Journal Pre-proof

The Use of Tranexamic Acid for Elective Resection of Intracranial Neoplasms: A Systematic Review

Nolan J. Brown, B.S., Bayard Wilson, M.D., Vera Ong, B.S., Julian L. Gendreau, M.D., Chen Yi Yang, B.S, Alexander S. Himstead, B.S., Shane Shahrestani, Ph.D M.S., Nathan A. Shlobin, B.A., Taylor Reardon, B.S., Elliot H. Choi, Ph.D. M.S., Jack Birkenbeuel, M.B.A, Sebastian J. Cohn, B.S., Ronald Sahyouni, M.D., M.S., PhD, Isaac Yang, M.D. F.A.A.N.S F.A.A.C.S

PII: S1878-8750(21)01962-8

DOI: <https://doi.org/10.1016/j.wneu.2021.12.117>

Reference: WNEU 18319

To appear in: *World Neurosurgery*

Received Date: 27 November 2021

Revised Date: 29 December 2021

Accepted Date: 30 December 2021

Please cite this article as: Brown NJ, Wilson B, Ong V, Gendreau JL, Yang CY, Himstead AS, Shahrestani S, Shlobin NA, Reardon T, Choi EH, Birkenbeuel J, Cohn SJ, Sahyouni R, Yang I, The Use of Tranexamic Acid for Elective Resection of Intracranial Neoplasms: A Systematic Review, *World Neurosurgery* (2022), doi: <https://doi.org/10.1016/j.wneu.2021.12.117>.

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2022 Elsevier Inc. All rights reserved.

The Use of Tranexamic Acid for Elective Resection of Intracranial Neoplasms: A Systematic Review

*Nolan J. Brown, B.S.¹, *Bayard Wilson, M.D.², *Vera Ong, B.S.³, Julian L. Gendreau, M.D.⁴ Chen Yi Yang, B.S.¹, Alexander S. Himstead, B.S.¹ Shane Shahrestani Ph.D M.S.^{5,6}, Nathan A. Shlobin, B.A.⁷, Taylor Reardon, B.S.⁸, Elliot H. Choi, Ph.D. M.S.¹, Jack Birkenbeuel, M.B.A.¹, Sebastian J. Cohn B.S.⁹, Ronald Sahyouni, M.D., M.S., PhD¹⁰, Isaac Yang, M.D. F.A.A.N.S F.A.A.C.S²

*The authors contributed equally to the present manuscript

¹Department of Neurological Surgery, University of California, Irvine, Irvine, CA

²Department of Neurological Surgery, University of California, Los Angeles, CA

³John A. Burns School of Medicine, University of Hawaii, Honolulu HI

⁴Department of Biomedical Engineering, Johns Hopkins Whiting School of Engineering, Baltimore, MD

⁵Keck School of Medicine of USC, Los Angeles, CA

⁶Medical Scientist Training Program, California Institute of Technology, Pasadena, CA

⁷Department of Neurological Surgery, Feinberg School of Medicine, Northwestern University, Chicago, IL

⁸Kentucky College of Osteopathic Medicine, University of Pikeville, Pikeville, KY

⁹Department of Neuroscience, University of Pittsburgh, PA

¹⁰Department of Neurological Surgery, University of California, San Diego, La Jolla, California

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Disclosure: The authors report no conflicts of interest.

Corresponding author:

Julian Gendreau, M.D.

Department of Biomedical Engineering

Johns Hopkins Whiting School of Engineering

3400 N Charles St, Baltimore, MD 21218

Email: jgendre1@jhu.edu

Key Words: Tranexamic Acid; Skull Base; Intracranial; Neoplasms

Abstract word count: 250

Text word count: 3888

Number of references: 47

Number of tables and/or figures: 8

Number of videos: 0

The Use of Tranexamic Acid for Elective Resection of Intracranial Neoplasms: A Systematic Review

*Nolan J. Brown, B.S.¹, *Bayard Wilson, M.D.², *Vera Ong, B.S.³, Julian L. Gendreau, M.D.⁴
Chen Yi Yang, B.S.¹, Alexander S. Himstead, B.S.¹, Shane Shahrestani Ph.D M.S.^{5,6}, Nathan A.
Shlobin, B.A.⁷, Taylor Reardon, B.S.⁸, Elliot H. Choi, Ph.D. M.S.¹, Jack Birkenbeuel, M.B.A.¹,
Sebastian J. Cohn B.S.⁹, Ronald Sahyouni, M.D., M.S., PhD¹⁰, Isaac Yang, M.D. F.A.A.N.S
F.A.A.C.S²

*The authors contributed equally to the present manuscript

¹Department of Neurological Surgery, University of California, Irvine, Irvine, CA

²Department of Neurological Surgery, University of California, Los Angeles, CA

³John A. Burns School of Medicine, University of Hawaii, Honolulu HI

⁴Department of Biomedical Engineering, Johns Hopkins Whiting School of Engineering,
Baltimore, MD

⁵Keck School of Medicine of USC, Los Angeles, CA

⁶Medical Scientist Training Program, California Institute of Technology, Pasadena, CA

⁷Department of Neurological Surgery, Feinberg School of Medicine, Northwestern University,
Chicago, IL

⁸Kentucky College of Osteopathic Medicine, University of Pikeville, Pikeville, KY

⁹Department of Neuroscience, University of Pittsburgh, PA

¹⁰Department of Neurological Surgery, University of California, San Diego, La Jolla, California

Funding: This research did not receive any specific grant from funding agencies in the public,
commercial, or not-for-profit sectors.

Disclosure: The authors report no conflicts of interest.

Corresponding author:

Julian Gendreau, M.D.

