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Review

Tranexamic acid for reducing blood loss, transfusion requirements, and dosage in pediatric craniosynostosis surgery: a systematic review and meta-analysis

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Abstract

Background: Craniosynostosis surgery is a high risk of substantial blood loss, frequently requiring transfusion. This study evaluates the efficacy of tranexamic acid (TXA) in reducing blood loss and transfusion requirements and examines the administered TXA dosages.

Methods: A systematic literature search was performed across databases including PubMed, EBSCO, ScienceDirect, ProQuest, EMBASE, and others, to evaluate the effects of TXA in craniosynostosis surgery. Pooled weighted mean differences (WMDs) were calculated to evaluate reductions in blood loss, transfusion requirements, and duration of Intensive Care Unit (ICU) and hospital stays. The meta-analysis was conducted using Review Manager 5.4 software. This study is registered with PROSPERO.

Results: Four randomized controlled trials and 10 retrospective cohort studies, with 2,180 patients, were included. The pooled analysis revealed a significant reduction in blood loss during craniosynostosis surgery, with a WMD of -18.54 (95% CI: -27.15 to -9.93, $p < 0.0001$; $I^2 = 90\%$). Additionally, there was a significant decrease in transfusion requirements, with a WMD of -5.08 (95% CI: -8.86 to -1.30, $p = 0.009$; $I^2 = 92\%$). Furthermore, the analysis revealed a significant reduction in the length of hospital stay, with a WMD of -0.48 (95% CI: -0.94 to -0.02, $p = 0.04$; $I^2 = 76\%$). The dosage of TXA ranged from a 10-50 mg/kg loading dose to a maintenance dose of 3-10 mg/kg/h. No significant reduction was noted in ICU stay duration.

Conclusions: TXA administration during craniosynostosis surgery significantly reduced blood loss and transfusion requirements, contributing to shorter hospital stays. These findings support minimizing transfusion and optimizing TXA dosing in surgical protocols, although no effect was seen on ICU stay duration.

Keywords

Tranexamic acid, craniosynostosis, blood loss, transfusion, dosage, surgery.

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Introduction

Craniosynostosis, characterized by the early fusion of cranial sutures, interferes with normal cranial development and leads to atypical craniofacial morphologies. This condition has a prevalence of approximately 3.5 to 4.5 per 10,000 live births, with the sagittal suture being the most frequently affected [1, 2]. Treatment typically entails surgical excision of the affected suture(s), with or without cranial vault remodeling, usually at approximately 5 to 6 months of age [2].

Cranial vault reconstruction is performed in infants to prevent potential complications associated with craniosynostosis and premature suture fusion, such as elevated intracranial pressure, cerebral compression, and vision loss [3]. The surgical correction of craniosynostosis is a common procedure within pediatric surgery; however, it is frequently accompanied by significant blood loss [4]. Substantial blood loss is frequently encountered during reconstruction surgery for pediatric craniosynostosis, necessitating careful management of transfusion requirements and presenting a potential risk for both short-term and long-term complications [5, 6].

Tranexamic acid (TXA) is an antifibrinolytic agent that functions by inhibiting the formation of plasmin [7]. TXA was initially utilized to reduce blood loss in patients experiencing menorrhagia and those with hereditary bleeding disorders. Its use has subsequently broadened to encompass the management of severe trauma characterized by substantial hemorrhage, as well as serving as a prophylactic strategy in elective surgical interventions [8].

The use of TXA in craniosynostosis surgeries has increased significantly in recent years, supported by growing evidence of its effectiveness in reducing perioperative hemorrhage. However, despite its widespread use across various surgical procedures, questions regarding the efficacy, optimal dosage, timing, and administration protocol remain [9]. A randomized control trial revealed that TXA significantly decreases perioperative blood loss and transfusion requirements in pediatric patients undergoing craniosynostosis reconstruction [10]. The elevated incidence of blood transfusion is associated with risks including the potential for infection, immunologic reactions to transfused blood, electrolyte imbalances, coagulation dysregulation, volume overload, and the risk of transfusion errors involving the wrong patient [11, 12]. Notably, infants under 12 months of age seem particularly vulnerable to adverse events related to transfusion [11].

Significant perioperative blood loss during cranial vault reconstruction in pediatric patients can lead to increased morbidity and mortality. We conducted a systematic review and meta-analysis to evaluate the efficacy of TXA in minimizing blood loss and transfusion requirements in pediatric craniosynostosis surgeries, as well as to evaluate the administered dosages of TXA.

Method

Study registration

This meta-analysis has been registered in the International Prospective Register of Systematic Reviews (PROSPERO) under registration number CRD42024607249.

