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Tranexamic Acid Dosing in Craniosynostosis Surgery: A Systematic Review with Meta-analysis

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Objective: This study aimed to compare operative time, blood loss, and transfusion requirement in patients receiving a high tranexamic acid (TXA) dose of greater than 10 mg/kg versus those receiving a low dose of 10 mg/kg or less.
Methods: PubMed, Cochrane Central, and Embase were queried to perform a systematic review with meta-analysis. Studies reporting outcomes of TXA use in craniosynostosis surgery were included. TXA dosing, operative time, blood loss, and transfusion requirement were the primary outcomes studied. Other variables studied included age and types of craniosynostosis.
Results: In total, 398 individuals in the included articles received TXA for craniosynostosis surgery. TXA loading doses ranged from 10 mg/kg to 50 mg/kg. Overall, administration of TXA was not associated with changes in operative time, but was associated with decreased blood loss and transfusion requirement on meta-analysis. Comparison of high dose TXA (>10 mg/kg) versus low dose (10 mg/kg or less) showed no statistical differences in changes in operative time, blood loss, or transfusion requirement.
Conclusions: Overall, TXA reduced blood loss and transfusion requirement in patients undergoing surgery for craniosynostosis. There was no difference in outcomes between high dose and low dose regimens amongst those receiving TXA. Low dose TXA appears adequate to achieve clinical efficacy with a low adverse event rate. *(Plast Reconstr Surg Glob Open 2022;10:e4526; doi: 10.1097/GOX.0000000000004526; Published online 17 October 2022.)*

INTRODUCTION

Craniosynostosis affects approximately one in every 2000–3000 live births[1–3]; surgical treatment is curative. Although the approach varies by suture involvement and pathological severity, significant dissection and calvarial remodeling is often inevitable. Patient outcomes are associated with procedural,[4] biological,[5] and socioeconomic[6] factors. Despite improvements in patient selection, surgical technique, anesthesia, and multidisciplinary monitoring,[7,8] perioperative blood loss remains a significant source of morbidity and mortality; reported losses range from 20% to 500% of circulating volume.[9–12]

Consequences of perioperative blood loss and subsequent blood-product administration can be grave, from hemodynamic instability to transfusion-related reactions and their sequelae. As a result, recent studies have explored pharmacological interventions targeting various processes, including hematopoietic differentiation,[13] coagulation and fibrinolysis,[14–25] electrolyte and fluid homeostasis,[26] and combination therapy.[14]

Tranexamic acid (TXA) is an antifibrinolytic that has demonstrated particularly promising outcome improvements for patients undergoing surgery for craniosynostosis. However, TXA use may increase the risk of neurological complications, including seizures and cerebrovascular accidents.[27] Optimal dosing guidelines remain unclear due to heterogeneity across institutional protocols.[28] Given the variations in loading doses, maintenance doses, and infusion durations, we performed a meta-analysis stratifying by

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high dose (>10 mg/kg) versus low dose (<10 mg/kg) TXA to determine dosing effect on patient outcomes.

METHODS

This systematic review with meta-analysis was performed in accordance with guidelines provided by the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA)[29] and the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) checklist.[30]

Articles were included in this study if they met all of the following inclusion criteria:

1. TXA versus control (no TXA or saline)
2. TXA dosing parameter reported
3. Randomized controlled trial or retrospective chart review
4. Reported blood loss and transfusion data as outcomes

Studies and patients were excluded if they met one of the following exclusion criteria:

1. TXA not compared to a control group
2. TXA used, but vague data reported
3. Case reports, case series studies, systematic reviews
4. TXA dosing parameters not reported

Search Strategy

We queried the databases of PubMed, Cochrane Central, and Embase on June 3, 2020. Search terms used were "craniofacial synostosis" OR "cranial vault remodeling" AND "tranexamic acid." There were no limits on the year of publication. The search was re-done on January 13, 2021 to check for new articles since the original date of search. No new articles of interest had been published and the authors proceeded with the original search results.

Selection Process

One author (D.B.O), retrieved the articles by the search process described above. Microsoft Excel (Microsoft Inc, Redmond, Wash.) was used to collect, organize, and remove duplicate articles. Another author (S.V.) screened titles and abstracts to remove articles were not available in English or did not have accompanying full manuscripts. Two authors (S.V.) and (J.G.) independently screened the remaining articles for the inclusion and exclusion criteria. All articles included were published via traditional academic methods and were affiliated with academic institutions. The results of the screen were confirmed by a third reviewer (J.F.D).

Data Collection

Primary outcomes were operative time, blood loss, and blood transfusion. Operative time includes the reported time of the operation. Studies that included only anesthesia time were excluded from statistical analysis on operative time. Blood loss was defined as total blood loss corrected for body weight, and studies that only reported intraoperative or postoperative blood loss, or did not correct for body weight, were excluded from statistical analysis. Transfusion was measured as blood volume transfusion per body weight. Studies that reported only red blood cell transfusion or did not correct for weight were excluded from statistical analysis. High loading dose was defined as a dose greater than 10 mg/kg. Low loading dose was defined as 10 mg/kg or less. This data were collected by two authors (D.B.O, J.G.) and confirmed by a third (S.V.). Other outcomes of interest included demographics, overall clinical course, intensive care unit length of stay, and outcomes.