Department of Biomedical Engineering

Johns Hopkins Whiting School of Engineering

3400 N Charles St, Baltimore, MD 21218

Email: jgendre1@jhu.edu

Key Words: Tranexamic Acid; Skull Base; Intracranial; Neoplasms

35 Abstract word count: 356
36 Text word count: 3931
37 Number of references: 47
38 Number of tables and/or figures: 8
39 Number of videos: 0

40

41

Journal Pre-proof

Abstract

Background: As an established antifibrinolytic agent, tranexamic acid (TXA) has garnered widespread use during surgery to limit intraoperative blood loss. Within the field of neurosurgery, it is often introduced in cases of traumatic brain injury or elective spine surgeries. However, its role during elective cranial surgeries is not well established. This study presents a systematic review of the use of TXA for elective surgical resection of intracranial neoplasms.

Methods: We performed a systematic review using PRISMA guidelines to identify studies investigating the TXA use in elective neurosurgical resection of intracranial neoplasms. Variables extracted included patient demographics, surgical indications, type of surgery performed, TXA administration dose and route, operative duration, blood loss, transfusion rate, postoperative hemoglobin (Hb) levels, and complications.

Results: After careful screening, 4 articles (consisting of 682 total patients) fit our inclusion/exclusion criteria. Two studies were prospective cohorts, one was a retrospective cohort, and one was a case series. Chi-squared testing of pooled data demonstrated that patients administered TXA had a significantly decreased need for blood transfusions during surgery (OR: 0.6273, 95% CI:0.4254-0.9251, $p=0.018$). Mean total blood loss was 821.9 mL in the TXA group and 1099.0 mL in the control group across studies. There was no significant difference in postoperative hemoglobin levels: means were 11.4 g/dL for both the TXA and control groups.

Conclusion: These results support the use of intraoperative TXA in tumor resection. However, its role in tumor resection has been less investigated when compared to the use of TXA in other areas of neurosurgery.

Introduction

Tranexamic acid (TXA) is an antifibrinolytic agent that works by competitively inhibiting the conversion of plasminogen to plasmin by blocking lysine-binding sites on plasminogen¹, thereby promoting clot formation and limiting ongoing blood loss (**Figure 1**). Interest in TXA as a therapeutic agent arose following publication of the CRASH-2 trial in 2010, which supported its use to limit blood loss in trauma patients.² Since then, various studies have supported the administration of TXA to reduce blood loss during orthopedic, cardiac, liver and prostate surgeries.³⁻⁶ Within neurosurgery specifically, the use of TXA has become common practice for certain types of spine surgery – particularly deformity correction surgery – and for cranial vault reconstruction surgery given the importance of limiting blood loss in pediatric patients.^{7-9,10} It has also demonstrated reduced non-operative mortality and hemorrhagic expansion in cases of traumatic brain injury, especially if given within 3 hours of injury.^{11,12} Despite these uses, no consensus currently exists supporting the use of TXA in elective skull base and/or cranial operations (e.g., intracranial neoplasm resection). To better understand this discrepancy, we performed a systematic review on the use of TXA during elective resection of intracranial neoplasms.

Methods

Search Strategy

To identify studies investigating the use of TXA during elective neurosurgical resection of intracranial neoplasms, we conducted a literature search using PubMed, Web of Science, and Cochrane databases from database inception to April 9th, 2021. We followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) recommendations.¹³

91 Additionally, references of selected articles were reviewed to screen for relevant studies not found
92 during the database searches. The following Boolean search terms were used: (“tranexamic acid”
93 OR “TXA”) AND (“neurosurgery” OR “brain” OR “cranial” OR “skull base”). In total, our search
94 yielded 949 results across the 3 databases: 425 studies from PubMed, 522 studies from Web of
95 Science, and 2 studies from Cochrane. Reference sections were scrutinized in order to ensure that
96 relevant studies were not missed, duplicates were removed, and articles were screened
97 independently by two investigators (NJB and BVL) according to title and abstract. During this
98 screening process, IY served as the final arbiter with respect to inclusion in the final analysis
99 **(Figure 2).**

101 *Variables and Inclusion/Exclusion criteria*

102 Articles were eligible for inclusion if they met the following criteria: (1) manuscript
103 availability in English or an English translation and (2) primary clinical study investigating TXA
104 and involving cranial procedures for the resection of intracranial neoplasms. Articles were then
105 subjected to the following exclusion criteria: (1) inclusion of other anti-fibrinolytic agents in
106 addition to TXA, (2) cranial procedures for subdural hematoma (SDH) evacuation for traumatic
107 brain injury (TBI), and (3) non-elective procedures.

109 *Study Analysis*

110 The selected articles were then assessed for year of publication, institution and country of
111 authors, study design, sample size, patient demographics (i.e., gender and age), surgical
112 indications, type of surgery, complications, operative duration, TXA dose, TXA administration
113 route and timing, blood loss and need for transfusions, and postoperative hemoglobin (Hb) levels.

After these data were collected, a one-tailed chi-squared test on pooled data from all comparative studies was performed to assess the effect of TXA on the need for blood transfusions. Additionally, a pooled-variance t-test was used to compare operative duration between the TXA and control groups. When data for a particular outcome could not be pooled due to heterogeneous reporting, significant findings were reported separately for each study.

