Efficacy of Tranexamic Acid in Pediatric Craniosynostosis Surgery

A Double-blind, Placebo-controlled Trial

Susan M. Goobie, M.D., F.R.C.P.C.,* Petra M. Meier, M.D.,* Luis M. Pereira, Ph.D.,†
Francis X. McGowan, M.D.,‡ Randy P. Prescilla, M.D.,* Laurie A. Scharp, B.Sc.,§
Gary F. Rogers, M.D.,‖ Mark R. Proctor, M.D.,# John G. Meara, M.D.,** Sulpicio G. Soriano, M.D.,‡
David Zurakowski, Ph.D.,‡‡ Navil F. Sethna, M.D.§§

ABSTRACT

Background: Extensive blood loss is common in pediatric craniosynostosis reconstruction surgery. Tranexamic acid (TXA) is increasingly used to reduce perioperative blood loss in various settings, but data on its efficacy are limited in children. The purpose of this randomized, double-blind, placebo-controlled, parallel trial was to evaluate the efficacy of TXA in pediatric craniosynostosis correction surgery. The primary and secondary outcome variables were reduction in perioperative blood loss and reduction in blood transfusion, respectively.

Methods: Forty-three children, ages 2 months to 6 yr, received either placebo or TXA in a loading dose of 50 mg·kg^{-1}, followed by an infusion of 5 mg·kg^{-1}·h^{-1} during surgery. TXA plasma concentrations were measured.

Results: The TXA group had significantly lower perioperative mean blood loss (65 *vs.* 119 ml·kg^{-1}, $P < 0.001$) and lower perioperative mean blood transfusion (33 *vs.* 56 ml·kg^{-1}, $P = 0.006$) compared to the placebo group. The mean difference between the TXA and placebo groups for total

What We Already Know about This Topic

- Surgery to correct premature closing of skull sutures results in extensive blood loss.
- Antifibrinolytic drugs, such as tranexamic acid, can decrease surgical blood loss.

What This Article Tells Us That Is New

- In infants and young children undergoing craniosynostosis surgery, tranexamic acid significantly reduces blood loss and transfusion requirements.

blood loss was 54 ml·kg^{-1} (95% CI for the difference, 23–84 ml·kg^{-1}) and for packed erythrocytes transfused was 23 ml·kg^{-1} (95% CI for the difference, 7–39 ml·kg^{-1}). TXA administration also significantly diminished (by two thirds) the perioperative exposure of patients to transfused blood (median, 1 unit *vs.* 3 units; $P < 0.001$). TXA plasma concentrations were maintained above the *in vitro* thresholds reported for inhibition of fibrinolysis (10 μg·ml^{-1}) and plasmin-induced platelet activation (16 μg·ml^{-1}) throughout the infusion.

Conclusions: TXA is effective in reducing perioperative blood loss and transfusion requirement in children undergoing craniosynostosis reconstruction surgery.

C RANIOSYNOSTOSIS, or premature closure of the skull sutures, is a relatively common disorder, with an incidence of 0.4-1/1,000 births.[1] Conventional treatment involves expansion and remodeling of the cranium in early infancy to prevent increased intracranial pressure, cerebral compression, and blindness.[2] Such extensive procedures re-

MA Presented at the ANESTHESIOLOGY/FAER Session of the American Society of Anesthesiologists Annual Meeting, October 19, 2010.

◆ This article is accompanied by an Editorial View. Please see: Holcomb JB: Tranexamic acid in elective craniosynostosis surgery: It works, but how? ANESTHESIOLOGY 2011; 114: 737–8.

sult in considerable blood loss[3] and transfusion-related morbidity and mortality.[4,5] Complications related to perioperative bleeding include severe hypotension, metabolic acidosis, cardiac arrest, transfusion reactions, venous air embolism, coagulopathies, infections, acute lung injury, postoperative ventilation, and death.[5–12] Decreasing blood loss and transfusion requirements should improve patient safety, expedite postoperative recovery, and decrease hospital costs.

Antifibrinolytic agents decrease surgical blood loss and exposure to allogeneic blood transfusion under a variety of circumstances.[13,14] Tranexamic acid (TXA, trans-4-aminomethyl cyclohexane carboxylic acid) is a synthetic amino acid lysine analog that forms a reversible complex with both plasminogen and plasmin by binding at lysine-binding sites. This binding competitively blocks the conversion of plasminogen to plasmin. It inhibits the proteolytic action of plasmin on fibrin clot and platelet receptors and inhibits fibrinolysis at the surgical wound.[15] TXA binds poorly to plasma proteins and is excreted primarily by the kidneys unchanged. TXA has been used clinically for decades and has Food and Drug Administration approval for the indications of prophylaxis and treatment of bleeding during dental surgery in patients with hemophilia.[16] Randomized trials of TXA use in pediatric cardiac and major noncardiac surgery have found that TXA demonstrates efficacy in reducing perioperative blood loss and the amount of blood transfused without apparent morbidity or mortality.[14,17]

The aim of this prospective, randomized, double-blind, placebo-controlled, parallel trial was to evaluate the efficacy of a dose regimen of TXA to reduce blood loss and transfusion in children undergoing craniosynostosis reconstruction surgery. We hypothesized the primary and secondary outcome variables of the administration of TXA in this setting to be significantly reduced blood loss and significantly reduced blood transfusion, respectively.

