located at the convexity (41), parasagittal (34), olfactory groove (5), suprasellar (5), and sphenoid wing (5). There was no significant difference in preoperative laboratory parameters [Table 1]. The average dose of TXA received in Group T was 1723 mg.

### Intraoperative blood loss and intravenous fluid management

Intraoperative blood loss, transfusion requirements, and intraoperative fluid management are summarized in

**Table 1:** Patients characteristics.

Group	TXA group (n=45)	Placebo group (n=46)	P-value
Age (years)*	49.5±8.7	48.2±9.1	0.49
Sex**			
Male	23 (51)	26 (56)	
Female	22 (49)	20 (46)	
Weight (kg)*	70.5±8.9	69.9±9.3	0.74
ASA**			0.51
I	26 (59)	24 (52)	
II	19 (42)	22 (48)	
Tumor size (cm)*	5.05±1.07	5.30±1.23	0.31
Tumor location**			
Convexity	22 (48.8)	20 (43.6)	
Parasagittal	16 (36.3)	18 (39)	
Olfactory groove	2 (4.5)	3 (6.5)	
Suprasellar	2 (4.5)	3 (6.5)	
Sphenoid wing	3 (6.7)	2 (4.4)	
Hb preoperative (g/dl)*	12.55 ±1.27	12.35±0.98	0.56
Platelet count (1×10 <sup>3</sup> )*	367.27±47.07	375.22±63.65	0.50
Fibrinogen*	2.36±0.97	2.55±1.26	0.41
Intraoperative MAP (mmHg)	67±22	69±18	0.68
Duration of surgery (min)*	220±31.2	215±25.8	0.14
Duration of anesthesia (min)*	276±76.1	302±86.3	0.37

\*Data are given as mean (±SD). \*\*Data given as number (%) of patients. TXA: Tranexamic acid, ASA: American Society of Anesthesiologists, MAP: Mean arterial pressure

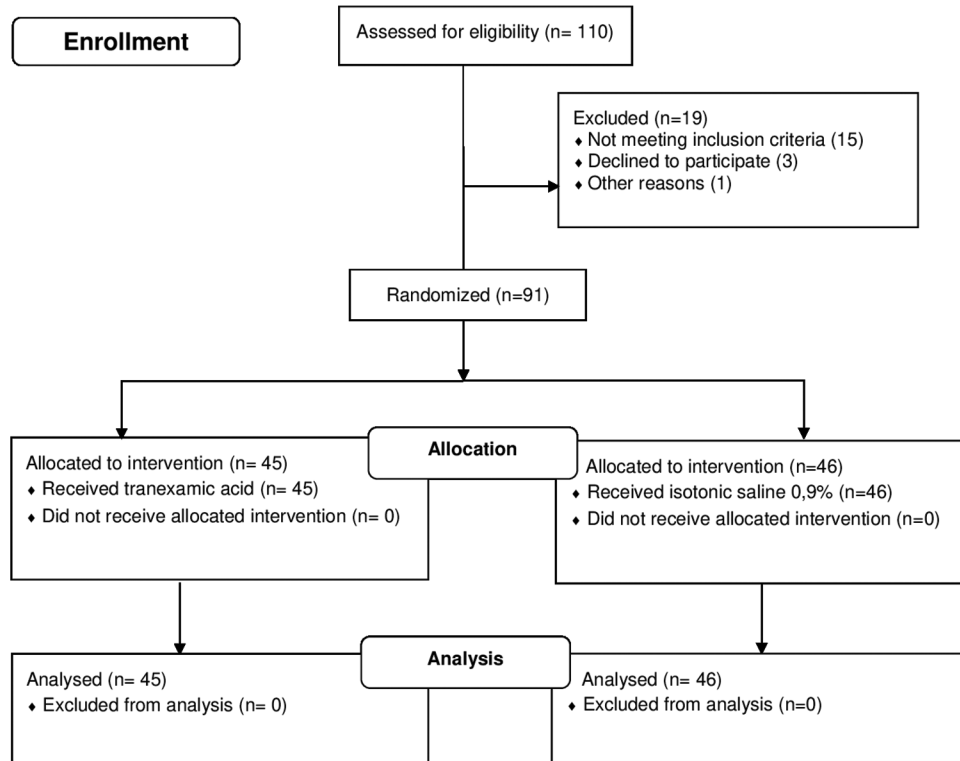


Figure 1: Flowchart of patient progress through the study.

