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Original Article

Tranexamic acid to reduce operative blood loss in brain tumor surgery: A meta-analysis

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ABSTRACT

Background: Major blood loss during neurosurgery may result in a variety of complications, such as potentially fatal hemodynamic instability. Brain tumor and skull base surgery is among the high bleeding risk procedures. Tranexamic acid (TXA) has been found to reduce bleeding events in various fields of medicine.

Methods: We searched for all randomized controlled trials published in English or Bahasa which compared the use of TXA with placebo in brain tumor surgery. The studies should include adult patients with intracranial tumor who received TXA before skin incision. The primary and secondary outcomes are intraoperative blood loss and the need of transfusion.

Results: This meta-analysis included a total of 200 patients from three studies. TXA resulted in less blood loss with pooled mean difference of −292.80 (95% CI, −431.63, −153.96, P<0.05). The need of transfusion was not significant between TXA and control group (pooled mean difference −85.36, 95% CI, −213.23 – (42.51), P=0.19).

Conclusion: TXA reduced the volume of blood loss but did not reduce the need of blood transfusion.

Keywords: Brain tumor, Intraoperative bleeding, Tranexamic acid, Transfusion

INTRODUCTION

Major blood loss during neurosurgical procedures will complicate the treatment and reduce tissue perfusion to vital brain tissue.[1] Excessive blood loss is indeed not desired by neurosurgeons as anemia and related hypoperfusion is deleterious for the brain.[15,24] Anemia was significantly higher in patients who had a blood volume deficit of more than 20% in the postoperative cycle.[29] Brain tumor and skull base surgery is among the procedures most likely to cause high-volume bleeding.[21,25,29]

Tranexamic acid (TXA) is a synthetic derivative of the amino acid lysine that acts as antifibrinolytic. TXA has been used in various setting to reduce blood loss.[10] This meta-analysis aims to analyze the effect of TXA on the volume of blood loss in brain tumor surgery.

MATERIALS AND METHODS

Types of studies

We searched for all randomized controlled trials (RCTs), prospective, and retrospective studies published in English or Bahasa which compared the use of TXA with other agents or placebo.

Types of participants

Adult (≥18 years old) patients of either gender diagnosed with intracranial tumor who underwent craniotomy and tumor resection procedure.

Types of interventions

Studies with intravenous administration of tranexamic acid at any dose, by bolus and/or by intravenous drip, will be included. The comparison could be placebo or other antifibrinolytic agents.

Types of outcome measure

Primary outcome

- Mean blood loss

Secondary outcome

- The need of PRC and/or whole blood transfusion
- The need of colloid administration as volume expander

Search methods for identification of studies

The sampling technique in this study was using online literature search results filtering based on the flow of Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) according to the PICO that has been determined. We searched PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), and ProQuest. Search was limited to papers published between 2010 and 2020. Our search strategy is shown in [Table 1].

We also searched Google Scholar using any of the possible combination mentioned above.

Data collection and analysis

Selection of studies

The search results were first excluded based on the relevancy of the titles and then on the relevancy of the abstracts. Non-English/non-Bahasa publications were automatically excluded. Full-text articles were then assessed by all authors (JW, RP, IBIH, and RIS) for potentially eligible RCTs. The reasons of exclusion were noted and reported.

Table 1: Search strategy.

Search terms	
1	Tranexamic acid [MeSH Terms]
2	Meningioma [MeSH Terms]
3	Antifibrinolytics [MeSH Terms]
4	Agents, antifibrinolytic [MeSH Terms]
5	Antifibrinolytic*
6	Meningioma
7	Tranexamic acid
8	Brain neoplasm [MeSH Terms]
9	Brain tumor
10	Glioma [MeSH Terms]
11	Glioma
Combination	
12	#1 and #2
13	(#3 OR #4) AND #2
14	#6 AND #7
15	#5 AND #6
16	(#1 OR #3 OR #4 OR #5 OR #7) AND (#8 OR #9)
17	(#1 OR #3 OR #4 OR #5 OR #7) AND (#10 OR #11)

Data extraction and management

Demographic data about age, sex, diagnosis, TXA dose and administration, blood loss, and transfusion requirement were collected and presented in [Table 1]. Base hemostasis data were also noted when available.

