**Title: Tranexamic Acid Use in Meningioma Surgery – A Systematic Review and Meta-Analysis**

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**Author Contributions**

All authors contributed to the study conception and design. Data collection and analysis was performed by Abigail Clynch, Conor S Gillespie, with support from George E Richardson and Ali Bakhsh. The first draft of the manuscript was written by Abigail Clynch and all authors commented on versions of the manuscript. The final manuscript was read and approved by all authors.

*Abstract:*

Tranexamic Acid (TXA) has been used in medical and surgical practice to reduce haemorrhage. The aim of this review was to evaluate the effect of TXA use on intraoperative and postoperative outcomes of meningioma surgery. A systematic review and meta-analysis was conducted in accordance with the PRISMA statement and registered in PROSPERO (CRD42021292157). Six databases were searched up to November 2021 for phase 2-4 control trials or cohort studies in the English language, examining TXA use during meningioma surgery. Studies ran outside of dedicated neurosurgical departments or centres were excluded. Risk of bias was assessed using the Cochrane Risk of Bias 2 tool. Random effects meta-analysis were performed to delineate differences in operative and postoperative outcomes. Four studies (281 patients) were included. TXA use significantly reduced intraoperative blood loss (mean difference 315.7 mls [95% confidence interval [CI] -532.8, -98.5]). Factors not affected by TXA use were transfusion requirement (odds ratio= 0.52; 95% CI 0.27, 0.98), operation time (mean difference= -0.2 hours ; 95% CI -0.8, 0.4), postoperative seizures (Odds Ratio [OR]= 0.88; 95% CI 0.31, 2.53), hospital stay (mean difference = -1.2; 95% CI -3.4, 0.9) and disability after surgery (OR= 0.50; 95% CI 0.23, 1.06). The key limitations of this review were the small sample size, limited data for secondary outcomes and a lack of standardised method for measuring blood loss. TXA use reduces blood loss in meningioma surgery, but not transfusion requirement or postoperative complications. Larger trials are required to investigate the impact of TXA on patient-reported postoperative outcomes.

*Keywords*

TXA; meningioma; blood loss; tranexamic acid; neurosurgery; bleeding.

*Introduction*

Meningioma is the most common primary brain tumour [1]. In meningioma that are symptomatic, growing, or a threat to neurovascular structures, surgical resection is often the preferred initial management strategy [2]. Surgery for intracranial meningioma can be associated with major intraoperative bleeding, leading to hypovolemic shock and sepsis, necessitating blood transfusion [3, 4, 5]. This risk increases with larger tumours and prolonged operation time [6]. Blood transfusion requirement is postulated to correlate with increased surgical time, hospital stay and postoperative complications (e.g., acute renal failure, pneumonia, re-craniotomy, and seizures) [4, 7].

Tranexamic acid (TXA) is an antifibrinolytic agent that has been demonstrated to have a significant impact on reducing blood loss within major trauma and surgery, with no increased risk of vaso-occlusive events [6, 8, 9, 10]. It is licensed within the UK for conditions including menorrhagia and epistaxis [8, 11, 12]. TXA has been shown to be of benefit in managing neurosurgical conditions including paediatric scoliosis and traumatic brain injury (TBI), but not in acute intracerebral haemorrhage [12, 13, 14, 15].

There is currently limited data on the effect of TXA on blood loss during neuro-oncological surgery, specifically meningioma resection surgery. A few small cohort trials have been performed with heterogenous outcomes unable to reach statistical significance [11, 16, 17, 18]. The effect of TXA on intra-operative, and patient outcomes, is still to be delineated.

This systematic review and meta-analysis aimed to answer the question: In patients undergoing surgery for meningiomas, is the use of TXA associated with reduced blood loss, postoperative complications, and improved patient outcomes?

*Materials and Methods*

A systematic review and meta-analysis were conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement [19]. The study was registered with prospero (CRD42021292157).

Search Strategy

A systematic search was performed from inception on MEDLINE, PubMed, CINAHL Plus, Cochrane Register of Controlled Trials and WHO international clinical trials registry up to and including 20th November 2021. Searches were performed in line with search combinations agreed by all authors (Online Material 1). The MEDLINE search strategy was adapted for the other online electronic registries. Papers were limited to English Language due to the feasibility of translation. The results were then exported to the online platform Rayyan [20], a repository to facilitate de-duplication and independent screening of potential records.