Takeaways

Question: Is low dose tranexamic acid effective at improving hemostasis during craniosynostosis surgery compared with that of a high dose regimen while minimizing adverse effects?

Findings: There was no difference in outcomes (blood loss and transfusion requirements) between the high and low dose regimens.

Meaning: Low dose (10 mg/kg) tranexamic acid regimens appear to achieve a similar clinical efficacy when compared with that of high dose (>10 mg/kg), with a low risk of adverse events.

Synthesis Methods, Effect Measures, and Statistical Analysis

Characteristics and outcomes were tabulated as seen in the tables. Variables of interest were extracted, organized, and pooled together to perform meta-analysis. Meta-analysis was run with 95% confidence limits on primary outcome data from articles with adequate quantitative data to acquire confidence intervals, *P* value, and create forest plots using a random effects model. Weights were calculated by using the inverse variance of effect estimates; more precise studies were given more weight. I2 = 0 suggests low heterogeneity. I2 less than I2 between 25% and 50%, and I2 greater than 50% were categorized as low, moderate, and high heterogeneity, respectively. Meta-analysis was done using "Comprehensive Meta Analysis v. 3.3.070" software. Categorical variables were evaluated using Fisher's exact or Pearson's chi-squared tests, as appropriate. The Shapiro-Wilk test was used to test for normal distribution of continuous variables, and normally distributed variables were compared using the Student *t*-test. Analysis on categorical and continuous variables was performed using SPSS (IBM SPSS Statistics for Windows, version 28.0; IBM Corp, Armonk, N.Y.).

Study Risk of Bias Assessment

Two reviewers (D.B.O.) and (S.V.) independently assessed the risk of bias using the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Case Series.[31] High risk was defined as answering yes for less than 50%. Moderate risk was an answer of yes for 50–69%, and low risk was 70% or greater (**See figure 1, Supplemental Digital Content 1,** which shows JBI Critical Appraisal Checklist for Case Series. **http://links.lww.com/PRSGO/C158**). Funnel plots were also created to represent publication bias (**See figure 2, Supplemental Digital Content 2,** which shows publication bias funnel plot of various studies. **http://links.lww.com/PRSGO/C159**).

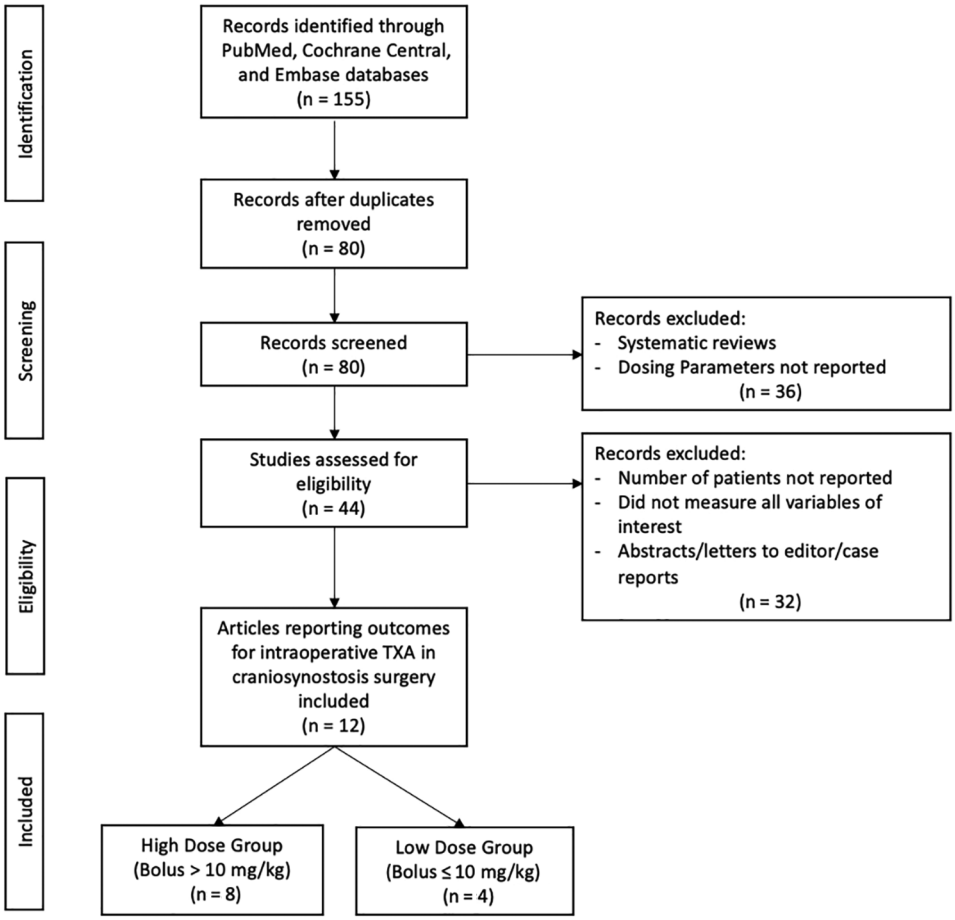

Figure 1. PRISMA flow diagram.