Materials and Methods

Patient Population

After the authors received approval of the Committee on Clinical Investigation, Children's Hospital Boston, Boston, Massachusetts, and obtained informed parental consent for this study, 46 children (age range, 2 months to 6 yr) undergoing craniosynostosis reconstruction surgery were recruited for the study. Patients were excluded if there was a history of (1) hematologic abnormalities or coagulation, hepatic, renal, or vascular disorders or (2) ingestion of nonsteroidal antiinflammatory agents within 2 days or acetylsalicylic acid within 14 days before the scheduled surgery date.

Patients were randomly assigned using a simple randomization procedure to receive either intravenous TXA (TXA group) or 0.9% saline (placebo group). A 1:1 allocation ratio computer-generated, random number table was used, and the results were kept in sealed envelopes.

Perioperative Management

After induction of anesthesia and before skin incision, patients received a loading dose of 50 mg·kg^{-1} TXA (Cyclokapron®; Pharmacia and Upjohn Co., Pfizer Inc., New York, NY) diluted in saline to a volume of 1 ml·kg^{-1} administered as an infusion over 15 min, followed immediately by an infusion of 5 mg·kg^{-1}·h^{-1} (0.1 ml·kg^{-1}·h^{-1}). Patients in the placebo group received 1 ml·kg^{-1} saline (0.9%) over 15 min followed immediately by an infusion of 0.1 ml·kg^{-1}·h^{-1}. Both the loading dose and infusion of TXA and saline were administered *via* standard programmable syringe pumps. All solutions were prepared in identical 50-ml syringes by the hospital pharmacy. The anesthesiologists, operating room personnel, and study staff were unaware of the treatment assignment. The TXA dose was deliberately selected at 50% of the dose we previously investigated in children 7 yr and older.[18] This extrapolation was based on 1-month and 1-yr-old infants' 50th percentile body surface area measuring one third and one half, respectively, that of a 7-yr-old child.[19] We recognize that, in the absence of pharmacokinetic knowledge of TXA in children, there is no single reliable scaling method that would guide the prediction of the appropriate dose.

Anesthetic management was standardized and consisted of an inhalation induction with sevoflurane, nitrous oxide, and oxygen followed by intravenous vecuronium (0.1 mg·kg^{-1}). Anesthesia was maintained using sevoflurane (age-adjusted, end-tidal concentration of approximately 1 minimum alveolar concentration) in oxygen–air, intravenous sufentanil, and intermittent vecuronium as required. A loading dose of 0.2–0.5 μg·kg^{-1} sufentanil was administered before incision followed by an intravenous infusion of 0.1–0.5 μg·kg^{-1}·h^{-1}. The dose of sufentanil was adjusted to maintain mean blood pressure above 45 mmHg and within 20% of the preinduction baseline. All patients were intubated and mechanically ventilated to maintain normocapnia. Each patient had at least two large-bore intravenous lines established, along with an arterial and a urinary catheter. Esophageal temperature was maintained between 35.5° and 36.5°C. A precordial doppler probe was placed to monitor for venous air embolus.

Fluid therapy and blood loss were managed by the administration of crystalloid solutions, human albumin (5%), and blood products. Decisions regarding replacement and maintenance of intravascular volume were at the discretion of the individual anesthesiologist and guided by monitoring arterial blood pressure, urinary output (≥ 1 ml·kg^{-1}·h^{-1}), hematocrit, and arterial blood gas measurements performed every 30 min. Packed erythrocytes (PRBC) were transfused if the hematocrit was ≤ 0.25.

Fresh frozen plasma, platelets, and cryoprecipitate were administered intraoperatively in accordance with the recommendations of the American Society of Anesthesiologists Task Force on Blood Component Therapy.[20] PRBC were transfused at 10–15 ml·kg^{-1} increments to increase the he-

matocrit by approximately 7–10% and achieve a target hematocrit of approximately 0.30 at the end of the surgery.

Arterial blood samples were analyzed for hematocrit and electrolytes before the administration of the study drug and every 30 min thereafter until the end of surgery and at 24 h in the intensive care unit. Prothrombin time, partial thromboplastin time, platelet count, and fibrinogen concentration were measured preoperatively, intraoperatively after the estimated loss of approximately one blood volume, and postoperatively.

At the end of the surgery, the trachea was extubated successfully in all patients. All surgical procedures were performed by one of two plastic surgeons and a single neurosurgeon. Anesthesia management was provided by one of the study investigators.

Arterial blood samples for the measurement of TXA were collected before administration of the study drug (TXA or saline), at the completion of the loading dose, at 15-min intervals for the first hour, 30-min intervals for the second hour, and 60-min intervals for the remainder of the operation. Final samples were drawn at the end of the operation and 24 h after discontinuation of the infusion. The blood samples were immediately anticoagulated with EDTA and stored on ice. Plasma was separated by centrifugation (1,000 g for 10 min at 4°C) and stored at -70°C pending TXA analysis.

Measurement of TXA Concentrations

Measurement of TXA in plasma was performed using high-performance liquid chromatography (HPLC) as described in detail by Davey et al.[21] and Dowd et al.[22] with some modifications as described in the appendix. All TXA samples were analyzed in duplicate. Samples in the placebo group were also analyzed for TXA concentration.

Assessment of Coagulation and Blood Loss

An additional 1.8 ml blood was collected for thromboelastography (TEG®; Hemoscope, Niles, IL) analysis before study drug administration, before blood product transfusion, and at the end of the operation.