Study Selection and Screening

AC removed duplicates in Rayyan prior to screening. Two independent reviewers (AC and CSG) screened the search results. All peer-reviewed Phase 2-4 controlled trials and cohort studies comparing patients who underwent meningioma resection and received TXA compared to no intervention were included. Study titles and abstracts were screened according to the PICOS model and Inclusion/Exclusion criteria outlined in Table 1 and Online Material 2.

|  |  |
| --- | --- |
| Population | Individuals of any age with operated meningioma |
| Intervention | TXA |
| Comparator | Placebo or no TXA administered |
| Outcomes | Primary:   * Transfusion Requirement (number of participants requiring transfusion)   Secondary:   * Intraoperative blood loss in ml * Postoperative hospital stay in days * Operation Timein hours * Postoperative complications |
| Setting | Studies taking place in any neurosurgical department or centre internationally |
| Study Design | Phase 2, 3 or 4 control trials and multiple cohort studies |
| Follow Up | Any |

Table 1: PICOS model used for screening

The primary outcome of interest was transfusion requirement, this was defined as the number of participants requiring transfusion in each study. The secondary outcomes of interest were intraoperative blood loss (in millilitres), postoperative hospital stay (in days), operation time (in hours) and frequency of postoperative complications occurring in the 30 day postoperative period (seizure, disability, haematoma, thromboembolic events, infection, myocardial infarction and new neurological deficit). Postoperative seizures were defined as seizures in any individual regardless of seizure history. Postoperative thromboembolic events were defined as a pulmonary embolus or deep vein thrombosis.

Studies that remained underwent full-text screening. If any disagreements occurred, a discussion took place between AC, CSG and the senior author (MDJ) to reach a consensus on included studies. If necessary corresponding authors were contacted via email to request unavailable data.

Data Extraction, Data Items and Management

Data was extracted from included full-text articles into an excel spreadsheet by two authors (AC and CSG) using a standardised piloted data collection proforma (Online Material 3). Data included: authors, year of publication, title, country of origin, study design, population size, baseline characteristics (age and sex distribution), preoperative meningioma volume, intervention (TXA vs Placebo/no TXA) and outcomes (intraoperative blood loss, postoperative blood loss, postoperative complications, operative time, thromboembolic events, length of hospital stay).

Online Material 4 provides definitions for outcome measures of interest in this review.

Statistical Analysis

Meta-analysis of the primary and secondary outcomes was performed using a random effects model, accounting for variance across studies. The effect size measured was mean difference (MD) for continuous variables. Odds ratios (OR) (95% confidence interval [CI]) or risk differences (95% CI) were used for categorical outcomes based on the presence of zero event arms. If the 95% CI included zero, it was deemed not statistically significant. The Mantel- Haenszel model was used to combine the results from the studies included with weighting per study performed using random effects.

Heterogeneity across studies was estimated using the I2 statistic and classified into low (≤50%), moderate (50-75%) and high (≥75%). P values for the I2 test were determined from the chi-squared distribution of the Cochran Q test. For pooled means of continuous variables with missing standard deviations, we imputed missing values using the method proposed by the Cochrane handbook [21]. All statistical analysis was performed using Review Manager 5.4 (RevMan 5.4). Risk of bias was assessed using the Cochrane Collaboration’s tool for assessing risk of bias [22].

*Results*

Study selection process and baseline characteristics

Figure 1 describes the study selection and screening process. A list of all abstract and full text articles screened and reasons for exclusion are outlined in Online Material 5 [27 abstracts and 5 full-text articles were screened]. After screening, four studies with 281 participants were included (141 control, 140 intervention). All studies used saline as the control placebo. Three studies originated from India and one from Tunisia. Table 2 shows the baseline characteristics of included studies and participants.

**Fig. 1** PRISMA Flow Diagram demonstrating the study selection and screening process

Study outcomes

All four studies investigated transfusion requirements (281 patients). Intraoperative blood loss was reported in three studies (181 patients). Postoperative hospital stay was reported in three studies (251 patients). Length of surgery was reported in two studies (191 patients). Postoperative complications were variably reported across studies. Postoperative thromboembolic events were recorded in four studies. Postoperative seizures were reported in three studies. Postoperative haematoma and disability were reported in two studies. Postoperative myocardial infarction and new neurological deficit were reported in one study. Postoperative infection was not measured. A summary of included studies can be found in Table 2.