Search strategy

The methodology of this meta-analysis was guided by the criteria outlined in the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 checklist. A comprehensive systematic literature search was conducted across multiple databases, including PubMed, EBSCO, ScienceDirect, ProQuest, EMBASE, and others, to identify eligible studies published from January 2003 until October 2024. The search strategy involved the use of the following keywords ("tranexamic acid" OR "tranexamic acid/therapeutic use" OR "tranexamic acid/administration & dosage" OR "tranexamic acid/adverse effects" OR "tranexamic acid/pharmacokinetics") AND ("craniosynostoses" OR "craniosynostoses/surgery"). The data search was restricted to articles published in the English

language. Furthermore, manual searches of the reference lists of pertinent papers were performed to identify any additional relevant articles.

Inclusion and exclusion criteria

Eligible studies were selected according to the following inclusion criteria: 1) original studies, including cross-sectional, case-control, cohort studies, or randomized-controlled trials; 2) patients aged 0-18 years diagnosed with craniosynostosis; 3) patients who underwent surgical intervention; and 4) studies that provided comparative outcomes such as blood loss (measured in ml/kg), volume of transfusion (measured in ml/kg), duration of stay in both the Intensive Care Unit (ICU) and hospital, with adequate data available for extraction and pooling. The following exclusion criteria were implemented: 1) review articles, case reports, editorials, letters, and meeting abstracts; 2) studies focusing on non-human subjects; 3) studies lacking sufficient data for the estimation of odds ratios (ORs) or weighted mean difference (WMD), along with corresponding 95% confidence intervals (CIs); and 4) studies exhibiting overlapping content or duplicates.

Data extraction

Data extraction from the selected studies was carried out independently by two authors (A.H.H. and S.G.). Any discrepancies in their assessments were resolved through discussion with the supervising author (S.I.). The studies that met the inclusion criteria underwent data extraction, from which the following information was gathered: first author's name, year of publication, country of origin, study design, sample size, gender distribution, type of craniosynostosis, TXA protocol, age distribution, duration of surgery, duration of anesthesia, volume of blood loss, volume of transfusion, length of stay in the ICU, length of hospital stay, dosage, and adverse events.

Quality assessment

The quality assessment of each included study was systematically performed utilizing the Newcastle-Ottawa Scale (NOS). The NOS total score ranges from 0 to 9, considering three domains: selection (0-4 points), comparability (0-2 points), and outcome (0-3 points). Studies with a score of 7 points or higher were classified as high-quality studies, while those achieving scores between 5 and 6 points were classified as moderate-quality studies. Studies with a total score of 4 points or less were classified as low-quality studies.

Statistical analysis

This meta-analysis utilized Review Manager 5.4 software (The Nordic Cochrane Centre, Copenhagen) for the statistical assessment. The WMD and corresponding 95% CI were calculated using the inverse variance method to evaluate the association between blood loss volume, transfusion volume, ICU duration, and length of hospital stay. Heterogeneity among the included studies was evaluated using Cochran's Q Chi-square test and I^2 statistic. A fixed-effects model was utilized to derive the pooled WMD and 95% CI when $p \geq 0.05$ and $I^2 \leq 50\%$, indicating an absence of significant heterogeneity. If $p < 0.05$ or $I^2 > 50\%$, a random-effects model was utilized to calculate the pooled WMD due to considerable heterogeneity. A p-value of < 0.05 was considered statistically significant for all analytical tests. In addition, potential publication bias was evaluated through a visual examination of funnel plots.

Result

Literature search

The systematic literature search of electronic databases initially yielded a total of 316 potential articles, with an additional 13 articles identified through manual hand-searching of relevant literature. After the removal of duplicates, 197 articles were screened based on their titles and abstracts, resulting in the exclusion of 183 articles – specifically, 6 case reports, 71 review articles or editorials, and 100 studies not relevant. Subsequently, 20 articles were reviewed in full text, resulting in the exclusion of 6 studies that had insufficient data. Ultimately, our meta-analysis incorporated 14 studies. The flow chart detailing the literature search process is presented in **Fig. 1**.

Study characteristic and quality assessment

This meta-analysis included 14 studies, which collectively encompassed a total of 2,180 patients [2, 8-10, 13-22]. The studies incorporated in this analysis covered the period from 2003 to 2024. Of these, 4 were identified as randomized control trials, while 10 were identified as retrospective cohort studies. Two