Because the estimation of blood loss is known to be inaccurate in this setting, blood loss was calculated using a formula previously described for this population,[6,23,24]

$$\mathrm{ERCV_{lost}} = \mathrm{ERCV_{preop}} + \mathrm{ERCV_{transfused}} - \mathrm{ERCV_{postop}}$$
$$(1)$$

where

$$\mathrm{ERCV(estimated\ red\ cell\ volume)} =$$
$$\mathrm{estimated\ blood\ volume\ (EBV)} \times \mathrm{hematocrit}/100 \quad (2)$$

The estimated blood volume was 80 ml·kg^{-1} for infants younger than 12 months and 75 ml·kg^{-1} for children older than 12 months.

$\mathrm{ERCV_{transfused}}$ was calculated as follows:

$$\mathrm{ERCV_{transfused}} = \mathrm{PRBC\ (ml)\ transfused} \times$$
$$\mathrm{hematocrit_{transfused\ PRBC}}/100 \quad (3)$$

where hematocrit$_{transfused\ PRBC}$ was 0.65 for Citrate Phosphate Dextrose Adenine-1 units given to infants younger than 12 months (as measured by Children's Hospital Boston blood bank for the last 40 units given [Steven Sloan, M.D., Ph.D., Assistant Professor of Pathology, Medical Director, Pediatric Transfusion Medicine, Children's Hospital Boston, Harvard Medical School, Boston, Massachusetts, written communication, August 2010]) and 0.6 for Additive Solution-3 units given to children older than 1 yr.[25]

The estimated blood volume loss was calculated by:

$$\mathrm{EBV_{lost}(ml/kg)} = \mathrm{ERCV_{lost}(ml)}/[\mathrm{wt(kg)}$$
$$\times \mathrm{hematocrit_{preop}}/100]. \quad (4)$$

All patients were examined postoperatively for clinical evidence of adverse events related to TXA, including clinically evident thromboembolic (including deep vein thrombosis) or neurologic events. Surgeons examined patients during outpatient clinic follow-up visits, and parents received a follow-up phone call from one of the investigators within 6 months after surgery to inquire about any apparent late adverse effects.

The primary and secondary outcome variables were reduction in perioperative blood loss and reduction in perioperative blood transfusion, respectively.

Statistical Analysis

The TXA and placebo groups were compared with respect to demographics, baseline characteristics, intraoperative and postoperative laboratory and vital data, thromboelastography data, the amount of blood loss, PRBC transfusion, and length of stay in the intensive care unit and hospital. The distribution of all continuous variables that followed a normal Gaussian distribution as assessed by the Kolmogorov-Smirnov Lilliefors goodness-of-fit test[26] are presented as mean $\pm$ SD and compared between groups by the two-sample Student t test. Mean differences in total blood loss and PRBC transfused between the two groups were described with 95% confidence intervals. Categorical data, such as gender, race, American Society of Anesthesiologists (ASA) physical status, and presence of increased intracranial pressure, were compared by the Pearson chi-square test. Continuous data not conforming to a normal distribution because of skewness, including length of stay and units of transfused blood, are reported using medians and ranges and compared with the nonparametric Mann–Whitney U test. Fisher exact test was used to test differences in proportions based on small numbers in a two-by-two table, such as percentage of patients in each group needing fresh frozen plasma, cryoprecipitate, or platelets. Multiple linear regression analysis was applied to compare total blood loss and total PRBC

Table 1. Demographics and Baseline Characteristics of the Two Treatment Groups

Variable	TXA Group (n = 23)	Placebo Group (n = 20)	P Value
Age (months)	23 ± 19	25 ± 20	0.80
Weight (kg)	11.4 ± 3.5	11.7 ± 4.2	0.81
Gender			0.55
Male	15 (65%)	11 (55%)	—
Female	8 (35%)	9 (45%)	—
Race			0.59
Caucasian	18 (78%)	16 (80%)	—
Hispanic	3 (13%)	1 (5%)	—
African American	2 (9%)	2 (10%)	—
Asian	0 (0%)	1 (5%)	—
ASA physical status			0.44
I	5 (22%)	2 (10%)	—
II	12 (52%)	14 (70%)	—
III	6 (26%)	4 (20%)	—
Presence of syndrome*	4 (17%)	5 (25%)	0.71
Reoperation†	6 (26%)	5 (25%)	0.99
Duration of surgery (min)	272 ± 76	252 ± 58	0.32
Percent bone involved	74 ± 17	66 ± 19	0.15
Number of sutures‡ median (range)	2 (1–4)	1 (1–4)	0.85
Preoperative hematocrit (%)	34.2 ± 2.7	35.0 ± 4.0	0.45
Preoperative platelets (10^3 cells · μl^{-1})	412 ± 92	408 ± 178	0.92
Preoperative PT (s)	10.5 ± 0.5	10.6 ± 0.4	0.50
Preoperative PTT (s)	27.7 ± 3.1	26.7 ± 2.7	0.77
Preoperative INR	0.98 ± 0.05	0.99 ± 0.04	0.53
Preoperative fibrinogen (mg·dl^{-1})	280 ± 58	260 ± 33	0.40
Creatinine (mg·dl^{-1})	0.26 ± 0.07	0.27 ± 0.07	0.89
Increased ICP	11 (48%)	7 (35%)	0.54

* Syndromes include Pfeiffer, Crouzon, Saethre-Chotzen, Apert, and Rubinstein-Taybi. † Indicates patients had previous craniosynostosis surgery. ‡ Sutures include sagittal, metopic, coronal, and lambdoid.

