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Effect of Tranexamic Acid on the Reduction of Blood Loss in Craniosynostosis Surgery: A Systematic Review and Meta-analysis

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Background: Although many published studies have investigated the benefits of tranexamic acid (TXA) in reducing perioperative bleeding, no large meta-analysis has been conducted to demonstrate its overall benefit.
Methods: A systematic review was performed by following the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines. PubMed, Cochrane, Ovid, Embase, Web of Science, ClinicalTraisl.Gov, and Scopus databases were searched for articles reporting the benefit of TXA in reducing perioperative bleeding in craniosynostosis surgery from establishment through October 2022. The results of our meta-analysis were pooled across the studies using a random-effects model, and presented as a weighted mean difference with 95% confidence interval (95% CI).
Results: The database search yielded 3207 articles, of which 27 studies with a corresponding number of 9696 operations were eligible. The meta-analysis included only 18 studies, accounting for 1564 operations. Of those operations, 882 patients received systemic TXA, whereas 682 patients received placebo (normal saline), no intervention, low dose TXA, or other control substances. This meta-analysis demonstrated a significant beneficial effect of TXA in reducing perioperative bleeding, particularly when compared with other controlled substances, with a weighted mean difference of −3.97 (95% CI = −5.29 to −2.28).
Conclusions: To our knowledge, this is the largest meta-analysis in the literature investigating the benefit of TXA in reducing perioperative blood loss in craniosynostosis surgery. We encourage implementing TXA-protocol systems in hospitals after the appraisal of the data presented in this study. *(Plast Reconstr Surg Glob Open 2023; 11:e5021; doi: 10.1097/GOX.0000000000005021; Published online 27 June 2023.)*

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INTRODUCTION

Blood loss is an essential factor that needs to be monitored and minimized in every surgery. It represents a potential cause of significant morbidity and mortality in craniosynostosis surgery (CS).[1] Particularly, patients undergoing CS require blood transfusions to replace the blood that is lost.[2] Current techniques, particularly calvarial vault remodeling, are associated with complication rates as high as 16.5%, and more than 80% of patients eventually require blood transfusions.[3]

New diagnostic tools or adaptations in surgical techniques for treating patients with craniosynostosis have been reported in the literature. Novel approaches to reduce major blood loss include preoperative erythropoietin,

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intraoperative cell salvage, acute normovolemic hemodilution, antifibrinolytic drugs, fibrin sealants or fibrin glue, postoperative drain reinfusion, and preoperative autologous donation.[4]

Recent studies have shown that the utilization of antifibrinolytic agents, such as tranexamic acid (TXA), has significantly reduced blood loss in CS and, consequently, has reduced the need for blood transfusions.[5] TXA is a synthetic lysine derivative with antifibrinolytic effects, reducing blood loss in multiple operations, including craniosynostosis repair.[6]

As this protocol became widely applied in clinical practice, multiple articles have been published on this topic. Despite that, protocols still vary, and not every institution implements the use of TXA due to the feared potential complications.

Given this unmet standardization in clinical practice, a comprehensive systematic review was performed. Despite the presence of multiple published systematic reviews evaluating the safety and efficacy of TXA in CS, they all had a modest sample size and a limited number of included studies, necessitating additional research in this area.

Hence, we performed a comprehensive review of the published literature to meta-analyze the available data regarding the effects of TXA in reducing blood loss during CS.

Takeaways

Question: Does tranexamic acid reduce blood loss during craniosynostosis surgery?

Findings: This meta-analysis of over 1500 operations demonstrated a significant beneficial effect of tranexamic acid in reducing perioperative bleeding. Particularly when compared with other controlled substances with a weighted mean difference of −3.97 (95% CI = −5.29 to −2.28, $P < 0.00001$).

Meaning: We encourage implementing tranexamic acid-protocol systems in the hospitals after the appraisal of the data presented in this study.