RESULTS

Study Characteristics and Results of Synthesis

Overview of Articles and Cohort Demographics

After applying inclusion and exclusion criteria, 12 articles were selected. All articles were published between 2011 and 2020. Four articles were double blind randomized controlled trials comparing the effects of TXA versus saline on blood loss or transfusion volume in craniosynostosis surgery. The range of enrolled patients in these trials was 30–48, with a range of 15–23 in the TXA groups. The remaining eight articles were retrospective studies analyzing the effects of TXA administration on outcomes in children undergoing surgery for craniosynostosis (Fig.1). Overall sample sizes ranged from 30 to 268, with 15 to 134 patients receiving TXA. The average age of patients receiving TXA was 10.42 months (±4.94). All studies stated an association between TXA and reduced blood loss or volume of transfusion. Main findings of each article are summarized in Table 1.

In the 12 articles, 398 individuals received TXA for craniosynostosis surgery. Of those, 117 were female, and the average or median age ranged from 5.9 to 23 months. Five studies describe the specific cranial anomalies being treated: plagiocephaly (n = 10), scaphocephaly (n = 81), trigonocephaly (n = 64), brachycephaly (n = 2), or complex craniosynostosis operations (n = 9).[23–24,27–28,31] Seven studies identified the sutures involved, including bicoronal (n = 29), unicoronal (n = 85), metopic (n = 173), sagittal (n = 293), lambdoid (n = 24), frontosphenoidal (n = 2), sphenoidal (n = 2), and multiple (n = 35).[15,22,24–26,28,30] wood). Only three of the studies identified syndromic patients (n = 19)[14,20,25] (Table 1).

TXA Protocol and Dosage

TXA loading doses were given before surgical incision or at the beginning of surgery, and ranged from 10 mg/kg to 50 mg/kg. Most studies proceeded with TXA administration intraoperatively, either 5 mg/kg/h or 10 mg/kg/h until closure.[15–17,19,21,22,24] Martin et al gave a loading dose of 30 mg/kg without additional administration.[18] On the other hand, Kurkin et al[23] administered 5 mg/kg/h for 24 hours, Fenger-Erikson et al[25] gave 3 mg/kg/h for 8 hours, and Wood et al[20] administered 10 mg/kg/h for 5 hours postoperatively. After an initial loading dose of 40 mg/kg and intraoperative doses of 10 mg/kg/h, Escher et al 2021 administered three doses of 10 mg/kg given every 8 hours postoperatively.[14]

Breakdown of dosage distribution among craniosynostosis subtypes is demonstrated in Figure 2.

Outcomes

Operative Time

Ten studies reported mean operative time in both TXA and nonTXA groups (Table 1). The mean reported operative

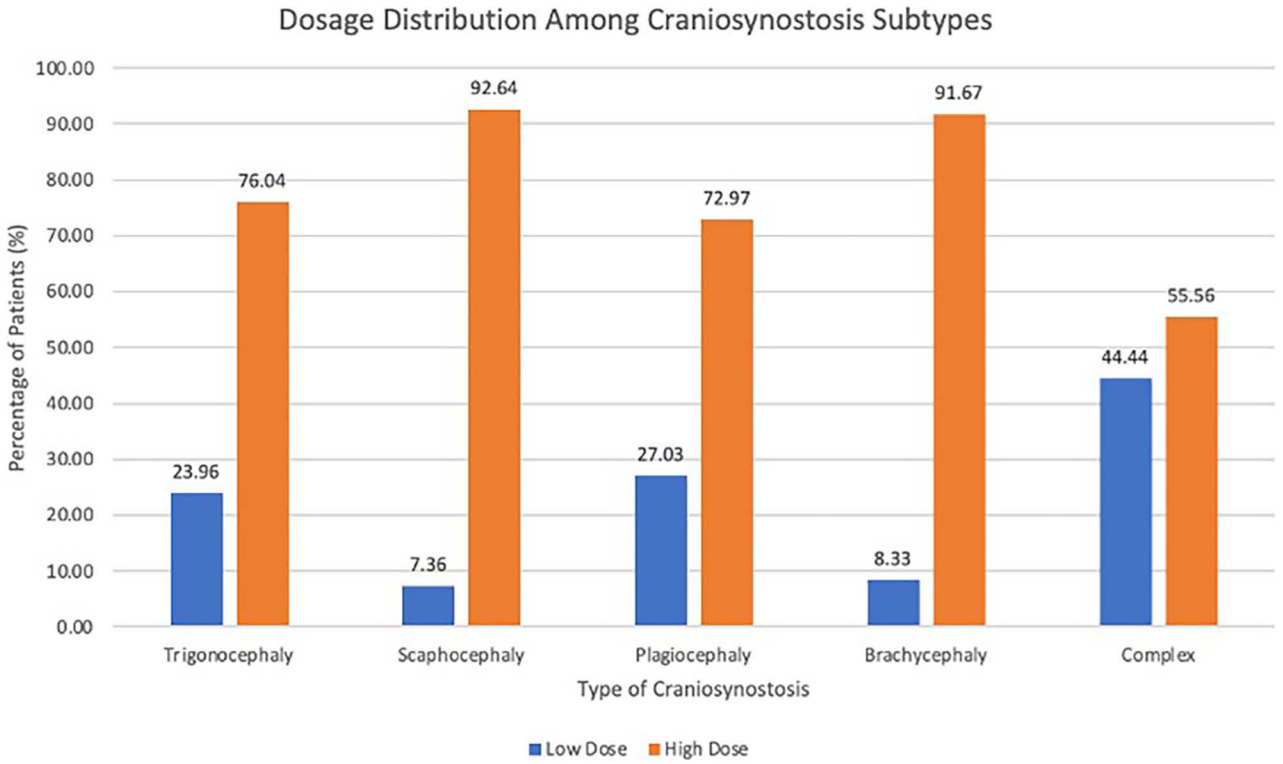

Figure 2. Dosage distribution among craniosynostosis subtypes.