ASA = American Society of Anesthesiologists; ICP = intracranial pressure, as detected by preoperative papilledema with or without intraoperative evidence of endocortical erosion of the cranial bones; INR = international normalized ratio; PT = prothrombin time; PTT = partial thromboplastin time; TXA = tranexamic acid.

transfused to test whether differences between the TXA and placebo groups hold after accounting for the effects of seven other covariates: body weight, duration of surgery, second operation, percentage of bone involved, number of sutures, postoperative hematocrit, and evidence of increased intracranial pressure.[27] Adjusted R^2 was used as a measure of model fit to the data.[28] In this prospective study, power analysis was performed *a priori* using the nQuery Advisor package (version 7.0; Statistical Solutions, Saugus, MA) to determine the required number of patients to randomize, and the sample sizes of 23 patients per group provided 80% statistical power (two-tailed $\alpha = 0.05$, $\beta = 0.20$) for detecting a moderate to large effect size (mean difference± SD) of 0.85 or greater in total blood loss between the two groups using the two-sample Student t test with a two-tailed α level of 0.05.[29] The desired effect size was 0.85 because we had expected to capture a mean difference in total blood loss between the TXA and placebo groups of approximately 50 ml/kg with an expected SD of 50–60 ml/kg. We used the traditional two-tailed α level of 0.05 as the criterion for statistical significance because the mean difference in total blood loss was the primary efficacy outcome of interest. For all statistical tests, a two-tailed value of $P < 0.05$ was considered the criterion for statistical significance. Statistical analysis was conducted

using the SPSS package version 18.0 (SPSS Inc./IBM, Chicago, IL).

Results

Patient Demographics

Forty-six patients, ages 2 months to 6 yr (23 ± 19 months), were enrolled in the study between February 2007 and August 2010. Three patients were excluded from analysis in the placebo group because of a protocol violation in one and a change in surgical procedure on the day of surgery in the other two. Forty-three patients completed the study and were randomly assigned to the TXA (n = 23) or placebo group (n = 20). Patients in the TXA group were similar to those in the placebo group in demographics (table 1).

Effect of TXA on Blood Loss and Transfusion

Figure 1 and table 2 show the amount of perioperative blood loss and PRBC transfusion in these patients. Intraoperative blood loss was lower in the TXA group than in the placebo group (mean, 62 *vs.* 101 ml·kg^{-1}; $P = 0.008$). Postoperative blood loss was lower in the TXA group than in the placebo group (median, 3 *vs.* 12 ml·kg^{-1}; $P < 0.001$). The mean difference between the TXA and placebo groups for total
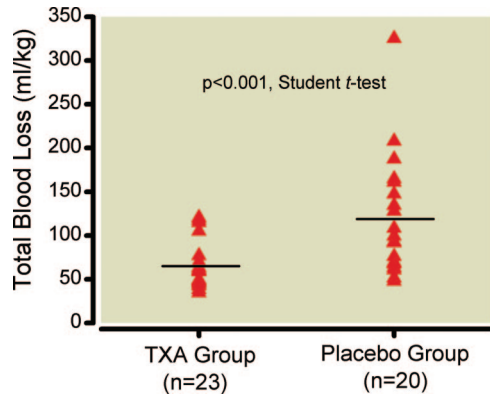
Fig. 1. Total blood loss in the tranexamic acid (TXA) and placebo groups. The *solid horizontal lines* represent mean blood loss volume in the TXA group (65 ml·kg^{-1}) compared with that in the placebo group (119 ml·kg^{-1}) ($P < 0.001$). *Triangles* represent individual patients.
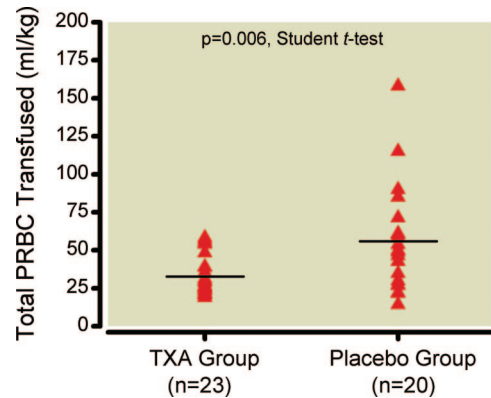

Fig. 2. Total packed erythrocyte (PRBC) volume transfusion in the tranexamic acid (TXA) and placebo groups. The *solid horizontal lines* represent mean PRBC volume transfused in the TXA group (33 ml·kg^{-1}) compared with that in the placebo group (56 ml·kg^{-1}) ($P = 0.006$). *Triangles* represent individual patients.

blood loss was 54 ml·kg^{-1} (95% CI for the difference: 23–84 ml·kg^{-1}).

All patients in both groups received blood transfusions (fig. 2). The volume of PRBC transfused intraoperatively was significantly lower in the TXA group than the placebo group (mean, 33 *vs.* 48 ml·kg^{-1}; $P = 0.03$), as was the PRBC volume transfused within 24 h after surgery (median, 0 *vs.* 5 ml·kg^{-1}; $P < 0.001$). The mean difference between the TXA and placebo groups for PRBC transfused was 23 ml·kg^{-1} (95% CI for the difference: 7–39 ml·kg^{-1}). The number of units of PRBC transfused intraoperatively (median, 1 *vs.* 2 units; $P < 0.001$) and within 24 h after surgery (median, 0 *vs.* 1 units; $P < 0.001$) was significantly lower in the TXA group than in the placebo group. Fifty percent of the patients in the placebo group

required postoperative blood transfusion, whereas no patients in the TXA group required such transfusion. In addition, more patients in the placebo group than in the TXA group were treated with intraoperative fresh frozen plasma (table 3).