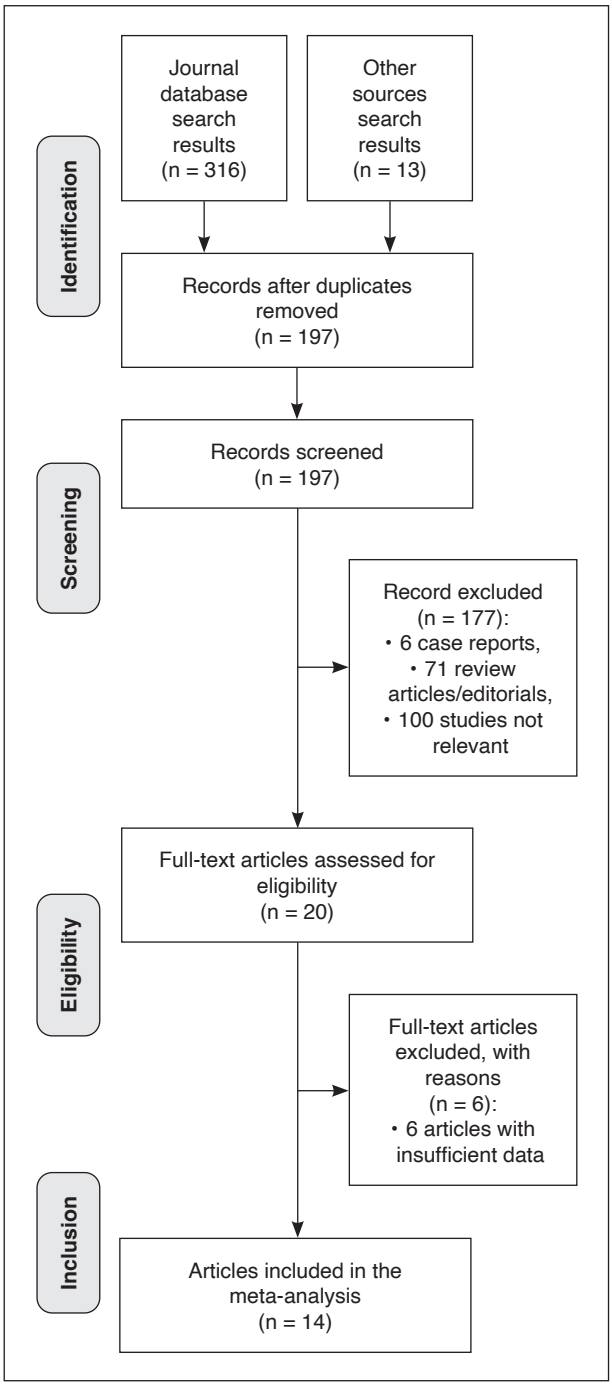

Figure 1. Flowchart of literature search.

studies were conducted in France, 5 in the USA, 2 in Germany, and 1 each in Korea, Denmark, Turkey, Portugal, and Bulgaria. The characteristics of the studies included in this meta-analysis are presented in **Tab. 1**.

The various types of craniosynostosis included sagittal craniosynostosis (scaphocephaly), lambdoid craniosynostosis, metopic (trigonocephaly), brachiocephaly, frontosphenoidal, unicoronal (plagiocephaly) and bicoronal craniosynostosis. An overview of craniosynostosis types is presented in **Tab. 2**. The TXA protocols implemented in the studies included in this analysis are detailed in **Tab. 3**.

The quality of the studies included in this meta-analysis was evaluated using the NOS. The NOS quality ratings varied between 7 to 9 stars, indicating an overall high standard of study quality, as detailed in **Tab. 4**.

Association between tranexamic acid administration and blood loss reduction

The association between TXA and blood loss was examined across 10 studies. A pooled analysis performed using a random-effects model revealed that TXA significantly decreases blood loss during craniosynostosis surgery (WMD = -18.54; 95% CI = -27.15 to -9.93; $p < 0.0001$; $I^2 = 90\%$). The forest plot illustrating these results is presented in **Fig. 2**.

Association between tranexamic acid administration and transfusion volume

The association between TXA administration and transfusion volume was examined across 12 studies. A pooled analysis performed using a random-effects model revealed that TXA significantly reduces the need for transfusions in craniosynostosis surgery (WMD = -5.08; 95% CI = -8.86 to -1.30; $p = 0.009$; $I^2 = 92\%$). The forest plot illustrating these results is presented in **Fig. 3**.

Association between tranexamic acid administration and Intensive Care Unit stay

The association between TXA administration and the duration of stay in the ICU was examined across 6 studies. A pooled analysis performed using a fixed-effects model revealed that TXA did not significantly reduce the length of stay in the ICU (WMD = -0.00, 95% CI = -0.03 to 0.03; $p = 0.98$; $I^2 = 33\%$). The forest plot illustrating these results is presented in **Fig. 4**.

Association between tranexamic acid administration and duration of hospital stay

The association between TXA administration and hospital length of stay was examined across 10 studies. A pooled analysis performed using a random-effects model revealed that TXA is associated with a reduction in hospital length of stay in the patients undergoing craniosynostosis surgery (WMD = -0.48, 95% CI = -0.94 to -0.02; $p = 0.04$; $I^2 = 76\%$). The forest plot illustrating these results is presented in **Fig. 5**.

Table 1. Characteristics of the studies included in the analysis.