time with TXA was 193.83 minutes (± 77.56 min).[14,15,18–25] NonTXA patients spent an average of 194.26 minutes (± 79.77 min) in the operating room.[14,15,18–25] The greatest decrease in operative time with TXA administration was seen in the study by Escher et al (32 min), with a protocol including a 40 mg/kg loading dose followed by 10 mg/kg/h until closure and 3 doses of 10 mg/kg every 8 hours postoperatively.[14] Crantford et al and Wood et al showed a difference of 12 minutes and 8 minutes, respectively, between TXA and nonTXA groups with a loading dose of 20 mg/kg followed by 10 mg/kg/h.[19,20] Kurnik et al showed a difference of 6 minutes between TXA and nonTXA with a loading dose of 10 mg/kg and 5 mg/kg/h for 24 hours.[23] No study showed significant differences in operative time on statistical analysis. On meta-analysis of pooled data, TXA was not significantly associated with decreased operative time (OR 0.87 95% CI 0.62–1.21 P = 0.397 I2 = 0 P = 0.113). (**See figure 3A, Supplemental Digital Content 3**, which shows the TXA operative time data. **http://links.lww.com/PRSGO/C160**.)

Blood Loss

Total blood loss was reported in 10 of the 12 articles[14,15,18–25] (Table 1). Of those, one article reported blood loss unadjusted for body weight,[14] and another article did not report SD of the mean.[19] The mean weight-adjusted blood loss reported was 37.31 ml/kg (± 28.21 mg/kg) for TXA patients and 56.08 ml/kg (± 41.70 ml/kg) for nonTXA patients.[15,16,20–25] All articles that reported adequate data reported less blood loss with TXA versus without TXA. The greatest decrease in blood loss was seen in Goobie (OR 0.14 95%CI 0.04–0.44 P = 0.001) and Fenger (OR 0.14 95%CI 0.04–0.58 P = 0.006) with protocols of 50 mg/kg with 5 mg/kg/h until closure and 10 mg/kg with 3 mg/kg/h for 8 hours, respectively. Meta-analysis of the eight studies showed a significant decrease in blood loss with TXA (OR 0.17 95%CI 0.06–0.48 P = 0.001 I2 = 0 P < 0.001). (**See figure 3B, Supplemental Digital Content 3**, which shows the TXA blood loss data. **http://links.lww.com/PRSGO/C160**.)

Blood Transfusion

Blood transfusion was reported in 10 of the 12 articles[15–19,21–25] and ranged from 7.2 ml/kg to 49.3 ml/kg. Eight of the 10 articles reported adequate data for statistical analysis.[15–17,21–25] The mean volume of blood transfused was 24.22 ml/kg (± 14.84) in patients receiving TXA and 50.98 ml/kg (± 40.71) in patients who did not receive TXA. All articles reported reduced volumes of transfusion in the TXA group compared with the nonTXA group. The greatest decrease in risk of transfusion was found in Kurnik (OR 0.22 95%CI (0.10–0.46) P = <.001 I2 = 86.8), with a protocol of 10 mg/kg followed by 5 mg/kg/h for 24 hours.[23] On meta-analysis of the eight articles, TXA was significantly associated with decreased volume of blood transfusion (OR 0.18 95%CI (0.06–0.54) P = 0.002 I2 = 86.8 P < 0.001) (**See figure 3C, Supplemental Digital Content 3**, which shows the TXA blood transfusion data. **http://links.lww.com/PRSGO/C160**.)

High versus Low Dose TXA

Patient Characteristics and Craniosynostosis Subtypes

312 patients received a high loading dose of greater than 10 mg/kg. Mean age of patients was 9.86 (± 5.68)