Multivariable analysis, adjusting for covariates with respect to total (intraoperative and postoperative) blood loss and total PRBC transfusion, revealed that among the eight variables tested (TXA treatment, body weight, duration of surgery, second operation, percentage of bone involved, number of sutures, postoperative hematocrit, and evidence of increased intracranial pressure), only administration of TXA and body weight independently predicted total blood loss and transfusion (table 4).

Table 2. Blood Loss, Packed Erythrocyte Cell Transfusion, and Length of Stay

Variable	TXA Group (n = 23)	Placebo Group (n = 20)	P Value
Blood loss (ml·kg^{-1})			
Intraoperative	62 ± 22	101 ± 63	0.008*
Postoperative	3 (0–25)	12 (5–64)	< 0.001*
Total	65 ± 26	119 ± 67	< 0.001*
PRBC transfused (ml·kg^{-1})			
Intraoperative	33 ± 13	48 ± 29	0.03*
Postoperative	0 (0–0)	5 (0–31)	< 0.001*
Total	33 ± 13	56 ± 35	0.006*
Number of patients transfused postoperatively	0 (0%)	10 (50%)	0.01*
Units of blood transfused			
Intraoperative	1 (1–2)	2 (1–4)	< 0.001*
Postoperative	0 (0–0)	1 (1–2)	< 0.001*
Total	1 (1–2)	3 (1–4)	< 0.001*
Length of stay (days)			
ICU	1 (1–14)	1 (1–3)	0.99
In hospital	3 (2–20)	3 (2–6)	0.62

Plus–minus values are mean ± SD with groups compared by the Student t test. Other data are summarized using the median (range) because of significant skewness, with groups compared by the nonparametric Mann–Whitney U test.

* Statistically significant.

ICU = intensive care unit; PRBC = packed erythrocytes; TXA = tranexamic acid.

Table 3. Intraoperative and Postoperative Data

Variable	TXA Group (n = 23)	Placebo Group (n = 20)	P Value
Intraoperative			—
Heart rate (beats/min)	117 ± 11	118 ± 10	0.78
SBP (mmHg)	85 ± 6	89 ± 9	0.16
DBP (mmHg)	42 ± 6	45 ± 7	0.24
MAP (mmHg)	50 ± 5	54 ± 7	0.17
SpO_2 (%)	100 ± 0.4	100 ± 0.2	0.51
Crystalloids (ml·kg^{-1})	48 ± 28	49 ± 18	0.92
Albumin (ml·kg^{-1})	21 ± 14	25 ± 19	0.47
Urine output (ml·kg^{-1})	9 ± 6	8 ± 5	0.74
Hematocrit (%)	32.0 ± 3.5	31.9 ± 4.2	0.90
Platelets (K cells/μl)	226 ± 77	231 ± 110	0.88
INR	1.24 ± 0.22	1.22 ± 0.12	0.77
Fibrinogen (mg·dl^{-1})	168 ± 57	156 ± 53	0.51
PT (s)	12.5 ± 0.9	12.8 ± 1.2	0.45
PTT (s)	27.6 ± 4.8	26.4 ± 4.3	0.47
Use of FFP	0 (0%)	4 (20%)	0.04*
Use of platelets	0 (0%)	0 (0%)	1.00
Postoperative			—
Hematocrit (%)	31.3 ± 3.8	28.2 ± 6.5	0.07
Platelets (10^3 cells·μl^{-1})	219 ± 62	203 ± 66	0.43
INR	1.15 ± 0.11	1.17 ± 0.22	0.85
Fibrinogen (mg·dl^{-1})	302 ± 51	269 ± 72	0.28
PT (s)	12.1 ± 0.9	12.0 ± 1.0	0.65
PTT (s)	31.6 ± 5.5	27.6 ± 3.0	0.15
Crystalloids (ml·kg^{-1})	53 ± 19	54 ± 24	0.88
JP drain output (ml·kg^{-1})	12 ± 4	12 ± 6	0.89
Use of FFP	1 (4%)	2 (10%)	0.59
Use of platelets	0 (0%)	2 (10%)	0.21
Use of cryoprecipitate	1 (4%)	2 (10%)	0.59

Plus–minus values are mean ± SD.

* Statistically significant.

DBP = diastolic blood pressure; FFP = fresh frozen plasma; INR = international normalized ratio; JP = Jackson Pratt; MAP = mean arterial pressure; PT = prothrombin time; PTT = partial thromboplastin time; SBP = systolic blood pressure; SpO_2 = oxygen saturation; TXA = tranexamic acid.

No patients in the TXA group had any complications. One patient in the placebo group, who required PRBC in the intensive care unit, had a transfusion reaction. No patient in either group had clinical evidence of thromboembolic or neurologic complications.