Assessment of risk of bias in included studies

Risk of bias was assessed by all four authors (JW, RP, IBIH, and RIS). Should conclusion be unmet, a third party from neurosurgery department would be asked to give his/her opinion. Assessed biases are those mentioned in the Cochrane Collaboration Tool for Assessing Risk of Bias in Randomized Trials published in 2011.[17]

Measures of treatment effect

We undertook statistical analysis using the statistical software, Review Manager 5.4, of the Cochrane Collaboration. We used risk ratios to measure treatment effect for proportions (dichotomous outcomes) among primary and secondary outcomes. Random effect model will be used should evidence of significant heterogeneity is present. A statistically significant difference between intervention and control groups was assumed if the 95% CI did not include the value of no differential effect.

Assessment of heterogeneity

Heterogeneity is addressed by the I^2 value on forest plot construction using RevMan 5.4. The statistical model used is switched to random effect should I^2 yield the value of ≥50% as the studies are deemed heterogeneous.[16]

RESULTS

Description of studies

Description of studies can be seen on [Appendix 1].

Results of the search

The exclusion processes based on the flow of PRISMA are shown in [Figure 1].

Included studies

After careful consideration from each authors, we decided to include three studies.[19,37,39] All of them were RCTs.

Excluded studies

There are four studies which most likely met our criteria and did report the required data for our primary outcome, but were unfortunately ruled out. Two of them were due to unavailability of full text[23,35] while the other two were due to being published in Arabic[36] and Russian.[27]

Ongoing studies

By the time of our search, we found one study which has not been concluded yet.[11]

Risk of bias in included studies

Risk of bias of included studies was assessed using the Cochrane Collaboration Tool for Assessing Risk of Bias in Randomized Trials published in 2011.[17] The domain of the biases is as follows:

1. Random sequence generation
2. Allocation concealment
3. Blinding of participant and personnel
4. Blinding of outcome and assessment
5. Incomplete outcome data
6. Selective reporting
7. Other bias

The result of the assessment is shown in [Figure 2].

Randomization and allocation concealment

Hooda *et al.* randomized the study's subjects using computer-generated randomization chart. The TXA infusion was prepared by an anesthesiologist who was not involved in patient management.[19] Sutanto *et al.* randomized the patient using an enclosed envelope based on the principle of consecutive sampling. It was not clearly stated who prepared the TXA.[37] Vel *et al.* used a computer-generated randomization chart to allocate the patient. Despite clearly stating that the anesthesiologists were blinded, it was not clear who prepared the drugs.[39]