[Table 2]. Three experienced neurosurgeons participated in the study, and the difference in blood loss according the operator was very small. Intraoperative blood loss was 495 ml (SD 81 ml) in the placebo group and 244 ml (SD 68 ml) in the TXA group, with a significant difference ( $P < 0.001$ ) [Figure 2]. There was a statistically significant difference in total blood loss between two groups ( $P < 0.001$ ) with a mean reduction of blood loss of 293 ml with the use of TXA as compared to placebo. Transfusion requirements were lower in the TXA group but were not statistically significant. The number of patients who were transfused by blood products was comparable between the two groups. Concerning the crystalloid given perioperative, there was a significant difference between the two groups ( $P = 0.02$ ) but for the colloid, there was no difference.

### Postoperative laboratory parameters and complications

During the postoperative period, Hb count shows statistical difference between the two groups ( $P = 0.02$ ) but platelet count was comparable between the two groups ( $P = 0.24$ ). However, the fibrinogen levels were significantly higher in TXA group compared to placebo group ( $P = 0.02$ ). Incidence of postoperative complications was comparable in the groups. The patient outcome was not affected by intraoperative use of TXA and none of the patient developed side effects. Duration of ICU and hospital stay was also similar in the two groups [Table 3].

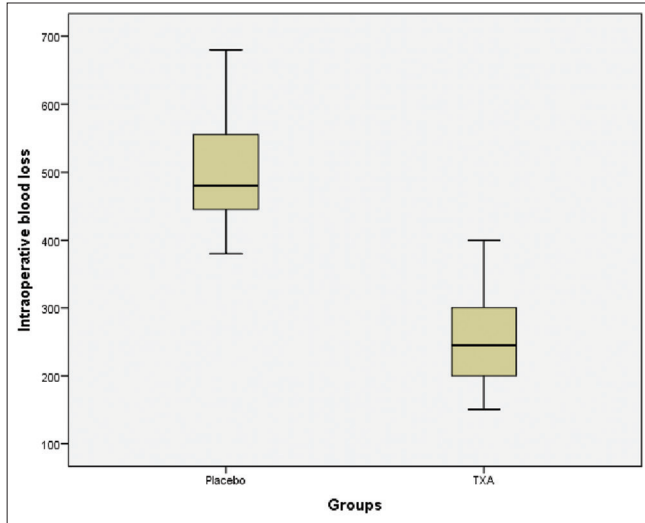
Table 2: Comparison of fluid infusion, total blood loss, and transfusion requirements.

Group	TXA group (n=45)	Placebo group (n=46)	P-value
Crystalloids (ml)	2590±497	2847±566	0.02
Colloid (ml)	45±145	108±256	0.15
Total blood loss (ml)	283±71	576±76	<0.001
RBC			
No. of patients transfused*	3 (6)	4 (8.6)	0.95
Volume	380	480	
FFP			
No. of patients transfused*	0	1 (2.1)	0.90
Volume	0	400	

\*Data given as number (%). TXA: Tranexamic acid, RBC: Red blood cell, FFP: Fresh frozen plasma

### DISCUSSION

In this randomized, double-blind, placebo-controlled study, we demonstrated that the use of TXA resulted in a significant reduction in perioperative bleeding in patient undergoing excision of intracranial meningioma ( $P < 0.001$ ). There was a mean reduction of blood loss of 293 ml (49%) with the use of TXA as compared to placebo. Nevertheless, we found no



**Figure 2:** Blood loss (ml) during operation in patient receiving placebo or tranexamic acid.

difference between the two groups (TXA versus placebo) regarding transfusion requirements ( $P = 0.95$ ).

It is known that intraoperative hemorrhage in neurosurgery, specifically during resection of intracranial meningioma, often requires large volume of blood products transfusions. Oka *et al.*<sup>[21]</sup> suggested that abnormal hyperfibrinolysis seems to play a crucial role in hemostatic difficulties in patients undergoing elective craniotomy for intracranial meningioma. It can also worsen by the consumptive coagulopathy induced by the surgical stress and dilution coagulopathy.