Results

Review of the literature

The article selection process is outlined in **Figure 2**. Initial query returned 949 articles. After removal of duplicates and scrutiny of reference lists, **604** unique articles remained. Title and abstract screen yielded **9** articles. **2** articles were excluded due to a primary focus on cranial TBI procedures (one of which focused on TXA for evacuation of subdural hematomas, specifically). After full-text review and application of inclusion and exclusion criteria, four articles remained. These four studies consisted of 682 total patients, all of whom underwent elective resection of an intracranial tumor (**Table 1**). Three studies were comparative trials and one was a case series on 3 pediatric patients. Two comparative trials were prospective, performed by Vel et al⁶ and Houda et al.¹⁴ The lone retrospective comparative trial was performed by Mebel et al.¹⁵ The 3 comparative trials consisted of a combined 679 patients and were published between the years 2015 and 2017.^{6, 14, 15}

Demographics

The 679 patients in the 3 comparative trials underwent surgery for the following indications: resection of an acoustic neuroma (49.1%), meningioma (32.0%), glioma (4.3%),

pituitary tumor (4.1%), schwannoma (unspecified type) (4.0%), craniopharyngioma (2.5%), epidermoid tumor (1.5%), chordoma (0.9%), colloid cyst (0.7%), cholesterol granuloma (0.3%), medulloblastoma (0.3%), pilocytic astrocytoma (0.3%), hemangioblastoma (0.3%), teratoma (0.1%), hemangioma (0.1%), and neurofibroma (0.1%). Houda et al. studied exclusively craniotomy for meningioma resection.¹⁴ Vel et al. studied craniotomy for resection of a variety of central nervous system neoplasms.⁶ Mebel et al. studied complex skull-base resections of acoustic neuromas and meningiomas.¹⁵ As shown in **Table 1** age and sex were relatively evenly distributed between those patients who received TXA and those who did not.

TXA Indications, Administration and Dosage

In all three comparative studies, TXA was given preoperatively as an initial decision before surgery began. TXA was not given due to episodes of increased amounts of blood loss intraoperatively. TXA also was not given due to patient comorbidities such as an intrinsic coagulopathy or perceived difficulty of tumor resection. However, it was given to minimize blood loss outright. Only in the case series of Phi et al., was it used for perceived difficulty of tumor resection, as the three patients were undergoing resection of vascular choroid plexus papillomas (CPPs). In this case series, the decision to give TXA was also made before surgery. TXA was administered intravenously using an initial loading dose followed by continuous administration in all studies (**Table 2**). Loading doses ranged from 10-25 mg/kg, and each was administered either as a bolus^{6,15} or a 20 minute infusion.¹⁴ Maintenance doses also varied; two studies reported maintenance rates of 1 mg/kg/h^{6, 15} and a third reported a rate of 5-10 mg/kg/h.¹⁴

Operative Time

Across all three comparative studies, TXA administration was associated with significantly longer operation times: 418.2 minutes in the TXA group as compared to 340.1 minutes in the non-TXA group ($p < 0.001$) (**Table 3**).

Blood Transfusions, Blood Loss, and Hemoglobin Levels

Pooled data from the three comparative studies found that TXA administration was associated with fewer blood transfusions. Overall, a smaller proportion of patients who received TXA required a blood transfusion (15.7%) than those who did not (22.9%). Chi-squared testing of these data revealed this difference to be statistically significant (OR: 0.63, 95% CI: 0.43-0.93, $p = 0.02$) (**Table 4**).

Two of three comparative studies reported mean total blood loss.^{6, 14} Both of these studies reported significantly less blood loss in patients given TXA as compared to those not give TXA ($P = 0.01^6$; $p = 0.03^{14}$). Pooled data from these studies resulted in a lower mean total blood loss in the TXA group (821.9 mL) than in the non-TXA group (1099.0 mL) (**Table 5**).

All three studies reported postoperative hemoglobin levels.^{6, 14, 15} Two studies failed to find a significant difference in postoperative hemoglobin levels according to TXA administration,^{14, 15} and one study reported higher immediate postoperative hemoglobin levels in patients who received TXA, but that this initially statistically significant difference became negligible by the fifth postoperative day (**Table 5**).⁶

Complications

All three studies also addressed surgical complications, although each study focused on different complications. Taken together, these complications included seizure, thromboses,

hydrocephalus, surgical re-exploration, novel neurological problems, and allergic reactions to TXA.^{6, 14, 15} None of the studies managed to find a significantly increased rate of any of these complications (**Table 6**).^{6,14,15}

Discussion

While TXA is well-studied as an adjuvant agent to limit blood loss in multiple surgical and non-surgical contexts, its value with respect to intracranial tumor surgery is unclear and relatively understudied when compared to the use of TXA in other areas of neurosurgery such as TBI and spine surgery.¹⁶ This review is the first to summarize the existing literature concerning its use in elective intracranial tumor surgery. Our results highlight the limited scope of evidence in support of intraoperative TXA for these surgeries. While a broad takeaway from this review might suggest that TXA can reduce surgical blood loss and limit the need for intraoperative blood transfusions in elective intracranial tumor surgery, the relatively small number of studies included in this review warrants a careful interpretation of our results.

Surgical Indications

Aside from the small case series included in this review, there was no specific pre-defined indication stated by the authors of the articles for undergoing TXA administration except to minimize blood loss. This is to be expected, as for the rather limited guidelines and sets of procedures that exist for the administration of TXA during intracranial tumor resection surgery.

However, when examining the patient populations specifically included in the studies, it is worth noting that complex skull base neurosurgical procedures are commonly associated with a risk of 300-1500 mL blood loss.¹⁵ These skull base tumors may be especially vulnerable to higher

blood loss during resection because of their proximity and potential involvement of critical vascular structures.¹⁵ This higher risk often warrants a greater volume of transfused allogeneic blood, which carries increased morbidity, mortality, and cost.^{15, 17, 18} For this reason, Mebel et al. focused on complex skull base surgeries in their retrospective review of 519 patients, which demonstrated that TXA was associated with a lower rate of blood transfusions without an associated increase in thrombotic complications or seizure.¹⁵ For skull base surgeries, the authors report that TXA was effective in reducing transfusion requirements while maintaining a favorable safety profile. These results are particularly noteworthy considering that average tumor size was larger in the TXA group (3.5cm) than in the non-TXA group (2.9cm).¹⁵ While the authors do not address a cause for this discrepancy in size, it is possible that TXA was administered more often for larger tumors given an anticipation for a more invasive and complex surgical approach.