Study	Origin	Method	Sample size	Mean age (months)	Male, n (%)	Duration of surgery (min)	Duration of anesthesia (min)	Adverse event, n (%)
Dadure et al., 2011 [13]	France	Randomized control trial	TXA: 19 Control: 20	TXA: 7 Control: 6	TXA: 17 (89.5) Control: 17 (85)	TXA: 110.2 ± 19.9 Control: 104.7 ± 19.8	TXA: 166.2 ± 51.2 Control: 175.5 ± 56.5	No adverse events
Goobie et al., 2011 [10]	USA	Randomized control trial	TXA: 23 Control: 20	TXA: 23 ± 19 Control: 25 ± 20	TXA: 15 (65) Control: 11(55)	TXA: 272 ± 76 Control: 252 ± 58	NR	NR
Engel et al., 2015 [15]	Germany	Retrospective cohort study	TXA: 17 Control: 16	TXA: 9.4 ± 3.0 Control: 10.4 ± 1.8	TXA: 14 (82.4) Control: 13 (81.3)	TXA: 132 ± 9.3 Control: 136 ± 12.0	NR	No adverse event
Martin et al., 2015 [21]	USA	Retrospective cohort study	TXA: 14 Control: 14	TXA: 10 ± 9 Control: 7 ± 2	TXA: 12 (85,71) Control: 13 (0.93)	TXA: 3.8 ± 0.6 Control: 3.3 ± 0.7	NR	NR
Martin et al., 2016 [20]	USA	Retrospective cohort study	TXA: 69 Control: 118	TXA: 8.0 Control: 8.4	TXA: 48 (69.6%) Control: 71 (60.2)	TXA: 2.8 Control: 3.0	NR	No adverse event
Kurnik et al., 2017 [19]	USA	Retrospective cohort study	TXA: 35 Control: 79	TXA: 16.2 ± 14 Control: 15.4 ± 13	NR	TXA: 187 ± 61 Control: 193 ± 63	NR	No adverse event
Kim et al., 2018 [18]	Korea	Randomized control trial	TXA: 23 Control: 25	TXA: 12 Control: 14	TXA: 14 (61) Control: 10 (40)	TXA: 264 ± 75.1 Control: 262.6 ± 48.4	TXA: 326 ± 58.4 Control: 352.4 ± 45.3	TXA: 0 Control: 4 (16)
Escher et al., 2019 [2]	Germany	Retrospective cohort study	TXA: 14 Control: 22	TXA: 7.0 ± 1.5 Control: 5.9 ± 1.3	TXA: 10 (71.4) Control: 18 (81.8)	TXA: 131.8 ± 34.5 Control: 136.1 ± 30.4	NR	No adverse event
Fenger-Eriksen et al., 2019 [17]	Denmark	Randomized control trial	TXA: 15 Control: 15	TXA: 8.6 Control: 8.2	17 (56)	TXA: 139 ± 36 Control: 139 ± 36	NR	No adverse event
Danforth et al., 2020 [14]	USA	Retrospective cohort study	TXA: 454 Control: 891	TXA: 8.7 ± 5.0 Control: 7.1 ± 4.7	TXA: 286 (63.0) Control: 589 (66.1)	NR	NR	TXA: 76 (16.7) Control: 99 (11.1)
Ongun et al., 2020 [9]	Turkey	Retrospective cohort study	TXA: 17 Control: 19	TXA: 8.85 ± 3.78 Control: 7.5 ± 3.25	TXA: 11 (64.7) Control: 12 (63.2)	TXA: 4 Control: 4	TXA: 6 Control: 5	No adverse event
Eustache et al., 2022 [16]	France	Retrospective cohort study	TXA: 70 Control: 32	TXA: 6.25 Control: 9.0	TXA: 55 (79) Control: 24 (75)	TXA: 102.5 Control: 130	TXA: 198.75 Control: 262.5	NR
Caneira et al., 2024 [8]	Portugal	Retrospective cohort study	TXA: 26 Control: 33	TXA: 11.35 Control: 8,33	TXA: 19 (73.1) Control: 25 (75.8)	NR	NR	TXA: 2 (7.69) Control: 5 (15.15)
Tanova et al., 2024 [22]	Bulgaria	Retrospective cohort study	TXA: 44 Control: 36	TXA: 5.5 ± 3.8 Control: 5.7 ± 4	TXA: 38 (86.3) Control: 33 (91.7)	TXA: 98 ± 25 Control: 94 ± 20	NR	NR

NR: not reported; TXA: tranexamic acid.

Table 2. Classification of craniosynostosis types.