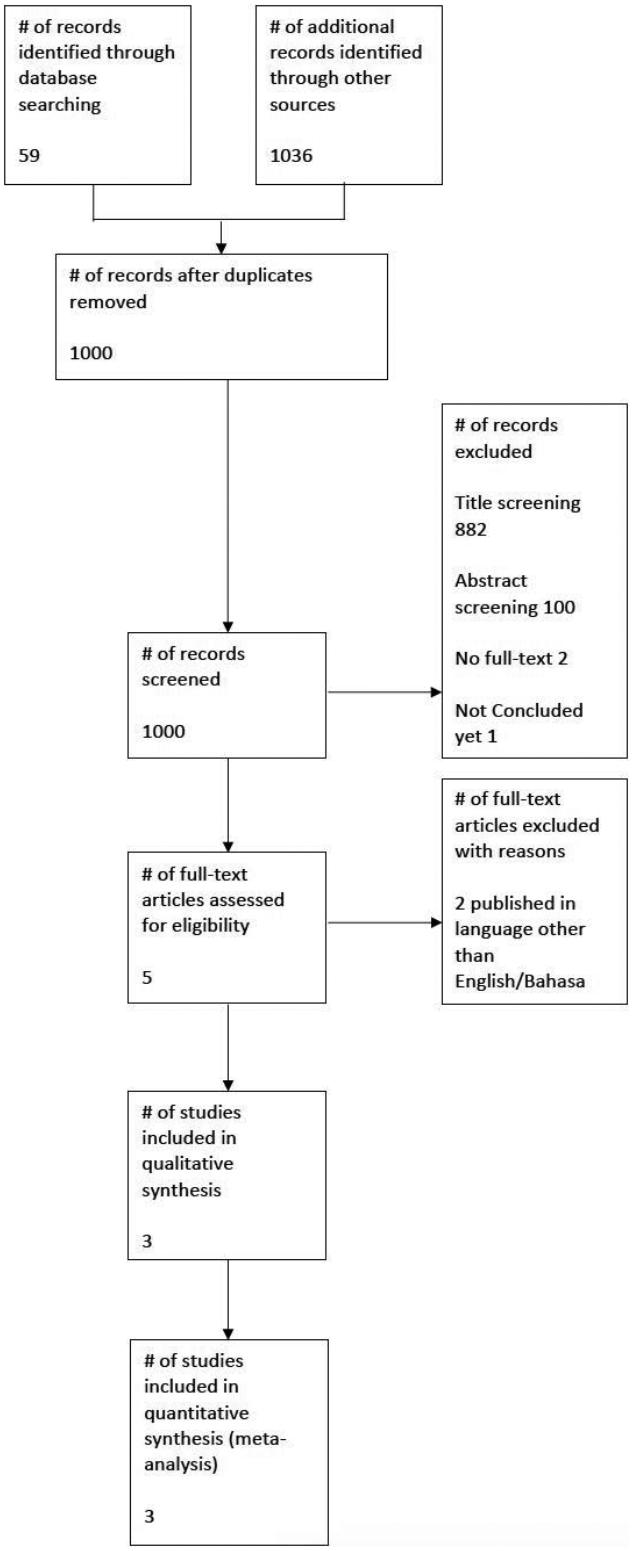

Figure 1: Study flow diagram according to PRISMA guidelines.

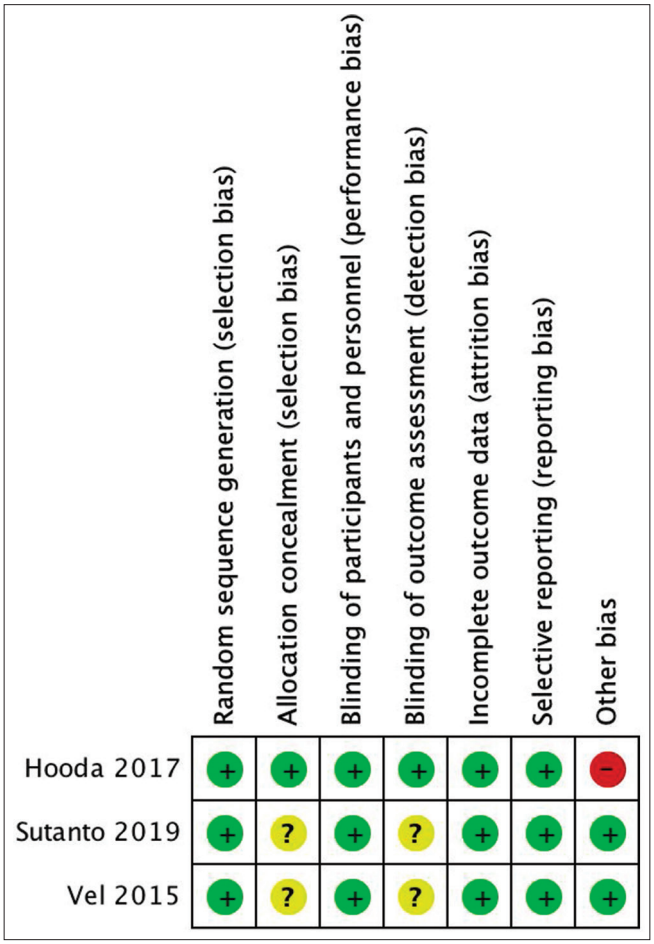

Figure 2: Risk of bias of included studies.