Hooda et al., in contrast, focused solely on meningioma surgery.¹⁴ Meningiomas may increase expression of tPA, which can increase clot lysis and potentially lead to an increased risk of hemorrhage.¹⁹ In this context, using TXA would follow an intuitive logic. In their analysis of meningioma surgery, the authors found a significant association between TXA use and intraoperative blood loss.¹⁴ Whether this reduction in blood loss accounts for any difference in measurable patient outcomes, however, remains to be seen.

When considering the use of TXA in other areas of neurosurgery including TBI, spinal surgery, and aneurysms, there is a larger body of evidence characterizing its utility.¹⁶ In TBI patients, a multicenter randomized CRASH-3 study found that administering TXA within < 3 hours after trauma reduced mortality for minimal to moderate severity TBI patients only. Patients with severe TBI with having either GCS 3 or unreactive unilateral or bilateral pupils showed no benefit from TXA administration.^{20,21} Therefore, thromboelastography may potentially be used

after 3 hours timeframe to detect for the possibility of patients with hypofibrinogenemia to minimize complications of its use after the 3-hour timeframe.²² For its evidence of benefit in TBI patients, the 2016 European guidelines on the management of major bleed and coagulopathy following trauma establishes TXA as a grade 1A (Strong) recommendation for administration within < 3 hours of TBI. As part of their guidelines, they also suggest administration of TXA while in route to the hospital (grade 2C).²³

In spine surgery, the evidence largely supports TXAs ability to reduce intraoperative blood loss, postoperative blood loss and blood transfusions. However, consensus guidelines on when to administer before, during or after surgery are still in process of being elucidated by clinical trials. The decisions of using TXA are still largely based on the individual practices of the neurosurgeon performing the surgery.^{16,24} In the use of TXA for subarachnoid hemorrhage from ruptured intracranial aneurysms, many studies have reported on this issue depicting conflicting results. TXA does appear to have benefit in limiting the ischemic events of rebleeding thus having benefit in patient functional outcomes, however it is largely inconclusive whether TXA appears to lower overall mortality in this patient population.^{16,25} Nonetheless, it is encouraged to be used in protocols for hemorrhagic stroke, but more specific and unified guidelines still need to be elucidated in future studies.

TXA Administration Routes

TXA can be administered intravenously, topically or intramuscularly,^{5, 12} and each of these formulations has been studied in the surgical population. IV TXA is frequently given as a 1 g loading dose (often over a period of 10 minutes) followed by a steady state infusion over the next 8 hours.⁵ Topical administration involves mixing the TXA with sterile water for direct application

to bleeding surfaces.²⁶ A recent literature review reports statistically significant reductions in peri- and postoperative bleeding for both topical and IV TXA in total hip and knee arthroplasty.²⁷ Oral TXA has been shown to reduce total blood loss and operative time in prostate surgery.²⁸ These improvements may reduce healthcare costs associated with increased perioperative mortality and prolonged hospital stay.¹⁷ To date, only IV TXA has been reported in the literature in cases of elective cranial neurosurgery, despite reports of using oral formulations of other antifibrinolytics for treatment of subarachnoid hemorrhage and intracerebral aneurysms in neurosurgery.^{29,30}

TXA Dosage

Optimal TXA dosage has been investigated in elective spinal and cardiac surgeries.^{8,31} In general, total doses of 1 g are considered adequate with no indication that a higher dose has additional benefit.³² Literature within spine surgery has provided conflicting evidence regarding the optimal dose. A 2013 meta-analysis of randomized controlled trials found that a dose greater than or equal to 15 mg/kg maximally decreased total blood loss and the need for blood transfusion.³³ However, a more recent meta-analysis determined that a bolus dose greater than 10 mg/kg followed by a maintenance dose of greater than 10 mg/kg/h was more effective in reducing intraoperative and postoperative blood loss, while dosing schedules lower than this were more effective for reducing total blood loss.³⁴ This study indicated that intraoperative blood loss may lead to reduction in TXA concentration in the blood, providing a rationale for the use of high dosage. A meta-analysis of randomized controlled trials in adult cardiac surgery reported that low dose TXA was as effective in reducing the transfusion requirement as high dose TXA without increasing the risk of seizure.³⁵ However, the effect of dose on these outcomes has not been studied

in elective cranial surgeries for brain tumor resections. The studies in our review did not consider TXA dosage as a factor for analysis, and instead reported a set TXA dosage or range of dosages.

In our series of patients, the doses used by Mebel et al. were in the medium range (10-25 mg/kg and 5-10 mg/kg/h), while Hooda et al. had a similar loading dose but lower maintenance dose (20 mg/kg and 1 mg/kg/h).^{14, 15} Hooda et al. found a significant difference between total TXA and control blood loss (830 vs 1124 mL, $p = 0.03$) in patients treated for meningiomas. Neither study found significant differences in postoperative hemoglobin levels between TXA and control groups. In contrast, Vel et al. used an even lower dose at 10mg/kg and maintenance dose of 1mg/kg/h. This was associated with a similar reduction in blood loss (817 vs 1084 mL, $p = 0.012$). Interestingly, despite lower dosing, Vel et al. report higher postoperative hemoglobin levels (10.64 vs 10.02 g/dL, $p = 0.02$) in the TXA group compared to controls. To the extent that these data allow, no significant inferences can be drawn as to the most efficacious dose of TXA for elective cranial neurosurgery cases. Further investigation is needed to determine the effects of TXA dosage on outcomes in surgery for intracranial neoplasms.

