

Intraoperative Tranexamic Acid Reduces Blood Transfusion in Children Undergoing Craniosynostosis Surgery

A Randomized Double-blind Study

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ABSTRACT

Background: Surgical correction of craniosynostosis in children is associated with substantial intraoperative bleeding. Tranexamic acid (TXA) decreases intraoperative blood loss during cardiac or orthopedic surgery in children. We hypothesized that intraoperative TXA would reduce blood transfusion relative to placebo in patients pretreated with erythropoietin.

Methods: Forty consecutive children, American Society of Anesthesiologists status 1 or 2, scheduled to undergo surgical correction of craniosynostosis were randomly assigned to receive either intravenous TXA or saline, 0.9%, intraoperatively. All children received preoperative erythropoietin (600 U/kg once a week for 3 weeks before surgery). Perioperative blood loss, number and volume of transfusions, percentage of children who underwent transfusion, and side effects were noted after surgery and at the end of the study. Surgeon satisfaction and cost of treatment were also recorded.

Results: There was no significant difference between groups in demographic or surgical data. In the TXA group, the volume of packed erythrocytes transfused was significantly reduced by 85% (from 11 to 1.6 ml/kg) intraoperatively and

What We Already Know about This Topic

- Major craniofacial surgical procedures in children are associated with substantial intraoperative bleeding, which is the main cause of perioperative mortality.
- Previous efforts to reduce intraoperative blood loss and transfusion requirements have been disappointing.

What This Article Tells Us That Is New

- The intraoperative infusion of tranexamic acid reduced erythrocyte transfusion in children pretreated with erythropoietin about to undergo surgical correction of craniosynostosis.
- No thrombotic complications were observed in this small study, but further work will be necessary to determine safety.

by 57% (from 16.6 to 7.2 ml/kg) throughout the study period ($P < 0.05$). Compared with the placebo group, the percentage of children requiring blood transfusion was lower in the TXA group during surgery (9 [45%] of 20 *vs.* 2 [11%] of 19 children; $P < 0.05$) and during the whole study period (14 [70%] of 20 *vs.* 7 [37%] of 19; $P < 0.05$). Preoperative and postoperative hematologic parameters were comparable in both groups. There were no adverse events.

Conclusion: In children undergoing surgical correction of craniosynostosis and pretreated with erythropoietin, intraoperative TXA reduces the transfusion requirement.

CRANIOSYNOSTOSIS is an abnormality of the suture, resulting from premature bony cranial fusion, leading to restriction of skull volume.¹ It occurs in children at a rate of approximately 1 per 1,800 births.² To avoid high intracranial pressure and consequent developmental delay and learning disability, surgical correction must be performed in the first year of life. The surgery is associated with

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substantial intraoperative bleeding, frequently requiring transfusion of packed erythrocytes (PRBCs).³ Blood loss is the main cause of mortality after major craniofacial procedures in children.⁴ Reported transfusion volumes for pediatric patients undergoing surgical correction of synostotic calvarial sutures vary between 20% and 500% of estimated blood volume.³ Erythrocyte transfusion is associated with many serious adverse events, including increased mortality in the pediatric surgical population.⁵

Numerous techniques intended to reduce intraoperative blood loss during craniostylosis surgery have been studied, including autologous blood predonation,⁶ short-term normovolemic hemodilution,⁷ and intraoperative blood salvage.^{3,8} Most of these techniques reported disappointing results, with relatively low benefits in terms of transfusion requirements. Preoperative erythropoietin administration has increased the hematocrit concentration before surgery and decreases transfusion requirements.^{9–11}

Tranexamic acid (TXA) is a synthetic antifibrinolytic drug that competitively decreases the activation of plasminogen to plasmin. TXA suppresses fibrinolysis by inhibiting plasminogen and the binding of plasmin to fibrin.¹² TXA has decreased intraoperative blood loss during cardiac surgery^{13–18} and surgical correction of scoliosis in children.^{19–21} Recently, Grant *et al.*²¹ showed that, during pediatric scoliosis surgery, the use of TXA decreased the number of intraoperative PRBC transfusions by 50%. In children undergoing craniofacial surgery, only two studies^{22,23} showed the effectiveness of an antifibrinolytic drug in reducing intraoperative blood loss. We hypothesized that TXA would decrease the number of blood transfusions compared with placebo. This prospective, randomized, double-blind study was designed to evaluate the effectiveness of continuous intraoperative intravenous infusion of TXA in reducing PRBC transfusions in children pretreated with erythropoietin and scheduled to undergo surgical craniosynostosis correction.