Study	TXA craniosynostosis, n (%)	Control craniosynostosis, n (%)
Dadure et al., 2011 [13]	Plagiocephaly: 0 Scaphocephaly: 16 (84) Trigonocephaly: 2 (11) Complex: 1 (5)	Plagiocephaly: 2 (10) Scaphocephaly: 14 (70) Trigonocephaly: 4 (20) Complex: 0
Goobie et al., 2011 [10]	NR	NR
Engel et al., 2015 [15]	Metopic: 17 (100)	Metopic: 16 (100)
Martin et al., 2015 [21]	NR	NR
Martin et al., 2016 [20]	Saggital: 41 (59.4) Metopic:16 (23.2) Coronal: 9 (13.0) Lambdoid: 3 (4.3) Frontosphenoidal: 0	Saggital: 61 (51.7) Metopic: 22 (18.6) Coronal: 27 (22.9) Lambdoid: 7 (5.9) Frontosphenoidal: 1 (0.8)
Kurnik et al., 2017 [19]	Saggital: 35 (100)	Saggital: 79 (100)
Kim et al., 2018 [18]	Saggital: 8 (35) Metopic: 2 (9) Unilateral coronal: 5 (22) Bilateral coronal: 2 (9) Lambdoid: 2 (9) Multiple: 4 (17)	Saggital: 7 (28) Metopic: 0 Unilateral coronal: 2 (8) Bilateral coronal: 3 (12) Lambdoid: 3 (12) Multiple: 10 (40)
Escher et al., 2019 [2]	Saggital: 14 (100)	Saggital: 22 (100)
Fenger-Eriksen et al., 2019 [17]	Plagiocephaly: 3 (20) Scaphocephaly: 4 (26.7) Trigonocephaly: 4 (26.7) Other: 4 (26.7)	Plagiocephaly: 2 (13.3) Scaphocephaly: 5 (33.3) Trigonocephaly: 4 (26.7) Other: 4 (26.7)
Danforth et al., 2020 [14]	NR	NR
Ongun et al., 2020 [9]	Trigonocephaly: 9 (52.9) Scaphocephaly: 7 (41.2) Brachiocephaly: 1 (5.9) Anterior plagiocephaly: 0	Trigonocephaly: 8 (42.1) Scaphocephaly: 7 (36.8) Brachiocephaly: 1 (5.3) Anterior plagiocephaly: 3 (15.8)
Eustache et al., 2022 [16]	Scaphocephaly: 51 (73) Trigonocephaly: 10 (14) Unicoronal: 9 (13)	Scaphocephaly: 23 (72) Trigonocephaly: 7 (22) Unicoronal: 2 (6)
Caneira et al., 2024 [8]	Sagittal: 26 (100)	Sagittal: 33 (100)
Tanova et al., 2024 [22]	Sagittal: 37 (46) Metopic: 28 (35) Unicoronal: 9 (12) Bicoronal: 2 (3)	NR

NR: not reported; TXA: tranexamic acid.

Table 3. Tranexamic acid (TXA) protocol.

Study	TXA protocol
Dadure et al., 2011 [13]	Following the induction of general anesthesia and before skin incision, TXA was administered intravenously at a dose of 15 mg/kg (1.5 ml/kg) over 15 minutes, with a subsequent continuous infusion of 1 ml/kg (10 mg/kg/h).
Goobie et al., 2011 [10]	Administer a loading dose of 50 mg/kg, followed by a continuous infusion of 5 mg/kg/h.
Engel et al., 2015 [15]	Administer a bolus of 10 mg/kg, subsequently followed by a continuous infusion at a rate of 5 mg/kg/h.
Martin et al., 2015 [21]	Administer a loading dose of 30 mg/kg after the induction of anesthesia and before the skin incision, followed by a continuous infusion at a rate of 10 mg/kg/h.
Martin et al., 2016 [20]	Administer a loading dose of 50 mg/kg before the procedure, followed by a continuous infusion at a rate of 5 mg/kg/h throughout the duration of the surgery.
Kurnik et al., 2017 [19]	A loading dose of 10 mg/kg should be administered, followed by a continuous infusion of 5 mg/kg/h for the initial 24 hours.
Kim et al., 2018 [18]	Administer a loading dose of 10 mg/kg intravenously over a period of 15 minutes, followed by a continuous intravenous infusion at a rate of 5 mg/kg/h until skin closure is achieved.
Escher et al., 2019 [2]	Administer a loading dose of 40 mg/kg intravenously perioperatively, followed by an intraoperative infusion of 10 mg/kg/h. Postoperatively, continue with an intravenous dose of 10 mg/kg every 8 hours for a total of 3 doses.
Fenger-Eriksen et al., 2019 [17]	Administer 10 mg/kg intravenously before the initial surgical incision, followed by a continuous infusion of 3 mg/kg/h for a duration of 8 hours.
Danforth et al., 2020 [14]	NR
Ongun et al., 2020 [9]	A loading dose of 50 mg/kg was administered, followed by a maintenance infusion of 5 mg/kg/h.
Eustache et al., 2022 [16]	A bolus dose of 10 mg/kg was administered over 15 minutes, followed by a continuous infusion at a rate of 10 mg/kg/h.
Caneira et al., 2024 [8]	A loading dose of 10 mg/kg was administered over the first 30 minutes of the surgical procedure, followed by a continuous infusion at a rate of 10 mg/kg/h.
Tanova et al., 2024 [22]	An initial loading dose of 30 mg/kg was administered over 15 minutes, succeeded by a continuous infusion of 5 mg/kg/h for a fixed duration of 5 hours.

NR: not reported; TXA: tranexamic acid.

Table 4. Assessment of study quality using the Newcastle-Ottawa Scale (NOS).