Table 1. Characteristics of Included Articles

Authors	Study Type	TXA Protocol	Craniosynostosis/Sutures	Operative Time (min)	Blood Loss (ml/kg)	Blood Transfusion Requirement (ml/kg)
High loading dose						
Goobie et al, 2011[15]	Randomized controlled trial	50 mg/kg 5 mg/kg/h until closure Placebo: 0.9% saline		TXA: 272 NonTXA: 252	TXA: 65 NonTXA: 119	TXA: 33 NonTXA: 56
Main finding: Patients receiving TXA had significantly reduced total blood loss and transfusion requirement. TXA and body weight were the only predictors of outcomes.						
Martin et al, 2016[16]	Retrospective chart review	50 mg/kg 5 mg/kg/h until closure	TXA: Coronal 9 Metopic 16 Sagittal 41 Lamboid 3 NonTXA: Coronal 27 Metopic 22 Sagittal 61 Lamboid 7 Frontosphenoid 1	TXA: 168* NonTXA: 180*	TXA: 26.3* NonTXA: 36.1*	TXA: 31.6* NonTXA: 41.8*
Main finding: TXA significantly reduced blood loss, transfusion volume, and length of stay.						
Ongun et al, 2020[17]	Retrospective Cohort	50 mg/kg 5 mg/kg/h until closure	TXA: Scaphocephaly 7 Trigonocephaly 9 Brachycephaly 1 NonTXA: Plagiocephaly , scaphocephaly 7 Trigonocephaly 8 Brachycephaly 1	TXA: 240* NonTXA: 240*		TXA: 9.02 NonTXA: 11.55
Main finding: Delivering TXA was associated with fewer blood transfusion volumes and better metabolic outcomes.						
Escher et al, 2021[14]	Retrospective cohort	40 mg/kg 10 mg/kg/h until closure 3×10 mg/kg/dose every 8 h postoperative	TXA: Bicoronal 4 Unicoronal 2 Metopic 9 NonTXA: Bicoronal 2 Unicoronal 9 Metopic 10	TXA: 263 NonTXA: 295	TXA: 191 NonTXA: 230	
Main Finding: TXA protocol was associated with lower rates of transfusion and lower transfusion volume.						
Martin et al, 2015[18]	Retrospective chart review	30 mg/kg	TXA: Scaphocephaly 14 NonTXA: Scaphocephaly 14	TXA: 222.8 NonTXA: 198		TXA: 49.3* NonTXA: 99.3*
Main finding: TXA reduced transfusion volume.						
Crantford et al, 2015[19]	Retrospective case series	20 mg/kg 10 mg/kg/h until closure	TXA: Bicoronal 5 Unicoronal 5 Metopic 4 Sagittal 2 Multiple 1 NonTXA: Bicoronal 4 Unicoronal 3 Metopic 7 Sagittal 3 Multiple 2	TXA: 281 NonTXA: 293	TXA: 9.4 NonTXA: 21.1	TXA: 12.8 NonTXA: 31.3

(Continued)

Table 1. Continued

Authors	Study Type	TXA Protocol	Craniosynostosis/Sutures	Operative Time (min)	Blood Loss (ml/kg)	Blood Transfusion Requirement (ml/kg)
Main finding: TXA group had significantly reduced perioperative blood loss and average blood transfusion volume.						
Wood et al, 2020[20]	Retrospective cohort	20 mg/kg 10 mg/kg/h until 5 h postop	TXA: Bicoronal 3 Unicoronal 14 Metopic 33 Sagittal 71 Multiple 8 Lamboid 2 Sphenoidal 2 Syndromic 1 NonTXA: Bicoronal 6 Unicoronal 9 Metopic 37 Sagittal 72 Multiple 10 Lamboid 7 Frontosphenoid 1 Syndromic 3	TXA: 67.3 NonTXA: 75.3	TXA: 6.6 NonTX: 24.8	
Main finding: Overall blood loss, operative times, and transfusion rate were reduced with TXA administration.						
Dadure et al, 2011[21]	Randomized controlled trial	15 mg/kg over 15 minutes 10 mg/kg/h until closure Placebo: 0.9% saline	TXA: Scaphocephaly 16 Trigonocephaly 2 Complex 1 NonTXA: Plagiocephaly 2 Scaphocephaly 14 Trigonocephaly 4	TXA: 110.2 NonTXA: 104.7	TXA: 64 NonTXA: 76	TXA: 7.2 NonTXA: 16.6
Main finding: TXA patients had less perioperative blood loss and required less blood transfusion than nonTXA patients. Low loading dose						
Engel et al, 2015[22]	Retrospective cohort study	10 mg/kg 5 mg/kg/h until closure	TXA: Trigonocephaly 17 NonTXA: Trigonocephaly 16	TXA: 132 NonTXA: 130	TXA: 19.1 NonTXA: 22.3	TXA: 27.9 NonTXA: 31.3
Main finding: There were no major complications associated with TXA. TXA reduced blood loss, transfusion volume, and hospital length of stay.						
Kurnik et al, 2017[23]	Retrospective chart review	10 mg/kg 5 mg/kg/h for 24 h	Open calvarial vault remodeling, anterior only	TXA: 187 NonTXA: 193	TXA: 25.9 NonTXA: 34.8	TXA: 28 NonTXA: 44.3
Main finding: TXA significantly reduced total transfusion volume and numbers of postoperative transfusions, blood loss, and ICU length of stay for open calvarial vault remodeling and anterior vault surgery.						
Kim et al, 2018[24]	Randomized controlled trial	10 mg/kg 5 mg/kg/h until closure Placebo: normal saline	TXA: Bicoronal 2 Unicoronal 5 Metopic 2 Sagittal 8 Multiple 4 Lamboid 2 NonTXA: Bicoronal 3 Unicoronal 2 Sagittal 7 Multiple 10 Lamboid 3	TXA: 264 NonTXA: 262.2	TXA: 80.6 NonTXA: 115.6	TXA: 48.8 NonTXA: 65.2

(Continued)