Operative Duration

When pooling data from all three comparative studies, TXA administration was associated with significantly longer operation times (418.2 +/- 128.3 mins vs. 340.1 +/- 143.4 mins, $P < 0.001$). Of the three comparative studies, only the retrospective review published by Mebel et al. independently reported a significant difference in operative duration.¹⁵ Establishing clear causation from this observed association is difficult, especially considering patients who received TXA in this study also had significantly larger tumors.¹⁵ At present, existing literature cannot lead to definitive conclusions as to whether TXA independently affects operative time.

Total Blood Loss, Blood Transfusions, and Hemoglobin Levels

Although Mebel et al. did not report blood loss, the two prospective cohort studies in this review each reported significantly less blood loss in patients who were given TXA intraoperatively.^{6,14} Conversely; neither prospective study reported significantly lower rate of blood transfusions, while Mebel et al. did (7% in TXA group vs. 12% in control group). When pooled together, however, data from all three studies did demonstrate a reduced rate of blood transfusions in patients who received TXA (OR: 0.6273, 95% CI: 0.4254-0.9251, P=0.018).^{6,14,15} These observed discrepancies may be due to a difference in the various surgical procedures being studied, since Mebel et al. focused solely on complex skull base tumor resections, while the remaining two articles were not restricted to the skull base. Given the higher risk of severe bleeding inherent to complex skull base procedures, it is possible that any marginal benefit of TXA could be more readily observed than for tumors with a lower hemorrhage risk. At present, existing literature does not definitively address this issue.

Although all three articles report postoperative hemoglobin levels, the value of this statistic on its face is unclear. Postoperative hemoglobin may reflect intraoperative losses, but only in the context of knowing how much blood was transfused during surgery. None of the articles addresses this limitation sufficiently, limiting any inferences that can be made of each study individually or of pooled data.

TXA Usage for Pediatric Patients with Choroid Plexus Papilloma

The 4th paper of our literature review was conducted by Phi et al. and reported 3 case studies that compared the use of TXA on infants with CPP.³⁶ The mean age was 6.7 months and gender

was unspecified (**Table 1**). Although CPPs compose about 0.4 to 0.9% of intracranial tumors, the current literature expresses the severity and regularity of hemorrhaging within patient cases.^{37,38} Considering this issue, TXA may serve as a potential solution. Within these pediatric patients, TXA dosage was 50 mg/kg followed by 5 mg/kg/h intraoperatively (**Table 2**).³⁶ Average operating time for the 2 patients who received TXA was 135 minutes as compared to 165 minutes for the patient who did not receive TXA (**Table 4**). Estimated blood loss for the TXA patients was averaged at 131 mL in comparison to 562 mL for the patient who did not receive antifibrinolytics (**Table 5**). Additionally, the patient who did not receive antifibrinolytics was noted to have significant intraoperative hypotension and low postoperative hematocrit (29%) with abnormal coagulation parameters (**Table 6**). Overall, this data provides more information for the potential benefits that TXA may have for the pediatric population possessing highly vascularized CPPs.

Complications

Our review failed to find any significant increases in the rate of postoperative complications relating to TXA administration. Given the mechanism of action of TXA and its potential utility in limiting blood loss, surgeons may choose to avoid its use to limit potential adverse events related to pro-thrombotic states. Reported complications of TXA have included seizure,³⁹ thromboembolism (VTE),⁴⁰ and allergic reaction.⁴¹ TXA has been associated with a dose-dependent increase in seizure risk after cardiac procedures, resulting in longer hospital stays and increased mortality rates.^{39,42,43} This may be related to TXA's ability to cross the blood-brain barrier and affect glycine receptors.⁴⁴ Its antifibrinolytic properties also raise concern for promoting a hypercoagulable state; one large randomized controlled trial found an increased risk of venous, but not arterial, VTE in patients treated with TXA for gastrointestinal bleeding.⁴⁰

Meanwhile other studies have reported no difference in risk of VTE when used for certain orthopedic procedures.^{45,46} Certainly, despite mixed evidence as to the exact risk, TXA must be used with extreme caution in patients at risk of VTE. Lastly, TXA allergy is another concern, but incidence is low; for patients at high risk of an allergic reaction, etamsylate (a well-established hemostatic agent that acts by improving platelet adhesion) is a viable substitute.⁴⁰ Our review suggests that the risk of these various complications is likely unchanged following administration of TXA during surgery; however, the relatively low incidence of these complications suggests that a difference – albeit small – might have been observed with greater statistical power.

Limitations

This study is subject to several limitations. First, there was heterogeneity in the type of surgical procedure and tumor across studies. However, the differences in procedure and tumor improve the generalizability of our results, which is a benefit as TXA is under consideration for use in many types of intracranial surgery. Second, the retrospective study introduces bias as the decision to give TXA was based on the surgeon's discretion, rather than randomized allocation.¹⁵ It is conceivable that TXA may have been administered more frequently in longer, more complicated cases that involved more blood loss. This may have contributed to the association of TXA with longer operative times. Third, our review relies on findings from just three articles for quantitative analysis and one case series, which further limits the conclusions we can make from this study. Finally, the relatively subjective assessment of intraoperative blood loss performed at the end of each surgery is a possible limitation, as it is difficult to estimate exactly how much blood loss occurred, especially during longer cases. Indeed, a recent meta-analysis found that the visual estimation of blood loss was less accurate than colorimetric and gravimetric methods.⁴⁷ Mebel et

al. did not report surgical blood loss due to difficulty obtaining a reliable estimate retrospectively. Vel et al. reported meticulous blood loss measurements at 2-hour intervals by weighing blood-soaked sponges and operative drapes, and subtracting the weight of irrigation used at the end of the procedure. Hooda et al. reported a more relaxed protocol involving quantifying volume of fluid in suction aspirate and subtracting the amount of irrigation fluid, then adding the estimated volume from a visual assessment of all soaked sponges and cottonoids. Given the inherent difficulty in obtaining accurate blood loss estimations, the different methods of calculating this variable may introduce bias towards TXA's efficacy in the less meticulous calculation employed by Hooda et al. However, the blood loss estimates by Vel et al. are unlikely to have been influenced by bias. Despite these limitations, our study remains the first systematic review on the use of TXA in neurosurgical operations for the resection of intracranial neoplasms. Future studies are needed to elucidate the safety and efficacy of TXA as well as its potential effect on blood loss and the need for blood transfusions in complex skull base and cranial procedures.