To reduce blood loss and transfusion requirements, several techniques have been suggested and investigated but none of these strategies are free of complications.<sup>[5,7,10]</sup> The efficacy of TXA has also been assessed in gynecological hemorrhage and major surgery [Table 4].<sup>[1,6,15,19,20,25,30]</sup> Few studies have evaluated the efficacy of intraoperative TXA administration in reducing blood loss in intracranial surgeries. In a recent randomized clinical trial, Hooda *et al.* evaluated the efficacy of TXA in reducing perioperative bleeding in 60 patients proposed for excision of intracranial meningiomas.<sup>[12]</sup> In this study, the estimated blood loss was significantly lower in the TXA group compared to placebo (830 ml vs. 1124 ml,  $P = 0.03$ ) and there was no significant difference in the amount of blood products transfused ( $P = 0.46$ ). Thus, as in our study, TXA did not show superiority in reducing blood transfusions in intracranial meningiomas resection. Another study conducted by Vel *et al.* has also confirmed the effectiveness of TXA in reducing intraoperative blood loss in 100 patients undergoing a supratentorial tumor (including meningiomas).<sup>[27]</sup> In this study, total bleeding estimated in the TXA group increased from 1084 mL to 817 mL, a reduction in bleeding of 24.6% ( $P < 0.01$ ). The number of

**Table 3:** Postoperative laboratory parameters and complications.

Group	TXA group (n=45)	Placebo group (n=46)	P-value
Hb postoperative (g/dl)	10.9±0.99	10.2±10	0.02
Platelet count (1×10 <sup>3</sup> )	220±54.1	235±70.5	0.24
Fibrinogen	2.7±0.3	2.5±0.38	0.02
postoperative complications*			
Convulsions	2 (4.4)	2 (4)	0.94
Hematoma	2 (4.4)	6 (13)	0.15
Thrombosis	0	0	1
ICU stay (days)	1±0.2	1.1±0.3	0.16
Hospital stay (days)	6.8±1.4	6.9±1.6	0.77
GOSE*			0.45
Good recovery	35 (79.5)	31 (67.3)	
Moderate disability	6 (13.7)	11 (23.9)	
Severe disability	3 (6.8)	4 (8.6)	

\*Data given as number (%). TXA: Tranexamic acid, Hb: Hemoglobin, ICU: Intensive care unit, GOSE: Glasgow Outcome Scale Extended

transfused patients was lower in the TXA group (21 vs. 30), but the difference was considered no significant ( $P = 0.10$ ). Total blood loss in our study population was much lower in the placebo group (mean 576 ml) compared with the study by Hooda *et al.*<sup>[12]</sup> (mean 1124) and Vel *et al.*<sup>[27]</sup> (mean 1084). These very different blood loss rates may be explained by potential differences in patient characteristics, surgical or anesthetic management, or it may illustrate the difficulties in correct estimation of blood loss.

In our study, the dose of TXA administered was 20 mg/kg for 20 min before surgical incision followed by perfusion of 1 mg/kg/h until closure of the skin. This same protocol was used in the study by Hooda *et al.*<sup>[12]</sup> However, in the study by Vel *et al.*,<sup>[27]</sup> the TXA was administered in bolus of 10 mg/kg for 10 min followed by 1 mg/kg/h until the end of surgery. It was a low dose, but the results were comparable to mine in reducing intraoperative blood loss and transfusion requirements. The dosing regimen for severe traumatic brain injury, aimed at limiting the extension of posttraumatic intraparenchymal bleeding, was similar to that of our study.<sup>[23]</sup> Indeed, in a meta-analysis including five clinical trials,<sup>[28]</sup> dose of TXA in the management of brain-damaged patients was 1 g over 10 min followed by 1 g over 8 h. The same protocol was used by Dewan *et al.*<sup>[8]</sup> In subarachnoid hemorrhage and subdural hematomas, TAX was administered as a higher dose to reaching 6 g during the 1<sup>st</sup> day of management.<sup>[2]</sup> Up to now, no study has compared the value of using TXA in high doses compared to usual doses in neuroresuscitation.

In our study, postoperatively, the decrease in Hb was greater in the control group but the rest of the biological parameters including platelet count, TP, and fibrinemia, did not show a statistically significant difference between

**Table 4:** Summary of surgical indications, dosing, and effects of TXA.

	Indication	Dose	Effects
Postpartum hemorrhage <sup>[29]</sup>	Postpartum hemorrhage with estimated blood loss >500 mL after vaginal birth, 1000 mL after cesarean section	1 g of TXA IV. If bleeding continues after 30 min or stopped and restarted within 24 h of the first dose, a second dose of 1 g can be given	TXA reduces death due to bleeding in women with postpartum hemorrhage with no adverse effects
Cardiothoracic surgery <sup>[19]</sup>	Coronary artery surgery at risk of bleeding complication	100 mg/kg IV of body weight administered >30 min after the induction of anesthesia	TXA was associated with a lower risk of bleeding than was placebo, without a higher risk of death or thrombotic complications within 30 days after surgery
Orthopedic surgeries <sup>[9,17,20,30]</sup>	Prophylaxis against blood loss in hip fracture surgery, total knee arthroplasty, and spine surgeries	10 mg/kg IV loading dose before skin incision followed by infusion of 1 mg/kg/h	TXA reduce intraoperative and total blood loss, but no significant reduction in blood transfusion without a risk of thrombotic complications
Trauma <sup>[8,23]</sup>	Adult trauma patients with, or at risk of, significant bleeding	1 g over 10 min then infusion of 1 g over 8 h	Early administration of TXA safely reduced the risk of death in bleeding trauma patients and is highly cost effective