Materials and Methods

After receiving Institutional Review Board approval (Sud Méditerranée IV, Montpellier, France) and obtaining informed parental consent, 40 consecutive children, American Society of Anesthesiologists status I or II, scheduled to undergo surgical correction of craniosynostosis were enrolled from April 1, 2007 to February 28, 2010. Children with bleeding diathesis and abnormal prothrombin time, partial thromboplastin time, or platelets counts; a history of convulsive seizures; or allergy to TXA were not included.

Children were randomly assigned to receive either TXA (TXA group) or saline, 0.9% (placebo group). Randomization was generated by our institutional biostatistics department using a computer-generated random sequence concealed in consecutively numbered opaque sealed envelopes. As is routine in our institution for pediatric surgery with a high risk of significant blood loss, all children received erythropoietin before surgery with elemental iron supplementa-

tion (6 mg/kg per day orally). A dose of 600 U/kg erythropoietin was injected subcutaneously 21 and 14 days before surgery; a third injection was given 7 days earlier if the hemoglobin value was lower than 15 g/dL.

All children underwent standard monitoring, including a radial artery catheter for invasive blood pressure, a subclavian central venous catheter, and a urinary output bladder catheter. After the induction of general anesthesia and before skin incision, patients received 15 mg/kg (1.5 ml/kg) TXA or 1.5 ml/kg saline, 0.9%, intravenously, during a 15-min period. This dose of TXA was within the dose range previously found effective.^{17–20,23} A continuous infusion of 1 ml/kg TXA (10 mg/kg per hour) or saline was then initiated until skin closure. All solutions were prepared in identical 50-ml syringes by a nurse anesthetist not involved in clinical management and were presented to the operating team in a blind manner. The patient, surgeon, anesthesiologist (C.D., M.S., O.R., A.R., N.C.), and clinical research assistant (S.B.) collecting the data were all blinded to the solution administered.

General anesthesia was induced by sevoflurane (end-tidal fraction at 5%) and 0.2 μ g/kg intravenous sufentanil. Tracheal intubation and mechanical ventilation were used for the duration of surgery. Anesthesia was maintained with nitrous oxide, 50%, in oxygen and sevoflurane (minimum alveolar concentration = 1). Additional sufentanil doses of 0.1 μ g/kg were administered to maintain adequate analgesia. Minute ventilation was adjusted to maintain arterial carbon dioxide between 30 and 35 mmHg. The esophageal temperature was maintained higher than 36°C. Preoperative fluid therapy was managed by the infusion of crystalloid solutions (4 ml/kg per hour), guided by a mean invasive arterial blood pressure between 45 and 65 mmHg, a urinary output of 1 ml/kg or more per hour, and hematocrit, hemoglobin, and arterial blood gas measurements every 30 min. If the mean blood pressure was lower than 45 mmHg and/or urinary output was lower than 1 ml/kg per hour, 10 ml/kg crystalloid solution was injected within 20 min. Thereafter, if the mean blood pressure was still lower than 45 mmHg and/or urinary output was lower than 1 ml/kg per hour, an injection of 10 ml/kg colloidal hydroxyethyl starch (Voluven; Fresenius Kabi, Louviers, France) was then administered. The transfusion threshold for PRBCs was a hemoglobin concentration of 7.0 g/dL during surgery and in the first 72 h postoperatively. The formula used to calculate the volume of PRBC transfusion was as follows (in ml): $3 \times \text{Weight of Child (in kg)} \times (12 - \text{Hemoglobin [g/dL] at transfusion})$.²⁴

The use of plasma, platelets, and other blood products was left to the discretion of the attending anesthesiologist. The same surgeon (M.B.) operated on all the patients. During surgery, the estimated blood loss was measured from surgical aspiration and by weighing sponges from the operative field. Blood loss on surgical gowns and drapes was not included. At the end of surgery, surgeon satisfaction in terms of bleeding and technical difficulty was recorded (not satisfied, satisfied, or very satisfied). All children were extubated at the end of surgery.