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Author and Year of Publication** | **Is this a single centre study** | **Country of Origin** | **Study Design** | **Population Size** | **Mean Age**  **(controls)** | **Mean Age (intervention)** | **Sex Distribution (M:F)** | **TXA Dose/Protocol** | **Outcome of Study** |
| Siddiqui AK et al. 2018 | Yes | India | Double-Blinded Phase 3 Randomised Control Trial | 100 | 49.4 +/- 13.4 | 50.1 +/- 14.6 | 60:40 | 2g TXA in 50ml 0.9% normal saline vs 50ml 0.9% normal saline | TXA has a positive impact on blood loss and transfusion requirement in Meningioma patients. |
| Ravi GK et al. 2021 | Yes | India | Double-Blinded Phase 3 Randomised Control Trial | 30 | 52.0 +/- 13.2 | 48.9 +/- 10.7 | 10:20 | 20mg/kg TXA pre-surgery and 1mg/kg/hr infusion til end of surgery vs corresponding saline dose | TXA has a positive impact on blood loss and transfusion requirement in Meningioma patients. |
| Hooda B et Al. 2018 | Yes | India | Double-Blinded Phase 3 Randomised Control Trial | 60 | 41.6 +/- 11.2 | 39.3 +/- 11.4 | 21:39 | 20mg/kg TXA pre-surgery and 1mg/kg/hr infusion til end of surgery vs corresponding saline dose | TXA has a positive impact on blood loss and transfusion requirement in meningioma patients. |
| Rebai L et Al. 2021 | Yes | Tunisia | Double-Blinded Phase 3 Randomised Control Trial | 91 | 48.2 +/- 9.1 | 49.5 +/- 8.7 | 49:42 | 20mg/kg TXA pre-surgery and 1mg/kg/hr infusion til end of surgery vs corresponding saline dose | TXA has a positive impact on blood loss and transfusion requirement in Meningioma patients. |

Table 2: Summary of Baseline Characteristics for Included Studies

Transfusion requirement

All included studies measured transfusion requirement. TXA was not associated with a significant reduction in transfusion requirement (Odds Ratio (OR)= 0.52; 95%; confidence interval (CI) 0.27, 0.98). Low heterogeneity existed between included studies (I2 = 0%) (Figure 2a).

Intraoperative blood loss

Three studies measured intraoperative blood loss (in millilitres). TXA patients had significantly lower blood loss (Mean difference (MD) = -315.7 mls; 95% CI -532.8, -98.5). Moderate heterogeneity existed between included studies (I2 = 58%) (Figure 2b).

Length of Surgery

Two studies measured length of surgery. Length of surgery was not affected by TXA use (MD= -0.2; 95% CI -0.8, 0.4). High heterogeneity existed between included studies (I2 = 85%) (Figure 2c).

Postoperative hospital stay

Three studies measured postoperative hospital stay. There was no significant difference in hospital stay between the TXA group and placebo (MD= -1.2; 95% CI= -3.4, 0.9]). High heterogeneity existed between studies (I2=90%) (Figure 2d).

**Fig. 2** Forest Plots demonstrating the effect of TXA on intraoperative complications and postoperative hospital stay. a) Forest Plot showing the effect of TXA on transfusion requirement, b) Forest Plot showing the effect of TXA on intraoperative blood loss, c) Forest Plot showing the effect of TXA on length of surgery, d) Forest Plot showing the effect of TXA on postoperative hospital stay.

Postoperative Complications

Seizure, disability, haematoma and thromboembolic events had sufficient data for meta-analysis. Whilst infection, myocardial infarction and new neurological deficit were not included in the meta-analysis.

Seizure

All studies with estimable data examined the effect of TXA on postoperative seizures. No significant effect was found following meta-analysis (OR = 0.88; 95% CI 0.31, 2.53). Low heterogeneity existed between studies (I2= 0%) (Figure 3a).

Disability

Two studies compared postoperative outcomes to the Glasgow Outcome Scale (GOSE) score at time of discharge. There was no significant difference in postoperative disability (OR=0.50; 95% CI = 0.23, 1.06). Low heterogeneity existed between groups (I2=0%) (Figure 3b).