the two groups. These results are consistent with Hooda *et al.* study.<sup>[12]</sup> However, Vel *et al.*<sup>[27]</sup> showed that postoperative fibrinemia was significantly higher in the TXA group in the immediate postoperative period and at 3, 6, and 9 h postoperatively. This could be explained by the action of TXA which inhibits fibrinolysis by blocking the conversion of plasminogen to plasmin, which would increase fibrinogen concentration. In our study, intraoperative bleeding is greater in the placebo group, but the Hb level remains above the transfusion threshold fixed in our protocol and necessary to maintain adequate cerebral metabolism, thus limiting cerebral and systemic complications of anemia.

The evaluation of the safety of TXA in our study was essential, especially since it was already a relatively high risk surgery for postoperative complications. Convulsions have been described particularly in the use of high-dose TXA in cardiac surgery.<sup>[18]</sup> The probable mechanism is the structural homology of TXA with gamma-amino butyric acid (GABA). This effect would, therefore, be related, at least in part, to the inhibition of GABA<sub>A</sub> receptors involved in the maintenance of inhibitory neurotransmission.<sup>[11]</sup> In our study, two patients had postoperative convulsions: one patient in the TXA group and one patient in the placebo group. The difference was, therefore, considered not significant. Our results were similar to those of Hooda *et al.* and Vel *et al.*<sup>[12,27]</sup> Nevertheless, this cannot completely exonerate the TXA, in front of the narrowness of the samples.

In our study, no thromboembolic event was noted in all patients, both groups included. This result has been found in similar studies.<sup>[12,27]</sup> These same reassuring data were found in the CRASH-2 study,<sup>[4]</sup> which included 20,211

polytraumatized. During this trial, no increase in the incidence of thromboembolic events associated with the use of TXA was observed, despite the theoretical high risk of thromboembolism in polytrauma patients. These results have even been found in other surgical specialties.<sup>[9,17]</sup> Indeed, even in the WOMAN trial,<sup>[29]</sup> no difference was found between TXA and placebo in the occurrence of postoperative thromboembolic events. Similarly, systematic reviews including patients scheduled for elective surgery, evaluated the major side effects of TXA. There was no significant increase in the incidence of myocardial infarction, stroke, deep vein thrombosis, and pulmonary embolism.<sup>[14]</sup>

In our series, there was no significant difference between the two groups in the length of stay in intensive care or the total duration of hospitalization. Moreover, as for the risk of occurrence of postoperative hematoma, the number of patients who had this complication was lower in the TXA group (only one patient versus four), but the difference between the two groups was considered statistically not significant ( $P = 0.6$ ), and this is due to the reduction of intraoperative bleeding and consequently a better local hemostasis. Our results were similar to the studies cited above.<sup>[12,27]</sup>

To the best of our knowledge, our study is the largest clinical trial which evaluating the efficacy of TXA treatment on blood loss and transfusion requirements in patient undergoing resection of intracranial meningioma. Our study has some limitations. The most important is related to the estimation of blood loss by the anesthesiologist; it was a dependent operator parameter and therefore subject to a margin of error. Another important limitation is the dose of TXA which was arbitrary according to the studies conducted in traumatic brain injury.

## CONCLUSION

The current study demonstrates that TXA significantly decreases intraoperative and total blood loss, but no significant reduction in blood transfusion in the TXA group compared with placebo, in patients undergoing resection of intracranial meningioma. The rate of thrombotic complications and convulsion in the TXA group was similar to that observed in patients receiving placebo, with a tendency to reduce the incidence of postoperative hematoma.

## Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

## Financial support and sponsorship

Nil.

## Conflicts of interest

There are no conflicts of interest.

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**How to cite this article:** Rebai L, Mahfoudhi N, Fitouhi N, Daghmouri MA, Bahri K. Intraoperative tranexamic acid use in patients undergoing excision of intracranial meningioma: Randomized, placebo-controlled trial. *Surg Neurol Int* 2021;12:289.