Table 1. Continued

Authors	Study Type	TXA Protocol	Craniosynostosis/Sutures	Operative Time (min)	Blood Loss (ml/kg)	Blood Transfusion Requirement (ml/kg)
Main finding: Patients receiving TXA had significantly less blood loss, fewer transfusions, and fewer complications.						
Fenger-Erikson et al, 2019[25]	Randomized controlled trial	10 mg/kg 3 mg/kg/h for 8 h Placebo: isotonic saline	TXA: Pagiocephaly 3 Scaphocephaly 4 Trigonocephaly 4 Complex 4 NonTXA: Plagiocephaly 2 Scaphocephaly 5, trigonocephaly 4 Complex 4	TXA: 139 NonTXA: 139	TXA: 11* NonTXA: 20	TXA: 8.2 NonTXA: 141.1
Main finding: Intraoperative and postoperative TXA reduced postoperative and overall blood loss and transfusion requirements.						

All data reported as mean unless indicated with "*" to signify median.

months in the high dose group, and 11.55 (± 3.42) months in the low dose group. This difference was not statistically significant ($P = 0.634$).

Amongst scaphocephaly patients receiving TXA, 92.64% received high dose TXA. The next largest proportion of high dose TXA was seen in patients with brachycephaly (91.67%). Those with trigonocephaly and plagiocephaly had similar distributions of high dose TXA (76.04%, 72.97%, respectively). Of patients with multiple suture craniosynostosis receiving TXA, 55.56% received high dose. (**See figure 3, Supplemental Digital Content 3**, which shows the TXA data. **http://links.lww.com/PRSGO/C160**.)

Outcomes

Mean operative time in those receiving a high loading dose was 202.72 minutes (± 91.50), compared with 180.50 minutes (± 60.80) for those receiving a low dose. Blood loss was higher in those receiving a high dose (40.48 ml/kg (± 28.89)) versus those receiving a low dose (34.15 (± 31.56)). Volume of blood transfused averaged 23.82 ml/kg (± 16.79) for patients receiving high dose TXA versus 28.23 ml/kg (± 16.58) in the low dose group. There were no statistically significant differences in operative time, blood loss, or transfusion volume between the two groups (Table 2).

Risk of Bias in the Studies

Due to the variety of studies included in this systematic review, assessment of bias was difficult to ascertain. Across studies, blood loss was measured by estimation, which is inherently inaccurate as it can under approximate the amount. Few studies used calculated blood loss, which is a more accurate representation. The variation in fused sutures included in each paper also contributes to bias because some sutures may be more complex to correct surgically, leading to differences in blood loss, surgical duration, and transfusion requirements between cases.

Two reviewers (D.B.O., S.V.) assessed bias using the JBI Critical Appraisal Checklist for Systematic Reviews.[31] Studies were deemed high risk if they scored less than 5. Moderate risk was a score of 5–7. Low risk studies received a score of 8 or above. All studies scored a low risk score on the JBI Critical Appraisal Checklist for Systematic Reviews. Funnel plot analysis showed varying degrees of asymmetry, suggesting publication bias cannot be ruled out. Breakdown of dosage distributed among craniosynostosis subtypes is demonstrated in Figure 2.

Table 2. Difference of Means with TXA Dose > 10 mg/kg

	TXA dose > 10 mg/kg	TXA dose < /= 10 mg/kg	*P* value
OpTime*	202.72 (± 91.50)	180.50 (± 60.80)	0.683
Blood loss†	40.48 (± 28.89)	34.15 (± 31.56)	0.777
Transfusion‡	23.82 (± 16.79)	28.23 (± 16.58)	0.694

*Out of 10 articles (High Dose (n = 222): Dadure, Goobie, Crantford, Martin15, Escher, Wood; Low Dose (n = 90): Engel, Kurnik, Kim, Fenger).
†Out of 8 articles (High Dose (n = 245): Dadure, Goobie, Martin16, Wood; Low Dose (n = 90): Engel, Kurnik, Kim, Fenger).
‡Out of 10 articles (High Dose (n = 159): Dadure, Goobie, Crantford, Martin15, Martin16, Ongun; Low Dose (n = 90): Engel, Kurnik, Kim, Fenger).