Hematocrit, prothrombin time, activated partial prothrombin time, platelet count, and fibrinogen values were analyzed 21 days before surgery, the day before surgery, at the end of surgery, and 24 h after surgery. Hematocrit was analyzed every 30 min during surgery and 4 times a day thereafter during the 72-h study period. Postoperatively, blood loss was evaluated from the volume of blood in drains at 72 h. Noninvasive blood pressure, urinary output, and fluid therapy were recorded four times a day during the postoperative period. Side effects, such as pruritus, nausea, vomiting, hematoma or hemorrhage, thrombotic complications, local infection, fever, or convulsive seizure, were noted.

The cost of overall blood transfusion and infused hemostatic drugs was calculated based on the following list prices of the French Red Cross Blood Service: US \$240 per PRBC and \$0.7 per 500 mg TXA.

Sample size calculation was centered on our primary hypothesis that TXA decreases the number of PRBC transfusions compared with placebo.⁹ We considered a 20% reduction in PRBC transfusion to be clinically relevant. Assuming two-sided type I error protection of 0.05 and a study power at 0.80, 20 patients were required in the TXA and placebo groups to reveal a clinically significant difference. Statistical analysis was performed by our institutional biostatistics department using software (SAS, version 8.02; SAS Institute Inc., Cary, NC). Continuous data were expressed as mean \pm SD or median (range) for nongaussian variables. Categorical data were expressed as frequencies (%). The conducted analyses were two tailed. Continuous variables were compared with the Student *t* test or the Mann–Whitney U test for the nongaussian variables. Categorical variables were compared with the χ^2 or Fisher test. A significance threshold of *P* < 0.05 was defined.

Results

Forty children (6 girls and 34 boys), American Society of Anesthesiologists physical status I or II, were enrolled in either the TXA (*n* = 20) or placebo (*n* = 20) group. One child in the TXA group was excluded for revocation of parental consent. There was no meaningful difference in age, weight, height, duration and type of surgery, and intraoperative sufentanil doses between the two groups. Hemodynamic monitoring, fluid therapy, and urinary output were comparable between the two groups. There were no significant intraoperative and postoperative differences between the two groups in the amounts of crystalloids and colloids infused. Patient, anesthesia, and surgery characteristics are listed in table 1.

The volume of PRBC transfusion was significantly reduced by 85% during the intraoperative period and by 57% during the whole study period in patients receiving TXA compared with the placebo group (table 2). Intraoperatively, 2 (10.5%) of the 19 children underwent transfusion in the TXA group compared with 9 (45%) of the 20 children in the placebo group (*P* < 0.05). Throughout the study period, only 7 (37%) of the 19 children in the TXA group under-

Table 1. Demographic Data and Characteristics of Children Who Underwent Craniostomosis Correction

Variable	TXA Group (n = 19)	Placebo Group (n = 20)
Male/Female Ratio	17:2	17:3
Age, mo*	7 (4–15)	6 (3–9)
Weight, kg*	8 (5.55–13)	8 (6.5–11.8)
ASA Status, 1/2/3	12/7/0	8/12/0
Type of Craniostomosis†		
Plagiocephaly	0	2 (10)
Scaphocephaly	16 (84)	14 (70)
Trigonocephaly	2 (11)	4 (20)
Complex	1 (5)	0
Surgical Time, min	110.2 \pm 19.9	104.7 \pm 19.8
Anesthesia Time, min	166.2 \pm 51.2	175.5 \pm 56.5
Crystalloid Infusion, ml/kg	55.6 \pm 25.1	66.7 \pm 28.4
Hydroxyethyl Starch Infusion, ml/kg	9.0 \pm 8.6	11.4 \pm 10.3
Intraoperative Urinary Output, ml/kg	11.6 \pm 7.3	9.5 \pm 4.9

Data are given as mean \pm SD unless otherwise indicated.

* Data are given as median (range). † Data are given as number (percentage) of each group.