Study	Selection	Comparability	Outcome	Total rating
Dadure et al., 2011 [13]	★★★★	★★	★★★	9★
Goobie et al., 2011 [10]	★★★★	★★	★★★	9★
Engel et al., 2015 [15]	★★★★	★	★★★	8★
Martin et al., 2015 [21]	★★★★	★	★★★	8★
Martin et al., 2016 [20]	★★★★	★★	★★★	9★
Kurnik et al., 2017 [19]	★★★★	★★	★★★	9★
Kim et al., 2018 [18]	★★★★	★	★★★	8★
Escher et al., 2019 [2]	★★★★	★	★★★	8★
Fenger-Eriksen et al., 2019 [17]	★★★★	★★	★★★	9★
Danforth et al., 2020 [14]	★★★★	★	★★★	8★
Ongun et al., 2020 [9]	★★★★	★	★★★	8★
Eustache et al., 2022 [16]	★★★★	★	★★★	8★
Caneira et al., 2024 [8]	★★★	★	★★★	7★
Tanova et al., 2024 [22]	★★★★	★	★★★	8★

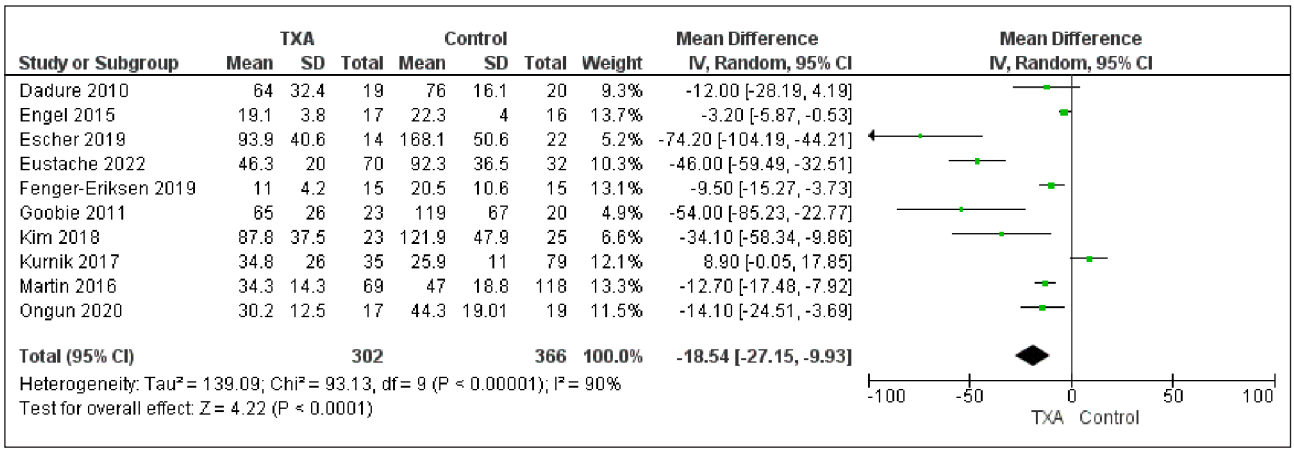

Figure 2. Forest plot illustrating the association between tranexamic acid (TXA) and blood loss.

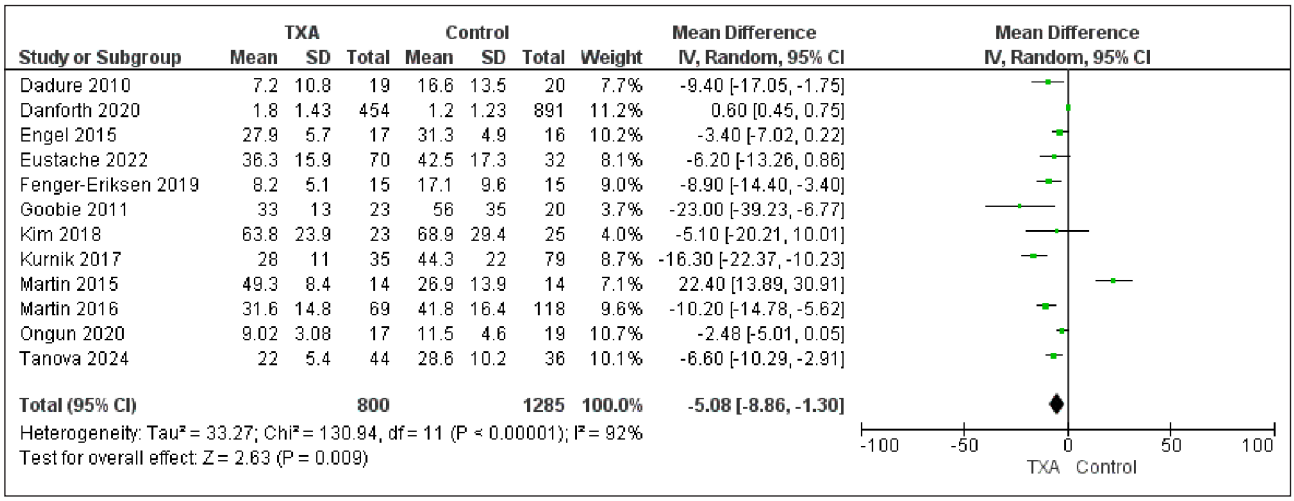

Figure 3. Forest plot illustrating the association between tranexamic acid (TXA) and transfusion volume.