METHODOLOGY

Material and Methods

This systematic review was performed by following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines searching multiple databases: PubMed, Embase, Ovid, Cochrane library and Google Scholar. No ethical approval was required because this review only included publicly available data.

Study Selection

Two reviewers (N.O. and L.A.) independently performed a query of the five different online databases from establishment through October 2022. Search terms included "craniosynostosis" OR "spring cranioplasty" OR "fronto-orbital remodeling" OR "posterior vault expansion" OR "cranial vault reconstruction" AND "tranexamic acid" OR "TXA." Duplicates were removed using Rayyan software. The articles were screened based on both titles and abstracts to remove articles that were not relevant, not in English, or their full-texts were not available. Secondary screening was carried out to thoroughly evaluate the extracted full texts for the inclusion and exclusion criteria. The senior author resolved any disagreement. The PRISMA flow chart is depicted in Figure 1.

Selection Criteria

The inclusion criteria for our meta-analysis were (1) randomized controlled trials; (2) comparative studies; and (3) studies that reported safety of TXA in CS or possible adverse effects and outcomes in terms of blood loss and transfusion requirement. Our study mainly included children because CS is limited to this age group, and other demographics were not manipulated.

We did not restrict our study to the number of participants, follow-up time, type of surgery performed to treat craniosynostosis, or the usage of other antifibrinolytics alongside TXA. As for our exclusion criteria, we excluded (1) case reports; (2) systematic reviews; (3) meta-analysis; (4) letters to the editor; and (5) case series. Other studies were excluded if they presented missing data (such as not reporting the means and standard deviations of blood loss quantities) or if access to the full text was limited.

Data Extraction

Data extraction was performed by all team members and further checked by the senior author for accuracy. The extracted variables included sample characteristics (eg, age), control-substance administered (if applicable), TXA transfusion volume, estimated blood loss, and TXA-related adverse outcomes; these variables were presented in tables.

Quality of Evidence

The quality of evidence of the included studies was assessed using two main tools: Jadad five-point scale for the clinical trials, and the retrospective cohort studies were assessed using the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) 22-point checklist. The first author (A.Q.) completed the quality assessments. The assessments are presented in Tables 1 and 2.

Statistical Analysis

Software Utilized

All analyses were conducted using RevMan (version 5.4.1; Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2020).

Weighted Analysis

The data extracted from the studies to estimate the weighted mean difference were as follows: (1) the mean and standard deviation of blood loss in the tranexamic acid arm, (2) the mean and standard deviation of blood