Blinding

All three studies did blind the neurosurgeons and the anesthesiologists involved in the surgical procedure.[19,37,39] The person in charge of assessing intraoperative blood loss were blinded in Hooda *et al.*[19] Despite blinding the neurosurgeons and the anesthesiologist, Sutanto *et al.* and Vel *et al.* did not make clear who counted the blood loss, thus we consider this a potential source of bias.[37,39]

Incomplete outcome data

All studies' subjects were included in the result section. No subjects dropped-out of the studies.[19,37,39]

Selective reporting

We found that all outcomes mentioned in the methods section were reported in the studies.[19,37,39]

Other potential sources of bias

Hooda *et al.* did not report the standard error of the mean blood loss. An attempt to contact the author has not been fruitful. To complete the missing data, we utilized RevMan Calculator tool by Cochrane which is accessible in their website.[30] Hooda *et al.* did not mention the mean and standard deviation for the need of transfusion either. Therefore, we used the estimation method described by Shi *et al.*[34] to find the mean transfusion volume based on the provided median, minimum, and maximum value.

Summary of findings

Summary of findings from each studies and quality of evidence for each outcome can be found in [Tables 2 and 3], respectively.

All three included studies reported their results on blood loss and the need of blood transfusion. Sutanto *et al.* included 40 subjects who were distributed evenly into the study arms. The study compared 20 mg/kg of TXA in 100 cc of NaCl 0.9% with 100 cc of NaCl 0.9%. Either of the infusions was administered for 5–10 min. Baseline PT and aPTT were not different between the two groups. The authors reported that there were patients in the control group who eventually needed fresh frozen plasma (FFP) transfusion (mean 73.50 ± 121.926 cc).[37]

Hooda *et al.* had 60 study subjects who were equally distributed into TXA group and placebo group. This study administered TXA continuously until the surgery concluded. The dose was 20 mg/kg bolus continued with continuous drip at a dose of 1 mg/kg/h. The comparison was 0.5 ml/kg bolus of NaCl 0.9% continued with 0.025 ml/kg/h NaCl 0.9% continuous drip. Four patients received FFP transfusion in each group, with administered volume of 600 cc and 900 cc in the TXA and placebo group, respectively. Three patients in the TXA group also received platelet transfusion (total transfused volume 250 cc), while two patients in the placebo group received 306 cc of platelet.[19] Vel *et al.* had the biggest number of patients (100). The intervention dose was 10 mg/kg bolus for 10 min continued with 1 mg/kg/h drip. The placebo dose was equivalent volume of NaCl 0.9% administered as bolus and drip. No FFP transfusion was reported in this study.

The differences between studies are (1) timing and ending of TXA administration, (2) type of tumor, (3) tumor size, (4) embolization history, and (5) pregnancy status, as shown in [Table 2]. Sutanto administered the TXA 30 min before skin incision while Hooda *et al.* and Vel *et al.* started the intervention 20 min before skin incision.[19,37,39] Besides the dose, the manner in which TXA was administered was also different. Vel *et al.* and Hooda *et al.*[19,39] continued the initial TXA dose with continuous drip while Sutanto *et al.* did not do so.[37] Sutanto *et al.* and Hooda *et al.*[19,37] only included meningioma cases while Vel *et al.* included all supratentorial tumor.[39]

Effects of interventions

The effect of intervention is shown in [Figure 3]. All studies did assess intraoperative blood loss and the need of PRC and/or WB transfusion. This meta-analysis amassed a total of 100 patients from three studies. All three studies showed that TXA reduced the volume of blood loss with pooled mean difference of −292.80 (95% CI, −431.63, −153.96, $P<0.05$). The studies were considered homogenous in terms of blood loss ($I^2 = 0\%$). That said, it is important to note that data from Hooda *et al.* for this meta-analysis were calculated using Cochrane's tool instead of actual number from the paper. Based on the need of transfusion, the studies were considerably heterogeneous ($I^2 = 74\%$). This can be seen on the forest plot as two studies' CI crossed the zero line, indicating inconsistency in the respective studies. The pooled mean difference for the need of transfusion was −85.36 (95% CI, −213.23 – (42.51), $P = 0.19$. The funnel plot is also shown in [Figure 4].

DISCUSSION

This meta-analysis sought to find out if TXA can reduce intraoperative blood loss and blood transfusion in brain tumor surgery. We identified five studies but unfortunately needed

Table 2: Summary of findings from each studies.