Effect of TXA on Coagulation Profile

Thromboelastography parameters of Reaction time (mm), Coagulation time (mm), Maximum amplitude (mm), α Angle (°), and Fibrinolysis at 30 and 60 minutes (%) were not significantly different between groups for the three time points measured:

Table 4. Predictors of Total Blood Loss and Total Packed Erythrocyte Transfusion

Variable	Total Blood Loss (ml·kg^{-1})		Total PRBC Transfusion (ml·kg^{-1})	
	Univariate Analysis Test, P Value	Multivariable P Value	Univariate Analysis Test, P Value	Multivariable P Value
TXA	t = 3.55, < 0.001	< 0.001*	t = 2.95, 0.006	< 0.001*
Body weight	r = −0.37, 0.02	0.003*	r = −0.50, < 0.001	< 0.001*
Duration	r = −0.26, 0.09	0.93	r = 0.32, 0.03	0.88
Reoperation	t = 0.94, 0.36	0.67	t = 0.82, 0.42	0.29
% Bone	r = −0.12, 0.44	0.92	r = 0.02, 0.90	0.36
Number of sutures	r = −0.06, 0.70	0.64	r = 0.01, 0.91	0.87
Postoperative hematocrit	r = −0.20, 0.18	0.32	r = −0.07, 0.65	0.52
Increased ICP	t = 1.05, 0.30	0.80	t = 0.92, 0.36	0.95

* Significant independent multivariable predictor based on multiple linear regression. Adjusted model R^2 = 0.48 for total blood loss, R^2 = 0.45 for total transfusion.

ICP = intracranial pressure; PRBC = packed erythrocytes; TXA = tranexamic acid.
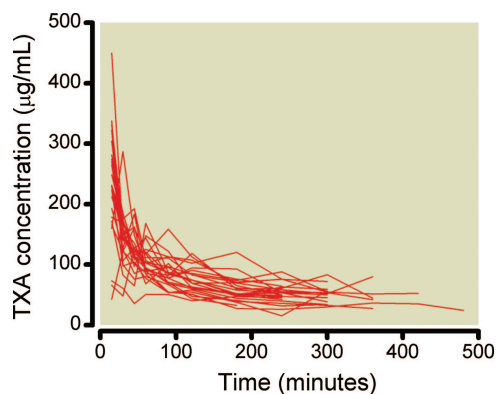
Fig. 3. Tranexamic acid (TXA) plasma concentrations *versus* time.

during surgery at baseline, before the first PRBC transfusion, and at the end of surgery.

TXA Plasma Concentrations

The observed TXA plasma concentration *versus* time curves of each patient during surgery are shown in figure 3. TXA plasma concentrations remained above 16 μg·ml^{-1} at all time points during the surgery in all patients. In the placebo group, no plasma TXA concentration was detected in any patient.

Discussion

The main findings of this study are that (1) administration of TXA significantly reduces both total blood loss and volume of PRBC transfused and (2) a 50 mg·kg^{-1} bolus dose followed by an infusion of 5 mg·kg^{-1}·h^{-1} maintains TXA plasma concentrations above the *in vitro* thresholds reported for inhibition of fibrinolysis (10 μg·ml^{-1})[30] and plasminogen-induced platelet activation (16 μg·ml^{-1})[30–32] throughout the infusion duration.

Intraoperative administration of TXA produced a significant reduction of blood loss (ml·kg^{-1}) by a mean value of 38% intraoperatively and 72% during the first 24 h after surgery. TXA also significantly reduced the volume of PRBC transfused (ml·kg^{-1}) by 32%. In the first 24 h after surgery, no child in the TXA group required blood transfusion, whereas 10 children (50%) in the placebo group required an average PRBC transfusion of 4.5 ml·kg^{-1} (table 2). TXA administration also significantly diminished the overall exposure of the patients to donor blood by two thirds (median, 1 unit *vs.* 3 units; $P < 0.001$) (table 2).

Multivariable analysis showed the strength of the relationship between TXA and a reduction in perioperative blood loss and transfusion. The efficacy of TXA holds after adjusting for the effects of seven other covariates (body weight, duration of surgery, second operation, percentage of bone involved, number of sutures, postoperative hematocrit, and evidence of increased intracranial pressure). The only predictor of blood loss and transfusion, besides TXA, was body weight less than 10 kg. Blood loss during craniosynostosis surgery may be disproportionately greater in infants with

smaller body weight than in older children because the head represents a larger percentage of total body surface area.[33] The findings of this study are in agreement with previous reports of the inverse relationship between body size and the amount of blood loss and transfusion requirements during craniosynostosis reconstruction surgery.[3,6,8]

Several strategies to reduce blood loss and transfusion in children undergoing craniosynostosis reconstruction surgery have been investigated. The interpretation of these studies, which use monotherapy and multimodal strategies, is difficult because of inconsistent experimental methodology. These strategies include increasing preoperative erythrocyte mass using erythropoietin,[34–37] perioperative blood salvage (cell saver),[38–41] normovolemic hemodilution,[42] and controlled hypotension.[43] Several studies have found that erythropoietin alone or in combination with other methods is effective in reducing allogeneic blood transfusion.[34–37] One potential drawback to using erythropoietin in healthy patients is the prohibitive cost and the logistical burden of weekly injections for 3–4 weeks before surgery. The use of cell saver has had mixed reviews with minimal, if any, benefit noted.[38–41] Other strategies for conserving blood, such as acute hemodilution or controlled hypotension, may compromise tissue oxygen delivery during rapid blood loss, particularly in infants.