Thromboembolic events

All studies examined thromboembolic events. There was no significant difference in postoperative thromboembolic events (RD= 0.00; 95% CI -0.03, 0.03). Low heterogeneity existed between groups (I2= 0%) (Figure 3c).

Haematoma

Two studies reported postoperative haematoma. There was no significant difference in postoperative haematoma (OR=0.5; 95% CI 0.14, 1.82). Low heterogeneity existed between groups (I2= 0%) (Figure 3d).

**Fig. 3** Forest plots demonstrating the effect of TXA on postoperative complications a) Forest Plot demonstrating the effect of TXA on postoperative seizures, b) Forest Plot demonstrating the effect of TXA on postoperative disability, c) Forest Plot demonstrating the effect of TXA on postoperative thromboembolic events, d) Forest Plot demonstrating the effect of TXA on postoperative haematoma.

Study quality

Two studies had a low risk of bias [16, 17]. Two studies had an unclear risk of bias due to selection, detection and/or reporting bias [11, 18]. Measurement of intraoperative blood loss varied across studies and was widely estimated, with one study using a modified gross formula. One study [18] did not report tumour volume or tumour location of included patients. All studies were randomised by computer generated lists and double-blinded. Risk of bias summary is shown in Online Material 6.

**Fig. 4** Risk of Bias plots demonstrating risk of bias for all included studies. Generated using Robvis.

*Discussion*

This systematic review and meta-analysis were carried out to assess the effect of TXA use in meningioma surgery in reducing blood loss, transfusion requirement and postoperative complications. Four studies with 281 participants (141 receiving TXA) were included and evaluated 8 key outcomes: intraoperative blood loss, transfusion requirement, length of operation, postoperative hospital stay, postoperative seizures, postoperative disability, postoperative thromboembolic events and postoperative haematoma. TXA significantly reduced intraoperative blood loss. Other outcomes were not affected by TXA use. Studies placed a large emphasis on blood loss and transfusion requirement, meaning this review aim was clearly met. However, a limited number of studies meant results did not provide a clear answer regarding the effect of TXA on postoperative complications and did not examine patient reported outcomes.

Reduced intraoperative blood loss was an anticipated phenomenon due to previous similar findings [5, 10]. In a meta-analysis of 129 trials, TXA administration and reduction of intraoperative blood loss translated into a reduction in blood transfusion requirements in several surgical specialities by approximately a third (including orthopaedic, cranial, and vascular) [23]. In patients with a meningioma, transfusion requirement has been associated with adverse patient outcomes [24]. Similarly, blood transfusion is an independent risk factor for death, myocardial infarction, stroke and malignancy [25]. Transfusion related acute lung injury (TRALI) and circulatory overload (TACO) are fatal complications caused by blood transfusion [26]. Therefore, it may be hypothesised that maintaining homeostasis and reducing transfusion requirement, utilising TXA, would reduce the risk of fatal complications and improve patient outcomes. The results of this meta-analysis do not support this.

There are a number of methods utilised to reduce intraoperative blood loss. This includes cell salvage, TXA administration, topical agents or anaesthetic techniques [27]. This meta-analysis found TXA was an effective way to reduce intraoperative blood loss. However, no conclusions could be drawn on the benefits and disadvantages of TXA use in meningioma surgery. A comparison of TXA to other blood loss reduction techniques is needed in order to ascertain its utility. A multimodal approach is often needed to reduce blood loss, and subsequently TXA use alone is not the answer to controlling intraoperative bleeding [28].

No significant effect was found on postoperative complications. However, there was large heterogeneity in postoperative complications examined in all four studies, meaning general conclusions on postoperative outcomes could not be drawn. Meta-analysis was performed for five complications, none reached statistical significance. No studies examined postoperative infection, despite this being an urgent complication of neurosurgical procedures, closely related to use of TXA [29]. Nonetheless, length of surgery, a risk factor for postoperative infection, was not associated with TXA use [30]. All four studies examined thromboembolic events, a potential side effect of TXA administration [31]. No significant difference was found in thromboembolic events between patients receiving TXA or placebo. This suggests TXA is safe to use in meningioma surgery. Therefore, the risk of anaphylaxis post-TXA administration can not be quantified in this population. Larger studies looking specifically at postoperative complications are needed to definitively answer if TXA improves postoperative complications.