Table 3. Craniosynostosis Types Separated by Dosing

Author	TXA	TXA Craniosynostosis	TXA Sutures	Control	Control Craniosynostosis	Control Sutures
High loading dose						
Goobie et al, 2011[15]	n = 23	N/A	N/A	n = 20	N/A	N/A
Martin et al, 2016[16]	n = 69	N/A	Coronal: n = 09 Metopic: n = 16 Sagittal n = 41 Multiple n = 0 Lambdoid n = 3 Frontosphenoidal: n = 0 Sphenoidal n = 0	n = 118	Coronal: n = 27 Metopic: n = 22 Sagittal n = 61 Multiple n = 0 Lambdoid n = 7 Frontosphenoidal: n = 1 Sphenoidal n = 0	Bicoronal: n = 0 Unicoronal: n = 9 Metopic: n = 16 Sagittal n = 41 Multiple n = 0 Lambdoid n = 3 Frontosphenoidal: n = 0 Sphenoidal n = 0
Ongun et al, 2020[17]	n = 17	Plagiocephaly: n = 0 Scaphocephaly: n = 7 Trigonocephaly: n = 9 Brachycephaly: n = 1 Complex: n = 0	N/A	n = 19	Plagiocephaly: n = 3 Scaphocephaly: n = 7 Trigonocephaly: n = 8 Brachycephaly: n = 1 Complex: n = 0	N/A
Escher et al, 2021[14]	n = 15 (syndromic n = 4)	N/A	Bicoronal: n = 4 Unicoronal: n = 2 Metopic: n = 9 Sagittal n = 0 Multiple n = 0 Lambdoid n = 0 Frontosphenoidal: n = 0 Sphenoidal n = 0	n = 21 (syndromic n = 3)	N/A	Bicoronal: n = 2 Unicoronal: n = 9 Metopic: n = 10 Sagittal n = 0 Multiple n = 0 Lambdoid n = 0 Frontosphenoidal: n = 0 Sphenoidal n = 0
Martin et al, 2015[18]	n = 14	Plagiocephaly: n = 0 Scaphocephaly: n = 14 Trigonocephaly: n = 0 Brachycephaly: n = 0 Complex: n = 0	Bicoronal: n = 0 Unicoronal: n = 0 Metopic: n = 0 Sagittal n = 14 Multiple n = 0 Lambdoid n = 0 Frontosphenoidal: n = 0 Sphenoidal n = 0	n = 14	Plagiocephaly: n = 0 Scaphocephaly: n = 14 Trigonocephaly: n = 0 Brachycephaly: n = 0 Complex: n = 0	Bicoronal: n = 0 Unicoronal: n = 0 Metopic: n = 0 Sagittal n = 14 Multiple n = 0 Lambdoid n = 0 Frontosphenoidal: n = 0 Sphenoidal n = 0
Crantford et al, 2015[19]	n = 17	N/A	Bicoronal: n = 5 Unicoronal: n = 5 Metopic: n = 4 Sagittal n = 2 Multiple n = 1 Lambdoid n = 0 Frontosphenoidal: n = 0 Sphenoidal n = 0	n = 20	N/A	Bicoronal: n = 4 Unicoronal: n = 3 Metopic: n = 7 Sagittal n = 3 Multiple n = 2 Lambdoid n = 0 Frontosphenoidal: n = 0 Sphenoidal n = 0
Wood et al, 2020[20]	n = 134	N/A	Bicoronal: n = 3 Unicoronal: n = 14 Metopic: n = 33 Sagittal n = 71 Multiple n = 8 Lambdoid n = 2 Frontosphenoidal: n = 0 Sphenoidal n = 2	n = 145	N/A	Bicoronal: n = 6 Unicoronal: n = 9 Metopic: n = 37 Sagittal n = 72 Multiple n = 10 Lambdoid n = 7 Frontosphenoidal: n = 1 Sphenoidal n = 0
Dadure et al, 2011[21]	n = 19	Plagiocephaly: n = 0 Scaphocephaly: n = 16 Trigonocephaly: n = 2 Brachycephaly: n = 0 Complex: n = 1	N/A	n = 20	Plagiocephaly: n = 2 Scaphocephaly: n = 14 Trigonocephaly: n = 4 Brachycephaly: n = 0 Complex: n = 0	N/A

(Continued)

Table 3. Continued

Author	TXA	TXA Craniosynostosis	TXA Sutures	Control	Control Craniosynostosis	Control Sutures
Low loading dose						
Engel et al, 2015[22]	n = 17	Plagiocephaly: n = 0	Bicoronal: n = 0	n = 16	Plagiocephaly: n = 0	Bicoronal: n = 0
		Scaphocephaly: n = 0	Unicoronal: n = 0		Scaphocephaly: n = 0	Unicoronal: n = 0
		Trigonocephaly: n = 17	Metopic: n = 17		Trigonocephaly: n = 16	Metopic: n = 16
		Brachycephaly: n = 0	Sagittal n = 0		Brachycephaly: n = 0	Sagittal n = 0
		Complex: n = 0	Multiple n = 0		Complex: n = 0	Multiple n = 0
			Lambdoid n = 0			Lambdoid n = 0
			Frontosphenoidal: n = 0			Frontosphenoidal: n = 0
			Sphenoidal n = 0			Sphenoidal n = 0
Kurnik et al, 2017[23]	n = 35 (includes syndromic)	N/A	N/A	n = 79 (includes syndromic)	N/A	N/A
Kim et al, 2018[24]	n = 23	N/A	Bicoronal: n = 2	n = 25	N/A	Bicoronal: n = 3
			Unicoronal: n = 5			Unicoronal: n = 2
			Metopic: n = 2			Metopic: n = 0
			Sagittal n = 8			Sagittal n = 7
			Multiple n = 4			Multiple n = 10
			Lambdoid n = 2			Lambdoid n = 3
			Frontosphenoidal: n = 0			Frontosphenoidal: n = 0
			Sphenoidal n = 0			Sphenoidal n = 0
Fenger-Erikson et al, 2019[25]	n = 15	Plagiocephaly: n = 3	N/A	n = 15	Plagiocephaly: n = 2	N/A
	(syndromic n = 4)	Scaphocephaly: n = 4		(syndromic n = 4)	Scaphocephaly: n = 5	
		Trigonocephaly: n = 4			Trigonocephaly: n = 4	
		Brachycephaly: n = 0			Brachycephaly: n = 0	
		Complex: n = 4			Complex: n = 4	