Tranexamic acid has been effectively used to reduce blood loss and transfusion in pediatric cardiac,[24,44,45] orthopedic,[18,46] and cranial remodeling surgery[47] without morbidity in small patient populations. However, it is difficult to compare these studies because TXA was used in wide dose ranges (from 10 to 100 mg·kg^{-1} loading doses and 1–10 mg·kg^{-1}·h^{-1} infusion rates) and the children were of different ages and undergoing different surgical procedures.

There is only one small prospective, randomized, placebo-controlled, single-blinded study that compared the effectiveness of TXA (n = 10) with placebo (n = 10) in reducing blood loss and transfusion in children undergoing cranial remodeling surgery.[47] TXA was administered intermittently; 15 mg·kg^{-1} before surgical incision, every 4 h during surgery, and every 8 h throughout the first 48 h after surgery. The results showed a significant reduction (by 31%) in intraoperative blood loss. There were no significant differences between the groups in blood transfusion requirement during the intra- and postoperative periods. This dosing regimen produced much less intraoperative and postoperative reductions in blood transfusion requirement than we found in our study.

TXA Plasma Concentrations

It is uncertain what the required plasma concentration of TXA is to inhibit fibrinolysis in children or adults. *In vitro* data suggest that the minimal plasma concentration of TXA needed to inhibit tissue activator activity by 80% is 10 μg·ml^{-1}.[30] TXA also may abolish plasmin-induced platelet activity *in vitro* at 16 μg·ml^{-1}.[31,32]

The dosing schedule selected in this study produced individual plasma concentrations of TXA above 16 μg·ml^{-1} in all patients at all times during surgery. Arguably, this dosing scheme may have been high, particularly the loading dose, because peak plasma concentrations were 4–20 times greater than the presumed therapeutic plasma concentration. Higher plasma concentrations may cause side effects. However, no incidences of neurologic events, including seizures or thromboembolic complications, were observed in our study or in other previous trials that used a wide range of TXA doses in a limited number of children undergoing noncardiac surgery. Recently, a large series of infants and children (1–19 months; n = 114) undergoing cardiac surgery reported a probable association of postoperative seizures to administration of high doses of TXA (50 mg·kg^{-1} at the beginning and end of cardiopulmonary bypass and 100 mg addition to the priming solution).[48] This higher seizure rate of 3.5% did not reach statistical significance compared with the seizure rate associated with the administration of aprotinin. The study did not analyze the possible causes (ischemic *vs.* nonischemic) of the seizures.

A significantly increased susceptibility to seizures after administration of large doses of TXA has been reported recently in adults undergoing cardiopulmonary bypass cardiac surgery.[49,50] We did not observe thrombotic or neurologic adverse effects or other side effects in the current study; however, our study was not powered to detect adverse events.

We noted a relatively wide interpatient variability in the plasma TXA concentrations, which might be attributable to elimination of TXA through rapid surgical blood loss or interindividual differences in TXA volume of distribution and elimination clearance. This also may explain the failure to achieve stable plasma concentrations at a steady infusion rate of TXA. Despite this large variability in plasma concentration, the TXA dosing schedule in the current study maintained concentrations above the presumed antifibrinolytic threshold of 16 μg·ml^{-1}. Additional studies of TXA pharmacokinetics and dose response are warranted to evaluate the optimal dose schedule for specific surgical procedures in children.

After discontinuation of TXA infusion, blood loss and the transfusion requirement remained significantly low for the following 24 h. The extended effect of TXA and reduction of blood transfusion requirement after discontinuation of the drug was observed in our study and in studies of children after craniofacial,[47] orthopedic,[18,46] and cardiac[44,51] surgeries, despite the short mean elimination half-life of 120 min. This effect probably was attributable to residual tissue TXA at the surgical wound site.[46]

Measurement of the thromboelastographic parameters of time, rate, and strength and stability of the clot were not, as expected, different between the groups, indicating that no patient experienced coagulopathy. The efficacy of TXA despite the absence of systemic fibrinolysis suggests that the mechanism of action of TXA is not systemic but rather a localized effect at the site of the surgery. Supporting this theory is the topical application of TXA in cardiac surgery and orthopedic surgery having been found to be effective at reducing bleeding and transfusion requirements.[52,53]

Conclusion

A dosing regimen of 50 mg·kg^{-1} TXA initially followed by a 5 mg·kg^{-1}·h^{-1} infusion is effective in reducing blood loss and transfusion requirements in children undergoing craniosynostosis surgery.