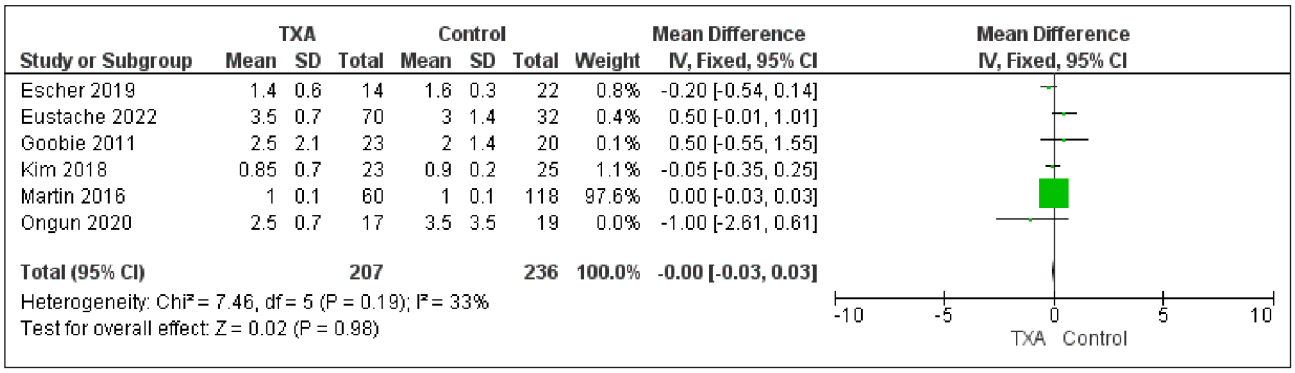

Figure 4. Forest plot illustrating the association between tranexamic acid (TXA) and duration of stay in the Intensive Care Unit (ICU).

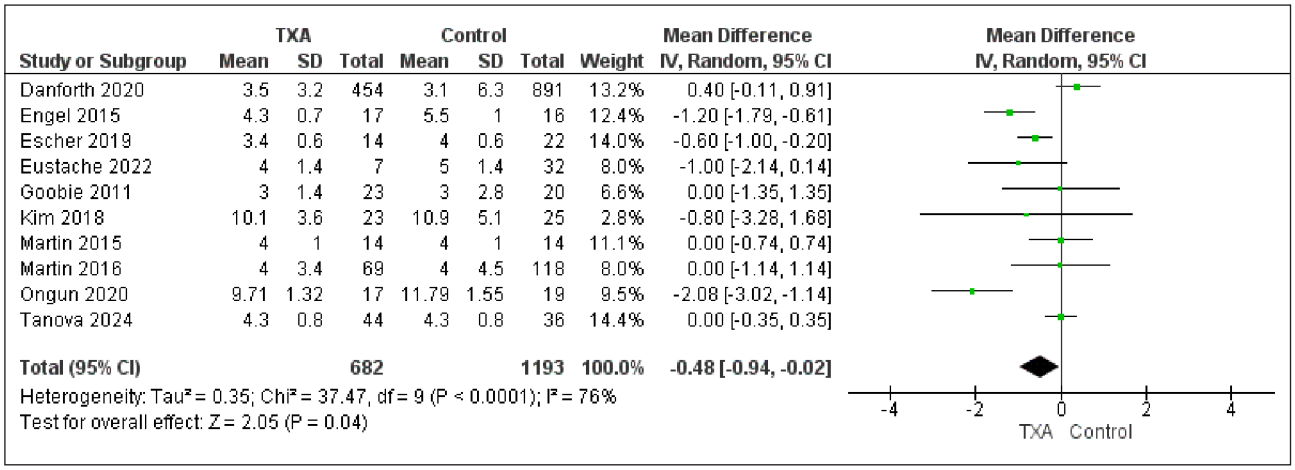

Figure 5. Forest plot illustrating the association between tranexamic acid (TXA) and hospital length of stay.

Publication bias

The publication bias cannot be established in our meta-analysis owing to the restricted number of included randomized controlled trials.

Discussion

This meta-analysis comprised 14 studies, which included 4 randomized control trials and 10 retrospective cohort studies. The aggregate data involved a total of 2,180 patients with craniosynostosis. In comparison to the control group, the pooled analysis demonstrated a significant association between TXA and a reduction in both blood loss and the necessity for transfusions. Moreover, the administration of TXA was associated with a reduction in hospital length of stay when compared to the control group. However, no significant differences were observed in the duration of ICU stay between the TXA and control group. A prior meta-analysis indicated that the TXA administration can significantly reduce blood loss and the necessity for blood transfusions in patients undergoing craniosynostosis surgery [23].