Conclusion

The present study is the most up to date systematic review assessing the use of TXA as an antifibrinolytic agent for the surgical resection of intracranial neoplasms. The included studies suggest that TXA may be effective for reducing blood loss and the need for blood transfusion while also having minimal reported complications. However, when comparing the use of TXA in intracranial neoplasm resection surgery to other areas of TXA use in neurosurgery, it is apparent that outcomes after TXA use in neoplasm resection surgery has been less investigated. Future prospective studies should be undertaken to clarify the role of TXA during the resection of intracranial neoplasms.

References

1. Hunt BJ. The current place of tranexamic acid in the management of bleeding. *Anaesthesia* 2015;70 Suppl 1:50-3, e18.
2. Shakur H, Roberts I, Bautista R, et al. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. *Lancet* 2010;376:23-32.
3. Aguilera X, Videla S, Almenara M, Fernandez JA, Gich I, Celaya F. Effectiveness of tranexamic acid in revision total knee arthroplasty. *Acta Orthop Belg* 2012;78:68-74.
4. Faraoni D, Willems A, Melot C, De Hert S, Van der Linden P. Efficacy of tranexamic acid in paediatric cardiac surgery: a systematic review and meta-analysis. *Eur J Cardiothorac Surg* 2012;42:781-6.
5. Yang B, Li H, Wang D, He X, Zhang C, Yang P. Systematic review and meta-analysis of perioperative intravenous tranexamic acid use in spinal surgery. *PLoS One* 2013;8:e55436.
6. Vel R, Udupi BP, Satya Prakash MV, Adinarayanan S, Mishra S, Babu L. Effect of low dose tranexamic acid on intra-operative blood loss in neurosurgical patients. *Saudi J Anaesth* 2015;9:42-8.
7. Neilipovitz DT. Tranexamic acid for major spinal surgery. *Eur Spine J* 2004;13 Suppl 1:S62-5.
8. Johnson DJ, Johnson CC, Goobie SM, et al. High-dose Versus Low-dose Tranexamic Acid to Reduce Transfusion Requirements in Pediatric Scoliosis Surgery. *J Pediatr Orthop* 2017;37:e552-e7.
9. Sethna NF, Zurakowski D, Brustowicz RM, Bacsik J, Sullivan LJ, Shapiro F. Tranexamic acid reduces intraoperative blood loss in pediatric patients undergoing scoliosis surgery. *Anesthesiology* 2005;102:727-32.
10. Goobie SM, Meier PM, Sethna NF, et al. Population pharmacokinetics of tranexamic acid in paediatric patients undergoing craniostomy surgery. *Clin Pharmacokinet* 2013;52:267-76.
11. collaborators" TC-t. 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. *The Lancet* 2019;394:1713-23.
12. July J, Pranata R. Tranexamic acid is associated with reduced mortality, hemorrhagic expansion, and vascular occlusive events in traumatic brain injury - meta-analysis of randomized controlled trials. *BMC Neurol* 2020;20:119.
13. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009;6:e1000097.
14. Hooda B, Chouhan RS, Rath GP, Bithal PK, Suri A, Lamsal R. 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.
15. Mebel D, Akagami R, Flexman AM. Use of Tranexamic Acid Is Associated with Reduced Blood Product Transfusion in Complex Skull Base Neurosurgical Procedures: A Retrospective Cohort Study. *Anesth Analg* 2016;122:503-8.
16. de Faria JL, Silva Brito JD, E Silva LT, et al. Tranexamic acid in Neurosurgery: a controversy indication—review. *Neurosurg Rev* 2021; 44(3):1287-1298.
17. Blanchette CM, Wang PF, Joshi AV, Asmussen M, Saunders W, Kruse P. Cost and utilization of blood transfusion associated with spinal surgeries in the United States. *Eur Spine J* 2007;16:353-63.