ASA = American Society of Anesthesiologists.

went transfusion compared with 14 (70%) of the 20 children in the placebo group (*P* < 0.05) (table 2). There was no significant difference in the amount of blood loss between the two groups during any period (table 2). In the TXA group, patients who underwent transfusion received only one PRBC unit. In the placebo group, 11 of the 14 patients who underwent transfusion received one PRBC unit and

Table 2. Intraoperative and Postoperative Data Concerning Erythrocyte Transfusion Requirement

Variable	TXA Group (n = 19)	Placebo Group (n = 20)	<i>P</i> Value
Patients Who Underwent Transfusion*			
Intraoperatively	2 (10.5)	9 (45)	0.02
Postoperatively	5 (26.3)	8 (40)	0.36
Total	7 (36.8)	14 (70)	0.04
Volume of Erythrocytes Transfused, ml/kg			
Intraoperatively	1.6 \pm 5.5	11.0 \pm 14.2	0.01
Postoperatively	5.6 \pm 10.27	5.6 \pm 7.6	0.65
Total	7.2 \pm 10.8	16.6 \pm 13.5	0.03
Blood Loss, ml/kg			
Estimated	51.4 \pm 28.3	61.1 \pm 16.8	0.25
Intraoperative			
Postoperative in Drains	5.6 \pm 10.3	4.8 \pm 7.7	0.97
Total	64.0 \pm 32.4	76.0 \pm 16.1	0.20

Data are given as mean \pm SD unless otherwise indicated.

* Data are given as number (percentage) of each group.

TXA = tranexamic acid.

three received two PRBC units (one during surgery and one thereafter). At 72 h after surgery, 63% of the children in the TXA group and 30% in the placebo group did not require blood transfusion ($P < 0.05$). The median (range) cost of perioperative treatment for blood loss in the TXA group (cost of PRBCs plus TXA) was US \$0.7 (US \$0.7–US \$240.7) versus US \$240 (US \$0–US \$480) in the placebo group (cost of PRBCs plus saline).

There was no difference between groups for fluid therapy, hemodynamic monitoring, and urinary output (table 1). Preoperative and postoperative laboratory variables (*i.e.*, platelet count, fibrinogen concentration, prothrombin time, hematocrit, and activated partial prothrombin time) were also comparable between the TXA and placebo groups. No adverse events were noted. There was no significant difference in surgeon's satisfaction between groups.

Discussion

In this randomized, double-blind, placebo-controlled study, we demonstrated that an intraoperative infusion of TXA reduces the number and volume of PRBC transfusions relative to placebo in children pretreated with erythropoietin.

Our findings are comparable with those of previous trials^{19,20,22} in cardiac or scoliosis surgery in children. Neilipovitz *et al.*¹⁹ reported that TXA reduced the volume of PRBCs by 30% compared with a placebo group in children undergoing posterior spinal fusion for scoliosis. Sethna *et al.*²⁰ noted a significant decrease of 42% in the mean total PRBC transfusion volume in patients with secondary scoliosis treated with TXA; however, there was no difference in patients with idiopathic scoliosis. For pediatric cardiac surgery, Schouten *et al.*²⁵ reported that TXA reduced PRBC transfusion by 7 ml/kg (95% CI, 10–5 ml/kg) compared with the placebo group. These results are similar to those of others studies¹⁸ for the same type of surgery. In young children, we report that TXA reduced the mean PRBC transfusion volume by 9.4 ml/kg during the study compared with a placebo group receiving saline. This is important in a population in whom estimated blood volume is low and the reduction of blood loss is primordial. In pediatric craniofacial surgery, antifibrinolytic therapy reduces bleeding and the subsequent transfusion requirement.^{22,23} D'Errico *et al.*²² showed that the amount of intraoperative blood for transfusion was significantly lower in children treated with aprotinin compared with placebo (32 ± 25 vs. 52 ± 34 ml/kg). Duran de la Fuente *et al.*²³ performed a comparative study using TXA and saline in pediatric cranial remodeling surgery. These researchers showed a significant decrease of bleeding in the TXA group during surgery. They stated a nonsignificant trend of blood transfusion requirement decrease in the treated group compared with the placebo group during surgery and the postoperative period.²³