TXA is a synthetic analog of lysine that exhibits antifibrinolytic properties. Its mechanism of action involves reversible inhibition of lysine binding sites on plasminogen molecules, thereby inhibiting the interaction between plasminogen, plasmin, and lysine residues present on the surface of fibrin [4]. Craniosynostosis surgery has historically been associated with significant blood loss and the requirement for transfusions of allogeneic blood products [22]. TXA is widely used in various surgical procedures because of its antifibrinolytic properties, which effectively reduce blood loss and transfusion requirements [9, 10]. TXA promotes its hemostatic effect by inhibiting the interactions between plasminogen and plasmin at the fibrin surface, thereby preventing the degradation of fibrin [18].

TXA demonstrates significant antifibrinolytic activity, resulting in a reduction of transfusion requirements up to postoperative day 2. The hemostatic effects of TXA persist for as long as

24 hours following discontinuation, despite its mean half-life of approximately 120 minutes in the context of pediatric craniosynostosis surgeries [18]. Currently, there is no established protocol for the administration of TXA in pediatric craniofacial surgery. Nonetheless, a commonly recommended approach involves the administration of a loading dose ranging from 10 mg/kg to 100 mg/kg following the induction of general anesthesia and before skin incision, succeeded by a continuous infusion of 5 to 10 mg/kg/h until the completion of skin closure [16].

The utilization of TXA has been associated with a significant reduction in blood loss and decreased drain output, factors that likely contributed to a shortened duration of hospitalization [6, 16]. Caneira et al. [8]. reported that there were 2 adverse events in the administration of TXA. There was no clinical evidence indicating that TXA elevates the incidence of thromboembolic events, such as myocardial infarction, stroke, deep-vein thrombosis, or pulmonary embolism; additionally, TXA is capable of crossing the blood-brain barrier, with cerebrospinal fluid concentration reported to be approximately 10% of those in plasma [8]. Our meta-analysis indicated that the adverse events were primarily attributed to surgical complications and other medical treatments.

A meta-analysis conducted by Alabdulkarim et al. [24]. has suggested that the optimal dosage of TXA is a bolus of 10 mg/kg, followed by a maintenance dose of 5 mg/kg. A loading dose is typically after the induction of general anesthesia and before the skin incision, with reported doses ranging from 10 mg/kg to 100 mg/kg, followed by a continuous infusion at a rate of 5 to 10 mg/kg/h until skin closure [16]. The review indicated that TXA is a safe and well-tolerable agent for patients. Furthermore, the most commonly reported adverse effects included orthostatic reactions, diarrhea, and nausea [24].

Our meta-analysis indicated that the recommended loading dosage of TXA ranges from 10 to 50 mg/kg before skin incision, with a subsequent maintenance dose of 3 to 10 mg/kg/h until the skin closure. This protocol was consistently shown to reduce perioperative blood loss and transfusion requirements in pediatric craniosynostosis surgeries across the studies included in this review. Studies that administered a loading dose within this range, such as those by Martin et al. [20] and Goobie et al. [10], demonstrated significant reductions in both blood loss and transfusion needs, supporting the efficacy of these dosing strategies.

The review also supported the loading dose after anesthetic induction, followed by continuous infusion until skin closure, even if the exact timing and total dosage varied among techniques. This approach ensures that TXA remains active throughout the period of greatest risk for hemorrhage, thereby maximizing its efficacy. The consistency among various studies confirms the advised approach and emphasizes its function as a useful reference for clinicians.

These findings suggest that adhering to the recommended dosage range and protocol can effectively reduce perioperative complications related to blood loss and transfusion in pediatric craniosynostosis surgeries. Implementing this standardized protocol may lead to improved surgical outcomes and better perioperative management of pediatric patients.

Study limitations

Our meta-analysis was subject to several limitations. Firstly, the studies included were primarily retrospective cohort studies, which inherently carry the risk of biases related to data collection and patient selection. Secondly, the variability in sample sizes across the included studies may have contributed to heterogeneity in the study outcomes. Thirdly, we were unable to generate a funnel plot due to the limited number of studies, thus preventing a definitive assessment of publication bias.

Conclusion

The systematic review and meta-analysis demonstrated that TXA effectively enhances hemostasis in craniosynostosis surgeries, significantly reducing blood loss, transfusion requirements, and potentially hospital stays, though no impact on ICU stay duration was observed. The recommended TXA dosage includes a 10-50 mg/kg loading dose after anesthesia, followed by a maintenance infusion of 3-10 mg/kg/h until skin closure. While these findings support TXA as a valuable intervention for reducing blood loss and transfusions, further studies are needed to evaluate its long-term safety, adverse events, and broader applicability in pediatric and other surgical settings.

Declaration of interest

The Authors declare no conflict of interest related to this research.

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