Authors	Participants+	TXA dose	Mean Blood Loss (cc)	MD (95% CI)	Mean PRC/WB Transfusion (cc)	MD (95% CI)
Sutanto 2019	40 patients	20 mg/kg in 100 cc of NaCl 0.9% for 5 – 10 minutes	1008.51 ± 327,192	-338.49 (-614.87, -62.105)	89.3 ± 152.97	-217.55 (-336.66, -98.4)
		100 cc of NaCl 0.9% for 5 – 10 minutes	1347.85 ± 539.12		306.85 ± 224.63	
Hooda 2017	60 patients	20 mg/kg bolus → 1 mg/kg/h until the end of surgery	830 ± 511.8*	-294.0 (-553, -34.9)	375.08 ± 189.92	-29.55 (-160.47, 101.37)
		0.5 ml/kg bolus of NaCl 0.9% → 0.025 ml/kg/h NaCl 0.9% until the end of surgery	1124 ± 511.8*		404.63 ± 312.7	
Vel 2015	100 patients	10 mg/kg bolus for 10 minutes → 1 mg/kg/h	817 ± 423.3	-267.0 (-471.62, -62.38)	445.2 ± 229.6	-14.48 (-108.04, 79.08)
		NaCl 0.9% of equal volume as TXA	1084±604.8		459.68 ± 247.4	

*not provided in the paper. Estimated using calculator provided by Cochrane[30]
+All studies distributed the subjects equally to both arms

Table 3: Quality of evidence for each outcome.

Tranexamic acid for intraoperative blood loss in brain tumor surgery
Patient or population: Adult with brain tumor
Settings: India and Indonesia
Intervention: Tranexamic acid
Comparison: Placebo

Outcomes	Relative effect (95% CI)	Number of participants (Studies)	Quality of the evidence (GRADE)	Comments
Blood loss	−292.80 (−431.63, −153.96)	100	⊕⊕⊕⊖ Moderate	Presence of bias
PRC/WB transfusion	−76.98 (−141.12, −12.84)	100	⊕⊕⊖⊖ Low	Presence of bias, imprecision (indicated by the CI range)

GRADE working group grades of evidence. High quality: Further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality: We are very uncertain about the estimate

to exclude two of them. The included studies yield a total of 200 patients. Massive blood loss from surgical procedure has been associated with mortality and morbidity.[22] A retrospective study found that blood loss exceeding 20% of estimated blood volume in brain tumor surgery strongly correlated with postoperative complications.[21] Another study found that the need of blood transfusion predicted perioperative complications.[31] Therefore, any means to reduce intraoperative blood loss are desirable.

The CRASH-3 trial, the most recent and largest clinical trial about TXA, found that TXA administration in the first 3 h of acute traumatic brain injury (TBI) reduced mortality. However, this trial did not specifically sought intraoperative blood loss or the need of transfusion.[23] In a meta-analysis, TXA reduced intracranial hemorrhage progression in TBI.[41] TXA has also been studied in other fields such as obstetrics and gynecology. Prophylactic use of TXA was found to reduce blood loss and transfusion volume in a meta-analysis.[40]

To this day, the use of TXA in neurosurgery has been limited to TBI or subarachnoid hemorrhage (SAH) cases, primarily due to the fear of thrombotic adverse effects.[12,13] The risk of thrombotic events in TXA theoretically could occur. However, evidence from the Clinical Randomization of an Antifibrinolytic in Significant Hemorrhage-2 trial of TXA in bleeding trauma patients showed a statistically significant reduction in mortality with no increase in thromboembolic effects.[28]

The evidence for use of TXA to treat massive blood loss during intracranial surgery is weak and is even more scarce in terms of brain tumor surgery.[2] In addition to the administration of massive volumes of crystalloids, significant intraoperative bleeding must also be supplemented by several units of blood and blood components.[38] However, the use of these substances can result in hypokalemia, anaphylactic reactions, pulmonary trauma, infection, hemolytic reactions, cardiovascular overload, and sepsis.[6,26,32]

The administration of TXA has demonstrated positive results in spine procedures. In most studies, the preferred TXA dose ranged from 10 mg/kg to 30 mg/kg immediately on performing an incision, a maintenance dose of 0.5–2 mg/kg/h, followed by a preferable 1-mg/kg/h dose until the end of the surgical procedure. High TXA doses did not necessarily increase rates of thromboembolism or convulsions in the case of ASA I and ASA II patients, with no risk factors for thromboembolism or significant renal changes.[4,5,33,42] According to Yutthakasemsunt *et al.* (2013),[40] the mean overall hemorrhage growth in TBI was smaller in the TXA community relative to the placebo group.