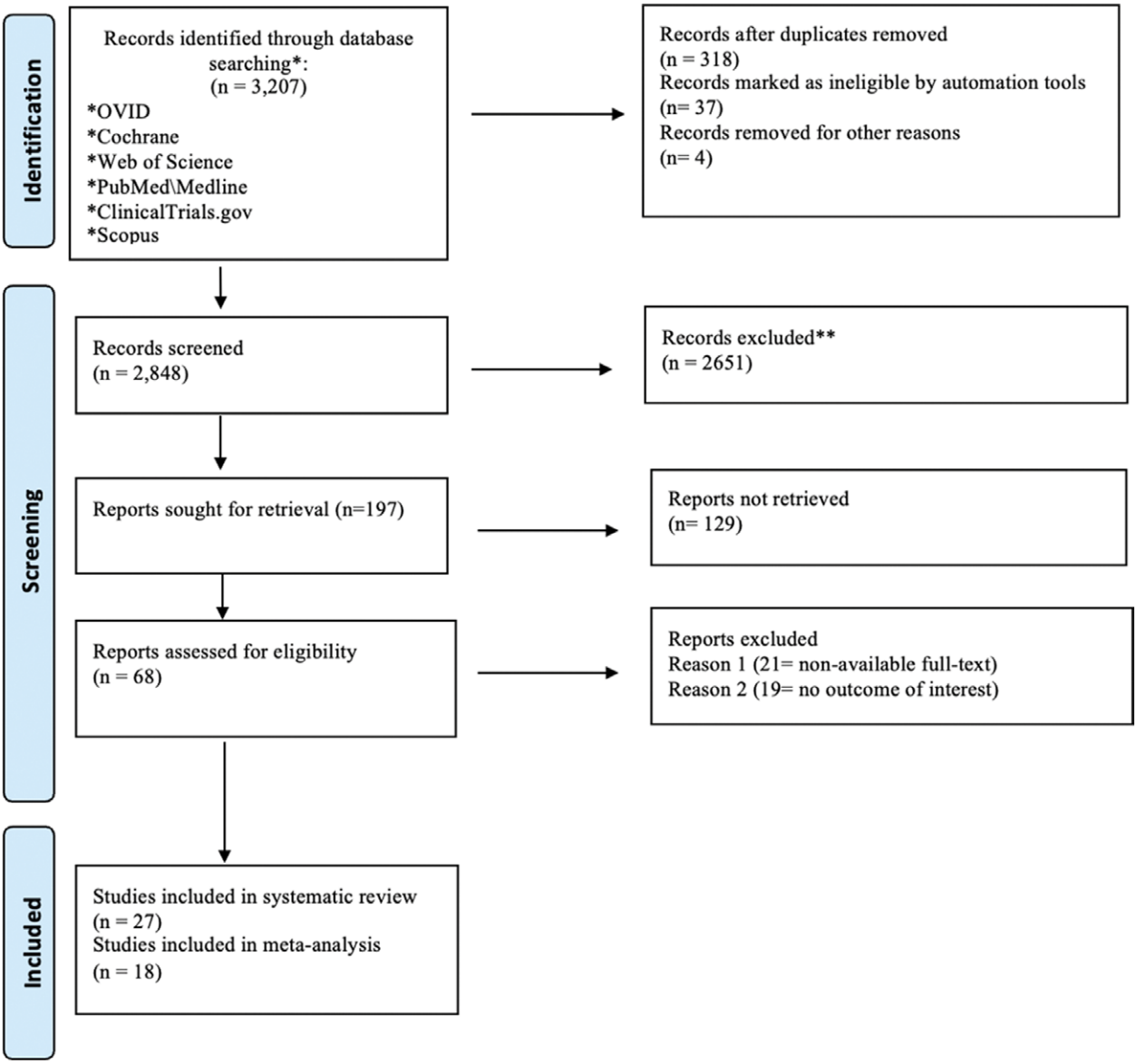

Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-analyses flow chart.

Table 1. Quality of Evidence of the Included Randomized Controlled Trial

Author	Study Design	Jadad Score	Assessment of Quality
Goobie et al 2020[15]	RCT	5	High
Dadure et al 2011[16]	RCT	5	High
Goobie 2011[17]	RCT	4	High
Kim et al 2018[14]	RCT	5	High
Goobie et al 2018[18]	RCT	4	High
Ebrahim Sultani et al 2022[19]	RCT	4	High
Fenger-Ekirsen et al 2020[20]	RCT	4	High
Fenger-Ekirsen et al. 2019[21]	RCT	3	High

RCT: Randomized controlled trial.

loss in the nontranexamic acid arm, and (3) the sample size in each arm.

These variables were entered into RevMan (version 5.4.1; Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2020), and the pooled data from the studies were classified as a "continuous" type of data. Furthermore, "inverse variance" was used as the statistical method, "random effects" as the analysis model,