1/3 of patients with a meningioma will develop seizures during their disease course [32]. This phenomenon is widely misunderstood [32]. Contributing factors are believed to be tumour progression, extent of resection and surgical complication. It may be hypothesised that TXA use would reduce blood loss, reduce length of operation and reduce surgical complication risk which may result in seizures. The results of this meta-analysis do not support this hypothesis.

Outcomes such as intraoperative blood loss and transfusion requirement are not patient reported outcomes and will not contribute anymore information to surgical TXA research [23]. For many clinicians and patients, the success of an operation is instead determined by the postoperative outcomes and patient quality of life. Therefore, focussing trials examining TXA use in brain tumour surgery around these clinical, poorly quantified outcomes reduces emphasis on patient-focussed care. There are currently no qualitative neurosurgical studies that have examined patient priorities in neuro-oncological surgery. A study examining patient priorities in general surgery found patients to value being free of cancer and surgical complications [33]. Length of stay was not important [33]. General surgical patients face different trade-offs to neurosurgical patients. However, some outcome measures that may be of importance are outlined in Online Material 7. Therefore, more qualitative research into neurosurgical patient priorities must be explored.

A larger, multi-centre, randomised control trial with a focus on postoperative and patient reported outcomes would allow clinicians to gain an insight into the effects of tranexamic acid from a perspective not yet explored in the literature. To ensure future trials focus on postoperative outcomes of significance to patients undergoing meningioma surgery, we would propose reference be made to the unified core set of defined outcomes for meningiomas currently under development [34]. Transfusion requirement and blood loss are both outcomes that have been studied in all published literature, and as stated by previous studies, any further studies examining these intraoperative outcomes would not contribute to current TXA research.

Study Limitations

All study populations excluded individuals with confounding conditions such as previous VTE or impaired renal function, meaning results could not be applied to comorbid populations (e.g. hepatic or renal impairment). Only four studies were included in this review with limited data. The populations were small with rare event occurrences. One study did not exclude individuals who may have underwent preoperative embolisation, a technique used to reduce intraoperative blood loss. Data to inform outcomes were also not always available. No data was available on patient quality of life postoperatively. Similarly, data regarding key demographic information (tumour volume and tumour location) were not always available.

There is no gold-standard technique for measuring intraoperative blood loss [35], and the practice of measuring and quantifying intraoperatively was recorded heterogeneously in the included studies. Preoperatively surgeons estimate anticipated blood loss as outlined in the WHO Surgical Safety Checklist [36]. Current methods for measuring blood loss within neurosurgery have a number of drawbacks, with visual estimation most frequently used [21]. This method has been highlighted to be inaccurate [21]. The practice of measuring and quantifying intraoperative blood loss was recorded heterogeneously in the included studies. Two studies used subtraction of irrigation fluid from suction in addition to estimation from surgical drapes, sponges and cotton pledges [11, 17]. Siddiqui et al also used suction blood estimation and sponge weight. Ravi et Al was the only study to use the Modified Gross formula for estimated blood loss or formula by Brecher et Al in the case of intraoperative blood transfusion [37]. These methods had areas where blood loss could have been under or overestimated, leading to a risk of detection bias. We recommend use of the Modified Gross formula or Brecher et Al formula in future TXA trials to estimate blood loss.

Limitations of our meta-analysis, include the significant heterogeneity that existed between included studies. This was particularly pronounced for blood loss, transfusion requirement, length of surgery, and postoperative hospital stay. The vast majority of studies reported differences in measurement for these key outcomes, limiting the respective findings. Three of the included studies utilised the same tranexamic acid administration protocol, while one did not. Most of studies included also had small sample sizes, with a questionable randomisation process. This indicates a clear need for a highly powered, robust trial with clear outcomes and minimise publication bias.

*Conclusion*

TXA use in Meningioma surgery reduced blood loss but did not affect transfusion requirement and postoperative outcomes. Current studies have failed to examine outcomes relevant to patients, including factors affecting postoperative quality of life. We recommend larger studies be undertaken with a focus on outcomes of value to the patient.

*Statements & Declarations*

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Competing Interests

Authors have no conflicts of interest to declare.

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