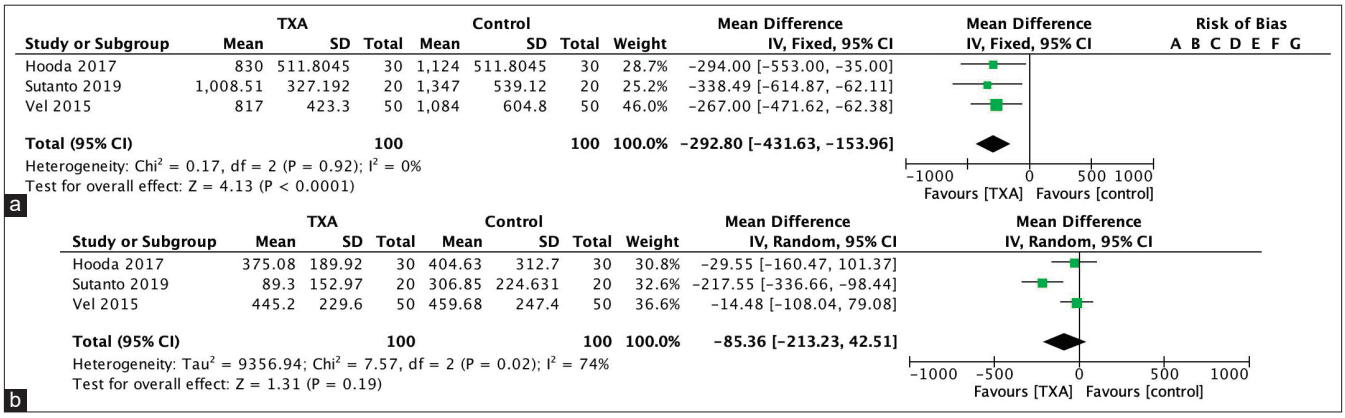

Figure 3: Pooled proportion of (a) blood loss and (b) the need of transfusion.

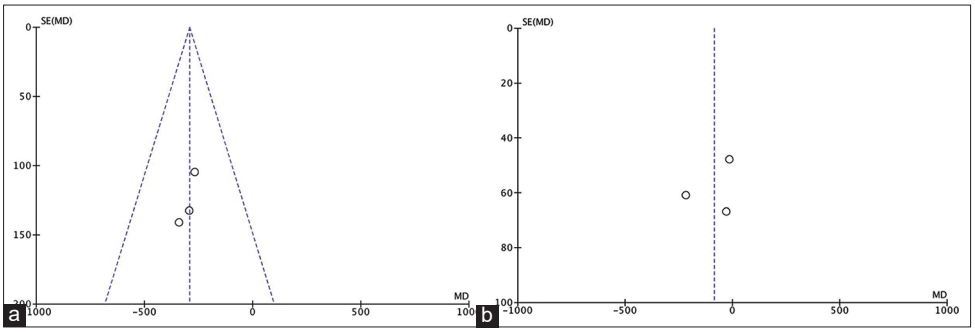

Figure 4: Funnel plot of (a) blood loss and (b) the need of transfusion.

The trials were pooled in a Cochrane study, which concluded that TXA may reduce mortality in TBI patients, but the standard of evidence is poor and there is significant uncertainty.[20] TXA therapy resulted in decreasing the rebleeding incidence, varying from 10.8% to 2.4%, and a reduction in mortality due to rebleeding by 80% in patients diagnosed with SAH within 48 h of first hospitalization, with no rise in drug-related ischemic and vasospasm cases.[18] Grant *et al.* (2009)[14] recently reported that using TXA during pediatric scoliosis surgery reduced the number of intraoperative PRBC transfusions by 50%. Just two researches[9] found that an antifibrinolytic treatment reduced intraoperative blood loss in children undergoing craniofacial surgery.[8]

The above trials were pooled in a Cochrane study, which concluded that TXA may reduce mortality in TBI patients, but the standard of evidence is poor and there is significant uncertainty.