DISCUSSION

Low versus High-dose Findings

Analysis of the included studies in this systematic review and meta-analysis revealed no differences in mean operative time, and blood loss or transfusion volume between high and low dose TXA. Average age in patients receiving high dose tended to be younger than those receiving low dose, but there was no statistically significant difference. This finding may represent patient selection favoring higher dose regimens for younger patients because of comparatively lower tolerance for blood loss before hemodynamic collapse.[32] This age selection is further supported by the higher incidence of high dose TXA used in patients with scaphocephaly and brachycephaly.[32] Furthermore, patients with complex repairs involving multiple sutures are known to be older and had the highest proportion of low dose TXA in our study.[32] However, the absence of statistical significance of these findings suggests the choice of protocol is not independently associated with the studied outcomes.

Pharmacokinetics

Low Dose

Kim et al, Engel et al, and Kurnik et al utilized a protocol of 10 mg/kg bolus with a 5 mg/kg/h maintenance.[22-24] These studies cite Goobie et al (2011 and 2013) as the rationale for the lower dose protocol. Through pharmacokinetic simulations, Goobie et al predicted an optimal loading dose of 10 mg/kg followed by 5 mg/kg/h because this produced steady-state TXA concentrations over the therapeutic threshold of 16 microgram/ml.[33] These plasma concentrations resulted in the same range of blood volume loss, possibly suggesting a threshold dose-response relationship.[33] Additionally, a recent study demonstrated adequate steady-state TXA concentrations with a loading dose of 10 mg/kg with a maintenance dose of 5 mg/kg/h.[19] Together, these findings suggest that a low dose of 10 mg/kg is adequate to receive clinical benefit.

High Dose

In the 2011 article, Goobie suggests that their choice of 50 mg/kg bolus followed by 5 mg/kg/h was arguably high because they saw peak plasma concentrations at four to 20 times greater than the expected therapeutic concentration.[15] However, a study exploring pharmacokinetics of TXA in young patients found that dosage required to maintain desired serum concentration changed between 2 and 12 months of age, with younger children requiring higher doses (12 mg/kg).[34] This is consistent with our study, as patients receiving a high dose tended to be younger than those receiving a low dose.

Clinical Outcomes

Low Dose

Kurnik et al had no adverse events and maintained higher hemoglobin and hematocrit levels throughout the surgery and hospital course. Fenger-Erikson et al used the lowest dosing protocol out of all included studies

and reported significantly reduced blood loss and transfusions.[25] Our findings are consistent with the literature showing that TXA loading dose of 10 mg/kg is not less effective than a dose of 50 mg/kg in reducing blood loss and transfusion in pediatric craniosynostosis surgery.[33]

High Dose

High dose TXA did not provide statistically significant decreased blood loss or transfusion when compared to low dose TXA. However, adverse events were reported with high dose TXA. Ongun et al observed seizures in two children, which is consistent with studies showing increased risk of seizure in a number of pediatric populations.[17,35–37] Of note, Ongun used a protocol of 50 mg/kg TXA. In a study by Escher et al, one patient had transient neutropenia and another had intraoperative and postoperative arrhythmias; both patients received 30 mg/kg of TXA.[14] Studies using doses of 15 mg/kg or 20 mg/kg did not report adverse events. As discussed in terms of pharmacokinetics, patient characteristics are of importance when weighing risks and benefits of TXA. For example, a study comparing minimally invasive versus open surgery for craniosynostosis used a dose of 100 mg/kg and reported no adverse events.[38] However, this study focuses on minimally invasive procedures which pose less overall risk, and any analysis on outcomes of open procedures did not reach statistical significance.[38] Another study analyzing TXA in pediatric scoliosis surgery patients concludes that high dose (50 mg/kg) TXA was more effective than low dose (10 mg/kg) in reducing blood loss and transfusion.[39] In that article, the population studied was markedly older than the population in our cohort. Therefore, although it may be safe and effective in certain populations or for certain indications, it may still pose an increased risk for adverse events in very young patients undergoing craniosynostosis surgery.

Previous studies have found similar results in various procedures showing the effects of TXA in improving hemostasis.[40–43] In this study, low dose TXA demonstrates lower rates of complications and provides efficacy for hemostasis during craniosynostosis surgery. However, at this time, further research is required to reduce the uncertainty given study heterogeneity for recommendations to be provided.

Limitations and Future Directions

Since some of the included studies were retrospective in nature, confounding factors cannot be ruled out. Many studies had a relatively small sample size and individual patient characteristics were not specified, limiting the specificity of the results. Additionally, the generalizability may be limited due to heterogeneity of studies. Publication bias is inherent to meta-analysis and may skew the results. Further prospective investigation of dosing strategy is required to assess efficacy and safety of TXA dosing in patients undergoing surgery for craniosynostosis.

CONCLUSIONS

The use of TXA reduced blood loss and transfusion requirement in patients undergoing surgery for craniosynostosis. Among patients receiving TXA, there was no difference in outcomes between high dose and low dose regimens. Low dose TXA appears adequate to achieve clinical efficacy with a low adverse event rate.

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