Table 2. Quality of Evidence of the Included Retrospective Cohort Study

Author	Study Design	STROBE Score	Assessment of Quality
Ongun et al, 2020[10]	R COH	19	High
Wood et al, 2020[22]	R COH	19	High
Kurnik et al, 2017[23]	R COH	20	High
Engel et al, 2015[24]	R COH	19	High
Escher et al, 2020[25]	R COH	21	High
Martin et al, 2015[26]	R COH	20	High
Escher et al, 2019[27]	R COH	20	High
Crantford et al, 2015[28]	R COH	19	High
Hansen et al, 2017[29]	R COH	19	High
Borst et al. 2021[30]	R COH	18	High
Varidel et al, 2021[31]	R COH	19	High
King et al, 2022[32]	R COH	19	High
Borst et al, 2020[33]	R COH	20	High
Danforth et al, 2020[34]	R COH	20	High
Maugans TA et al, 2011[35]	R COH	22	High
Kurnik NM et al, 2018[36]	R COH	20	High
Martin et al, 2016[37]	R COH	19	High

R COH: retrospective cohort study.

and "mean difference" as the effect measure. The analysis details were as follows: (1) Totals and subtotals were extracted with a 95% study confidence interval and 95% total confidence interval, and (2) Forest plots were created to evaluate the results of pooling. A P value less than 0.05 was considered significant; Heterogeneity between studies was assessed using the Higgin I^2 test, according to the Cochrane Handbook.

RESULTS

This systematic review and meta-analysis included a total of 27 studies, all demonstrating high-quality evidence in the assessment scoring; these trials provided data from more than 9000 operations. The authors analyzed the data to determine the efficacy of TXA in reducing perioperative bleeding.

The meta-analysis included only 18 studies, accounting for 1564 operations. Of those, 882 patients received TXA, whereas 682 received a placebo (normal saline), no intervention, low dose TXA, or other control substances. Furthermore, most studies reported no complications associated with TXA administration; however, few studies reported adverse events such as hematological complications, seizures, and others. In addition, four studies utilized a high-dosing protocol, eight utilized a low-dosing protocol, and five did not accurately report their dosing protocol; the average pooled initial dosing of TXA utilized in the studies was 28.35 kg. More details about the baseline characteristics of the included trials are presented in Supplemental Digital Content 1. (**See table, Supplemental Digital Content 1**, which shows baseline characteristics of the included studies. **http://links.lww.com/PRSGO/C576**).

The Overall Result of the Meta-analysis

The meta-analysis of over 1500 operations demonstrated a significant benefit of TXA in reducing perioperative bleeding (Fig. 2) compared with other controlled substances, with a weighted mean difference of −3.97 (95% CI = −5.29 to −2.28, $P < 0.00001$).

DISCUSSION

This study aimed to reach a consensus about the potential effect of TXA in reducing bleeding in CS to improve the current guidelines of this invasive intervention. We reviewed a total of 27 studies that reported data from 9696 operations; of those, only 18 trials were included in our meta-analysis. We found that TXA significantly reduced perioperative bleeding, compared with other control substances, such as normal saline or with no intervention.

Moreover, the review showed that TXA is a safe and tolerable substance for patients, as only a few overall complications were reported in the literature. Furthermore, the most frequent adverse responses observed are orthostatic reactions, diarrhea, and nausea.[7] According to studies, there is probably no elevated risk of thrombogenicity with TXA.[8] Although infrequent, some papers have documented hypersensitivity reactions.[9] Additionally, cranial vault surgery has been linked to seizures regardless of TXA or any other fibrinolytic use.[10]

The optimal TXA dose, as proposed by Kim et al, Engel et al, and Kurnik et al, is a 10 mg/kg bolus with 5 mg/kg maintenance.[11–13] When compared with the high dose (50 mg/kg bolus and 5 mg/kg maintenance), it is not less effective in reducing blood loss in CS and is not associated with as many adverse events as the high dose.[14,15] Our pooled analysis, however, has estimated that the averagely used TXA dose is 28.35 mg/kg. Nonetheless, studies using other high-dosing protocols of 15–20 mg/kg did not report any side effects intra- and postoperatively.[38]

With an incidence rate of one in every 2500 new births, craniosynostosis is a pediatric disease in which one or more cranial sutures prematurely fuse, resulting in abnormal