Headache, fatigue, vomiting, diarrhea, dyspepsia, dysmenorrhea, dizziness, back pain, numbness, phosphenes, and anemia are some of the side effects of TXA when used for an extended period of time.[20] However, if the patients have any history of an active thromboembolic case or illness, DIC, renal dysfunction, or a new coronary or vascular stent, TXA is not recommended.[3] Thrombotic threats have been the most common and concerning adverse events.[20]

Our meta-analysis revealed that TXA reduced intraoperative blood loss at a mean of 292.80 cc (95% CI, −431.63, −153.96). Despite consisting only of 100 subjects and a relatively few included studies, these studies were considered homogenous. The need of transfusion, however, did not seem to be affected by TXA. The pooled mean difference of blood transfusion was −85.36 (95% CI, −213.23 – [42.51]). The range of CI indicated that the TXA group did not always have less blood transfusion. It is also important to recognize the considerable heterogeneity among studies in regard to transfusion volume.

Overall completeness and applicability of evidence

The overall methodological quality of these studies is considered good. There was, however, a considerable heterogeneity in respect to the secondary outcome. One study did not provide the standard error of both mean blood loss and mean blood transfusion. The inclusion criteria between studies were quite similar as well.

Quality of the evidence

We deem that the conclusion for both our primary and secondary outcomes belongs to moderate and low-quality evidence, respectively, mainly due to the presence of at least one type of bias in all of the studies and the inconsistency with regard to transfusion volume. The studies were also heterogeneous in terms of transfusion volume.

Agreements and disagreements with previous meta-analysis or review

We are unaware of any such meta-analysis or review which compare different dose of mannitol for brain tumor surgery.

AUTHORS' CONCLUSIONS

Implications for practice

TXA is beneficial in reducing the volume of blood loss. However, this does not always translate to less blood transfusion.

Implications for research

Further research to assess (1) the most effective dose and (2) the timing of TXA administration is needed, as they are among the points not covered by this meta-analysis.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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APPENDIX

Appendix 1: Description of Studies.

Study ID	Inclusion Criteria	Exclusion Criteria	TXA administration
Sutanto 2019	Adult 18 – 65 y.o ASA I - II Elective meningioma surgery	History of thromboembolic events History of coagulopathy/is on anticoagulant Impaired renal function Impaired liver function History of allergic reaction to TXA Recurrent tumor Proven metastatic tumor Preoperative embolization Pregnant or is within first 6 weeks of post-partum	20 mg/kg in 100 cc of NaCl 0.9% for 5 – 10 minutes TXA administered 30 minutes prior to incision
Hooda 2017	Adult 18 – 60 y.o ASA I-II Elective meningioma surgery	History of allergic reaction to TXA History suggestive of bleeding diathesis History of hromboembolic episode prior to surgery or family history of thromboembolism On medication that could interfere with coagulation Epilepsy Plasma creatinine values more than 1.5 mg/dl Pregnant or lactating Patients who were planned for preoperative embolization, with tumor size less than 4 cm or operating neurosurgeon's estimate of likely intra-operative blood loss less than 20% of patient's EBV	20 mg/kg bolus → 1 mg/kg/h until the end of surgery TXA administered 20 minutes prior to incision Transfused blood was
Vel 2015	Adult 18-60 y.o ASA I-II Elective supratentorial tumor	Preexisting renal and hepatic disorders Bleeding diathesis/abnormal coagulation parameters On anticoagulant a week before surgery Patients undergoing intracranial vascular surgery	10 mg/kg bolus for 10 minutes → 1 mg/kg/h TXA administered 20 minutes prior to incision

ASA: American Society of Anesthesiologist Physical Status, EBV: Estimated Blood Volume, TXA: Tranexamic Acid, VTE: Venous thromboembolism