A few studies^{13,16,17,20,23} have shown that intraoperative TXA administration led to less blood loss compared with a placebo group for different types of surgery. Nevertheless,

some researchers^{19,22} did not report a significant difference in blood loss using TXA or aprotinin, despite a significant decrease in total blood transfusion in the treated patients. In our current study, the amount of intraoperative and total blood loss tended to decrease in patients receiving TXA compared with placebo (51.4 ± 28.3 vs. 61.1 ± 16.8 ml/kg and 64.0 ± 32.4 vs. 76.0 ± 16.1 ml/kg, respectively). The lack of a significant difference in blood loss should not lower the significance of our study. Blood loss, estimated by weighing sponges and measuring operative suction volume, has been highly imprecise.²⁶ The amount of blood transfused may be a more sensitive indicator of the severity of bleeding than the amount estimated by the circulating nurse in the operating room. Furthermore, blood loss from surgical gowns and drapes was not considered in our study. The action of TXA did not continue after TXA was discontinued during the postoperative period. There was no difference in the percentage of children who underwent transfusion and the number and volume of PRBC transfusions during the postoperative period. Moreover, most children in the TXA group who underwent transfusion received PRBCs after TXA was discontinued. The postoperative use of TXA in children is understudied. Recently, Elwatidy *et al.*²⁷ reported that patients who received TXA during spine surgery and 5 h thereafter had a significant reduction in blood loss (49%) and blood transfusion (80%) compared with patients who received placebo. Based on these results and our data, it should be interesting to continue administration of TXA in children treated for surgical correction of craniosynostosis.

The use of erythropoietin was identical in our two groups. Erythropoietin is routinely used in pediatric patients scheduled for surgery with a high risk of significant blood loss (*e.g.*, scoliosis surgery, major pelvic surgery, and craniosynostosis) at our institution. Erythropoietin treatment before craniofacial surgery increases hematocrit and decreases transfusion requirements in children.^{9–11} Fearon and Weinthal¹⁰ reported that 57% of children treated with subcutaneous erythropoietin and supplemental iron preoperatively required blood transfusion after craniosynostosis repair (*vs.* 93% in the control group). Helfaer *et al.*⁹ showed that 64% of patients treated with subcutaneous erythropoietin, plus oral elemental iron, received a transfusion compared with 100% of patients treated with placebo. This is comparable with our saline group: 70% of children in this group underwent transfusion during the study period. These previous results and our data suggest that a combination of preoperative erythropoietin and intraoperative infusion of TXA is useful for decreasing transfusion requirements because only 30% of children in the TXA group underwent transfusion. The association of both saving blood treatments dramatically minimized the transfusion requirement in this specific population.

No side or adverse events were noted in our study. In adults, a few cases of cerebral thrombosis,²⁸ pulmonary thromboembolism,^{29,30} or retinal artery occlusion³¹ were

noted after TXA therapy. However, a meta-analysis³² on the efficacy and safety of antifibrinolytic drugs during liver transplantation did not find increased risk of thrombosis. No thrombotic complication has been described in children, probably because of insufficient published data or because TXA is not prothrombotic in children. Nevertheless, the combination of two potentially thrombotic drugs, erythropoietin and TXA, can increase the risk of thrombotic effect. Convulsive seizures have occurred after TXA use in an animal model³³ and in adults.^{34,35} No studies have reported side effects or complications after TXA administration during pediatric surgery^{13,16–21,23,27}; likewise, we did not observe complications of TXA therapy in our small sample.

This study has several potential limitations. The dose of TXA was decided arbitrarily because of the lack of dose-response published data. In the literature,^{17,19–21} the dose of initial bolus ranged from 10 to 100 mg/kg TXA; and the continuous infusion ranged from 1 to 10 mg/kg per hour in the pediatric surgical population. In addition, a bolus of 15 mg/kg TXA was chosen, similar to that in the study by Duran de la Fuente *et al.*²³

In conclusion, the current study demonstrates that TXA, combined with preoperative subcutaneous erythropoietin therapy and supplemental iron, significantly decreases the number and volume of PRBC transfusions and the rate of transfusion in children undergoing surgical correction of craniosynostosis. TXA is an efficient drug, simple and cheap to use without apparent adverse events in our young pediatric population. This is one of the key elements in the strategy to limit transfusion requirements in major craniofacial surgery in young patients. Postoperative administration of TXA needs to be explored in further controlled trials.

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