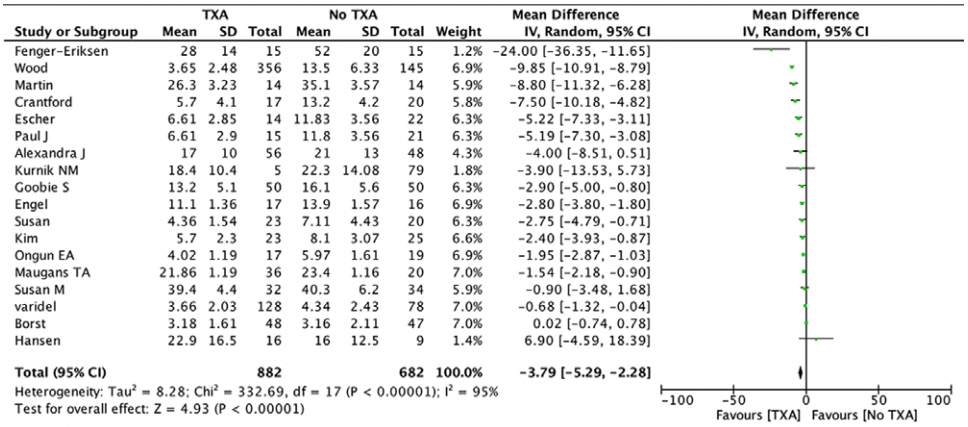

Fig. 2. The effect of tranexamic acid on the reduction of blood loss in craniosynostosis surgery (total of 1,564 operations).

cranial vault development. Although surgical correction is a common procedure, it remains complex and carries inherent risks to the patients.[39–41]

Efforts have been reported to develop protocols to improve patient care and postoperative outcomes. Many trials have examined the benefits of TXA in reducing perioperative bleeding, and almost all showed beneficial outcomes.[38]

Song et al reviewed only four trials investigating the overall benefit of administering TXA in CS.[42] Their study result showed a statistically significant reduction in packed red blood cell transfusion volumes in patients receiving systemic TXA, but no difference was noted in blood loss reduction. Alistair et al published another meta-analysis that included more trials and much more extensive data to examine the benefits of perioperative administration of TXA. They pooled their data from only seven trials, which account for 395 operations. They found a clear reduction in blood loss in patients receiving systemic TXA. However, their pooled data needed to be more significant to reach a consensus about the benefits of TXA in CS.[1] In our meta-analysis, we analyzed data from more than 1500 operations and found results similar to Alistair MS et al. Hence, we encourage perioperative systemic administration of TXA in patients undergoing CS to reduce the blood loss and, possibly, the associated complications.

This study has few limitations that must be addressed. We reported blood loss in patients who received TXA compared with those who did not receive TXA or have received substances other than TXA. However, there may be heterogeneity between methods of recording blood loss. Second, the results of our meta-analysis had a heterogeneity ($I^2 = 95\%$); however, this was expected because of the large number of trials (18) included in our study.

The authors of this study recommend further high-quality trials to be conducted examining the use of systemic TXA in CS, with accurate reporting. Moreover, we recommend that the efficacy of consistent TXA protocol systems be analyzed and reported across a large population with a reproducible blood loss measurement tool. Finally, we recommend future updated reviews with better statistical additions, such as funnel plots that demonstrate the publication bias, as the authors of this review were not able to extract the funnel plots given the available data.

CONCLUSIONS

This study proved a clear beneficial outcome in administering TXA perioperatively, as it significantly reduced blood loss in the treatment group, compared with the control group. To our knowledge, this study is the largest meta-analysis performed assessing the benefits of TXA in CS.

After appraising the data presented, we encourage hospitals to consider implementing TXA-protocol systems for CS, which might improve postoperative outcomes. We recommend further well-designed clinical trials on the benefits of TXA to be conducted to reduce the heterogeneity and reporting accuracy of the results.

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DISCLOSURE

The authors have no financial interests to declare in relation to the content of this article.

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