18. Dodd RY. The risk of transfusion-transmitted infection. *N Engl J Med* 1992;327:419-21.
19. Tsuda H, Oka K, Noutsuka Y, Sueishi K. Tissue-type plasminogen activator in patients with intracranial meningiomas. *Thromb Haemost* 1988;60:508-13..
20. 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; 394:1713-1723.
21. Roberts I, Edwards P, Prieto D, et al. Tranexamic acid in bleeding trauma patients: an exploration of benefits and harms. *Trials* 2017;18(1):48.
22. Na HS, Shin HJ, Lee YJ, et al. The effect of tranexamic acid on blood coagulation in total hip replacement arthroplasty: rotational thromboelastographic (ROTEM®) analysis. *Anaesthesia* 2016;71(1):67-75.
23. Rossaint R, Bouillon B, Cerny V, et al. The European guideline on management of major bleeding and coagulopathy following trauma: Fourth edition. *Crit Care* 2016; 20:1-55.
24. Elwatidy S, Jamjoom Z, Elgamal E, et al. Efficacy and safety of prophylactic large dose of tranexamic acid in spine surgery: a prospective, randomized, double-blind, placebo-controlled study. *Spine (Phila Pa 1976)* 2008;33:2577-80.
25. Gaberel T, Magheru C, Emery E, et al. Antifibrinolytic therapy in the management of aneurismal sub-arachnoid hemorrhage revisited. A meta-analysis. *Acta Neurochir (Wien)* 2012;154(1):1-9.
26. Ker K, Beecher D, Roberts I. Topical application of tranexamic acid for the reduction of bleeding. *Cochrane Database Syst Rev* 2013;Cd010562.
27. Georgiev GP, Tanchev PP, Zheleva Z, Kinov P. Comparison of topical and intravenous administration of tranexamic acid for blood loss control during total joint replacement: Review of literature. *J Orthop Translat* 2018;13:7-12.
28. Rannikko A, Péta A, Taari K. Tranexamic acid in control of primary hemorrhage during transurethral prostatectomy. *Urology* 2004;64:955-8.
29. Mullan S, Dawley J. Antifibrinolytic therapy for intracranial aneurysms. *J Neurosurg* 1968;28:21-3.
30. Leipzig TJ, Redelman K, Horner TG. Reducing the risk of rebleeding before early aneurysm surgery: a possible role for antifibrinolytic therapy. *J Neurosurg* 1997;86:220-5.
31. Couture P, Lebon JS, Laliberté É, et al. Low-Dose Versus High-Dose Tranexamic Acid Reduces the Risk of Nonischemic Seizures After Cardiac Surgery With Cardiopulmonary Bypass. *J Cardiothorac Vasc Anesth* 2017;31:1611-7.
32. Ker K, Prieto-Merino D, Roberts I. Systematic review, meta-analysis and meta-regression of the effect of tranexamic acid on surgical blood loss. *Br J Surg* 2013;100:1271-9.
33. Li Z-J, Fu X, Xing D, Zhang H-F, Zang J-C, Ma X-L. Is tranexamic acid effective and safe in spinal surgery? A meta-analysis of randomized controlled trials. *European Spine Journal* 2013;22:1950-7.
34. Cheriyan T, Maier SP, Bianco K, et al. Efficacy of tranexamic acid on surgical bleeding in spine surgery: a meta-analysis. *The Spine Journal* 2015;15:752-61.
35. Guo J, Gao X, Ma Y, et al. Different dose regimes and administration methods of tranexamic acid in cardiac surgery: a meta-analysis of randomized trials. *BMC Anesthesiology* 2019;19:129.
36. Phi JH, Goobie SM, Hong KH, Dholakia A, Smith ER. Use of tranexamic acid in infants undergoing choroid plexus papilloma surgery: a report of two cases. *Paediatr Anaesth* 2014;24:791-3.

37. Due-Tønnessen B, Helseth E, Skullerud K, Lundar T. Choroid plexus tumors in children and young adults: report of 16 consecutive cases. *Childs Nerv Syst* 2001;17:252-6.
38. Lafay-Cousin L, Keene D, Carret AS, et al. Choroid plexus tumors in children less than 36 months: the Canadian Pediatric Brain Tumor Consortium (CPBTC) experience. *Childs Nerv Syst* 2011;27:259-64.
39. Lin Z, Xiaoyi Z. Tranexamic acid-associated seizures: A meta-analysis. *Seizure* 2016;36:70-3.
40. The 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;395:1927-36.
41. Imbesi S, Nettis E, Minciullo PL, et al. Hypersensitivity to tranexamic acid: a wide spectrum of adverse reactions. *Pharm World Sci* 2010;32:416-9.
42. Kalavrouziotis D, Voisine P, Mohammadi S, Dionne S, Dagenais F. High-dose tranexamic acid is an independent predictor of early seizure after cardiopulmonary bypass. *Ann Thorac Surg* 2012;93:148-54.
43. Lecker I, Wang DS, Whissell PD, Avramescu S, Mazer CD, Orser BA. Tranexamic acid-associated seizures: Causes and treatment. *Ann Neurol* 2016;79:18-26.
44. Lecker I, Wang DS, Romaschin AD, Peterson M, Mazer CD, Orser BA. Tranexamic acid concentrations associated with human seizures inhibit glycine receptors. *J Clin Invest* 2012;122:4654-66.
45. Singh J, Ballal MS, Mitchell P, Denn PG. Effects of tranexamic acid on blood loss during total hip arthroplasty. *J Orthop Surg (Hong Kong)* 2010;18:282-6.
46. Yang ZG, Chen WP, Wu LD. Effectiveness and safety of tranexamic acid in reducing blood loss in total knee arthroplasty: a meta-analysis. *J Bone Joint Surg Am* 2012;94:1153-9.
47. 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* 2020; 35(2):245-258.

Figure Legend

Figure 1. Mechanism of action of TXA. Created using BioRender.com

Figure 2. PRISMA Flow Diagram

Table 1. Final List of Selected Studies

Authors	Title	Study Design	Level of Evidence	Institution	Sample Size (TXA/No TXA)	Mean Age	Gender (M/F)
Phi et al., 2014 ³²	Use of tranexamic acid in infants undergoing choroid plexus papilloma surgery: a report of two cases.	Case Report	5	Seoul National University Children's Hospital	3 (3/0)	6.7 months	N/A
Mebel et al., 2016 ¹⁵	Use of tranexamic acid is associated with reduced blood product transfusion in complex skull base neurosurgical procedures: A retrospective cohort study	Retrospective	3	Dept of Anesthesiology, Pharmacology, and Therapeutics, University of British Columbia	519 (245/274)	TXA: 49 years Control: 48 years	TXA: 41%/59 % Control: 39%/61 %
Hooda B et al., 2017 ¹⁴	Effect of tranexamic acid on intraoperative blood loss and transfusion requirements in patients undergoing excision of intracranial meningioma.	Randomized Prospective	2	Department of Neuroanaesthesiology & Critical Care, All India Institute of Medical Sciences (AIIMS), New Delhi, India	60 (30/30)	TXA: 39.3 years Control: 41.6 years	TXA: 47%/53 % Control: 23%/77 %
Vel R et al., 2015 ⁶	Effect of low dose tranexamic acid on intraoperative blood loss in neurosurgical patients	Randomized Prospective	2	Department of Anesthesiology and Critical Care, JIPMER	100 (50/50)	TXA: 40.4 years Control: 39.8 years	TXA+C ontrol: 43%/57 %

Table 2. Surgical Information

Study	Surgery Type	Indications for Surgical Resection	TXA Dose/Administration Period	TXA Administration Route
Phi et al., 2014³²	Not Specified	Choroid plexus papilloma	50 mg/kg followed by 5 mg/kg/h intraoperatively	Not specified
Mebel et al., 2016¹⁵	Anterolateral and Posterolateral Approaches for complex skull-base surgery	Acoustic neuroma (55%) Meningioma (25%)	10-25 mg/kg 20 minutes preoperatively followed by 5-10 mg/kg/h intraoperatively	Intravenous
Hooda B et al., 2017¹⁴	Craniotomy	Meningioma (100%)	20 mg/kg 20 minutes preoperatively followed by 1mg/kg/h intraoperatively	Intravenous
Vel R et al., 2015⁶	Craniotomy	Glioma (29%) Schwannoma (23%) Meningioma (26%) Epidermoid (9%) Pituitary macroadenoma (8%) Colloid cyst (5%)	10 mg/kg 20 minutes preoperatively followed by 1 mg/kg/h intraoperatively	Intravenous

Table 3. Operative Duration

Study	TXA	Control
Phi et al., 2014³²	Pt. 1: 270 mins Pt. 2: 150 mins	Pt. 3:165 mins
Mebel et al., 2016¹⁵	432 mins*	332 mins*
Hooda B et al., 2017¹⁴	346 mins	359 mins
Vel R et al., 2015⁶	394 mins	373 mins
*Denotes statistically significant difference between TXA and Control		

Table 4. Blood Transfusion 2x2 Contingency Table

	Did Not Receive Transfusion	Received Transfusion	Totals
TXA	274	51	325
Control	273	81	354
Total	547	132	679
Risk Ratio: 0.6858, 0.95 Confidence Interval: 0.4998-0.941 (P=0.018), Pearson One-Tailed Chi-Square Test Odds Ratio: 0.6273, 0.95 Confidence Interval: 0.4254-0.9251 (P=0.018)			

Table 5. Blood Analysis

Study	TXA Postoperative Hemoglobin Levels ^b	Control Postoperative Hemoglobin Levels ^b	TXA Total Blood Loss ^c	Control Total Blood Loss ^c	TXA RBC** Transfusions	Control RBC Transfusions
Phi et al., 2014³²	Pt.1: 132.0 g/dL Pt.2: 8.50 g/dL	Pt.3: 10.00 g/dL	Pt. 1: 100mL (<20% total blood volume) Pt. 2: 162 mL (<20% total blood volume)	Pt. 3: 569 mL (122% total blood volume)	Pt. 1: intraoperative 120 mL PRBC (20 mL/kg) Pt. 2: none received	Pt. 3: intraoperative 290 mL PRBC (53mL/kg)
Mebel et al., 2016¹⁵	11.60 g/dL	11.60 g/dL	N/A	N/A	7% * received transfusion	12% * received transfusion
Hooda B et al., 2017¹⁴	N/A ^a	N/A ^a	830 mL*	1124 mL*	43% received transfusion 554 mL ^d	57% received transfusion 645 mL ^d
Vel R et al., 2015⁶	10.64 g/dL*	10.02 g/dL*	817 mL*	1084 mL*	21% received transfusion 445.2 mL ^d	30% received transfusion 459.7 mL ^d

^aReported no significant difference in postoperative hemoglobin levels, but did not specify values
^bValues reported are averages except for those provided by Phi et al
^cValues reported are averages except for those provided by Phi et al
^dAverage value among patients receiving transfusion
*Denotes statistically significant difference between TXA and Control
**RBC=Red Blood Cells

Table 6. Complications

Study	TXA	Control
Phi et al., 2014 ³²	N/A	Pt.3: significant intraoperative hypotension, low postoperative hematocrit (29%) with abnormal coagulation parameters (including low fibrinogen)
Mebel et al., 2016 ¹⁵	Thrombosis: 0.8% Seizure: 3.3%	Thrombosis: 2.1% Seizure: 2.1%
Hooda B et al., 2017 ¹⁴ Postoperative complications similar between groups	Re-exploration: 1 (3.3%) Seizures: 1 (3.3%) Hydrocephalus: 0 Novel neurological deficits: 4 (13.8%)	Re-exploration: 3 (10%) Seizures: 2 (6.7%) Hydrocephalus: 1 (3.3%) Novel neurological deficits: 10 (33.3%)
Vel R et al., 2015 ⁶	N/A	N/A

Figure 1. Mechanism of action of TXA. Created using Biorender.com

Figure 2. Article Selection Process Using PRISMA Guidelines

Abbreviations

TXA - Tranexamic acid

PRISMA – Preferred Reporting Items for Systematic Reviews and Meta-analyses

SDH - subdural hematoma

TBI - traumatic brain injury

Hb – hemoglobin

OR - odds ratio

CI - confidence interval

IV – intravenous

tPA - tissue plasminogen activator

GCS – Glasgow coma scale

VTE - venous thromboembolism

Credit Author Statement

Conception and Design: Brown, Wilson, I Yang

Acquisition of Data: Brown, Ong, CY Yang, Himstead, Shahrestani, Shlobin, Reardon, Choi, Birkenbeuel, Cohn, Sahyouni

Analysis and Interpretation of Data: Brown, Wilson, Ong, Choi

Drafting the Article: Brown, Wilson, Ong, CY Yang, Himstead, Shahrestani, Sahyouni, Chan, Gendreau

Critically Revising the Article: All authors

Reviewed Submitted Version: All Authors

Approved Final Version on Behalf of all Authors: I Yang

Study Supervision: I Yang