References

1. Chadduck WM: Craniosynostosis, Pediatric Neurosurgery, 3rd Edition. Edited by Cheek WR. Philadelphia, WB Saunders, 1994, pp 111-23
2. Reiner D: Intracranial pressure in craniosynostosis: Pre- and postoperative recordings—correlation with functional results, Scientific Foundations and Surgical Treatment of Craniosynostosis. Edited by Persing JA, Edgerton MT, Jane JA. Baltimore, Williams & Wilkins, 1989, pp 263-9
3. White N, Marcus R, Dover S, Solanki G, Nishikawa H, Millar C, Carver ED: Predictors of blood loss in fronto-orbital advancement and remodeling. J Craniofac Surg 2009; 20: 378-81
4. Vamvakas EC: Long-term survival rate of pediatric patients after blood transfusion. Transfusion 2008; 48:2478-80
5. Czerwinski M, Hopper RA, Gruss J, Fearon JA: Major morbidity and mortality rates in craniofacial surgery: An analysis of 8101 major procedures. Plast Reconstr Surg 2010; 126:181-6
6. Stricker PA, Shaw TL, Desouza DG, Hernandez SV, Bartlett SP, Friedman DF, Sesok-Pizzini DA, Jobes DR: Blood loss, replacement, and associated morbidity in infants and children undergoing craniofacial surgery. Paediatr Anaesth 2010; 20:150-9
7. Phillips RJ, Mulliken JB: Venous air embolism during a craniofacial procedure. Plast Reconstr Surg 1988; 82:155-9
8. Faberowski LW, Black S, Mickle JP: Blood loss and transfusion practice in the perioperative management of craniosynostosis repair. J Neurosurg Anesthesiol 1999; 11:167-72
9. Ririe DG, Lantz PE, Glazier SS, Argenta LC: Transfusion-related acute lung injury in an infant during craniofacial surgery. Anesth Analg 2005; 101:1003-6
10. Tunçbilek G, Vargel I, Erdem A, Mavili ME, Benli K, Erk Y: Blood loss and transfusion rates during repair of craniofacial deformities. J Craniofac Surg 2005; 16:59-62
11. Williams GD, Ellenbogen RG, Gruss JS: Abnormal coagulation during pediatric craniofacial surgery. Pediatr Neurosurg 2001; 35:5-12
12. Buntain SG, Pabari M: Massive transfusion and hyperkalaemic cardiac arrest in craniofacial surgery in a child. Anaesth Intensive Care 1999; 27:530-3
13. Henry D, Carless P, Fergusson D, Laupacis A: The safety of aprotinin and lysine-derived antifibrinolytic drugs in cardiac surgery: A meta-analysis. CMAJ 2009; 180:183-93
14. Schouten ES, van de Pol AC, Schouten AN, Turner NM, Jansen NJ, Bollen CW: The effect of aprotinin, tranexamic acid, and aminocaproic acid on blood loss and use of blood products in major pediatric surgery: A meta-analysis. Pediatr Crit Care Med 2009; 10:182-90
15. Dunn CJ, Goa KL: Tranexamic acid: A review of its use in surgery and other indications. Drugs 1999; 57:1005-32

16. Cyklokapron [package insert]. New York: Pharmacia and Upjohn Co; 2008

17. Tzortzopoulou A, Cepeda MS, Schumann R, Carr DB: Antifibrinolytic agents for reducing blood loss in scoliosis surgery in children. Cochrane Database Syst Rev 2008: CD006883

18. Sethna NF, Zurakowski D, Brustowicz RM, Bacsik J, Sullivan LJ, Shapiro F: Tranexamic acid reduces intraoperative blood loss in pediatric patients undergoing scoliosis surgery. ANESTHESIOLOGY 2005; 102:727–32

19. Johnson TN: The problems in scaling adult drug doses to children. Arch Dis Child 2008; 93:207–11

20. Practice Guidelines for blood component therapy: A report by the American Society of Anesthesiologists Task Force on Blood Component Therapy. ANESTHESIOLOGY 1996; 84:732–47

21. Davey JF, Ersser RS: Amino acid analysis of physiological fluids by high-performance liquid chromatography with phenylisothiocyanate derivatization and comparison with ion-exchange chromatography. J Chromatogr 1990; 528:9–23

22. Dowd NP, Karski JM, Cheng DC, Carroll JA, Lin Y, James RL, Butterworth J: Pharmacokinetics of tranexamic acid during cardiopulmonary bypass. ANESTHESIOLOGY 2002; 97:390–9

23. Kearney RA, Rosales JK, Howes WJ: Craniosynostosis: An assessment of blood loss and transfusion practices. Can J Anaesth 1989; 36:473–7

24. Eaton MP: Antifibrinolytic therapy in surgery for congenital heart disease. Anesth Analg 2008; 106:1087–100

25. Blood components, Blood Transfusion Therapy: A Physician's Handbook 7th edition. Edited by Triulzi DJ, Aysola A, American Association of Blood Banks. Bethesda, American Association of Blood Banks, 2002, pp 1–37

26. Lilliefors H: On the Kolmogorov-Smirnov test for normality with mean and variance unknown. J Am Stat Assoc 1967; 62:399–402

27. Katz MH: Multivariable Analysis: A Practical Guide for Clinicians, 2nd edition. Cambridge, England, Cambridge University Press, 2006, pp 96–116

28. Chatterjee S, Hadi AS: Regression Analysis by Example, 4th edition. New York, Wiley Interscience, 2006, pp 53–84

29. Browner WS, Newton TB, Cummings SR, Hulley SB: Estimating Sample Size and Power: The Nittygritty, Designing Clinical Research, 2nd edition. Edited by Hully S, Cummings S, Browner W, Grady D, Hearst N, Newman T. Philadelphia, Lippincott Williams & Wilkins, 2001, pp 65–91

30. Andersson L, Nilsoon IM, Colleen S, Granstrand B, Melander B: Role of urokinase and tissue activator in sustaining bleeding and the management thereof with EACA and AMCA. Ann N Y Acad Sci 1968; 146:642–58

31. Andersson L, Eriksson O, Hedlund PO, Kjellman H, Lindqvist B: Special considerations with regard to the dosage of tranexamic acid in patients with chronic renal diseases. Urol Res 1978; 6:83–8

32. Soslau G, Horrow J, Brodsky I: Effect of tranexamic acid on platelet ADP during extracorporeal circulation. Am J Hematol 1991; 38:113–9

33. Livingston EH, Lee S: Percentage of burned body surface area determination in obese and nonobese patients. J Surg Res 2000; 91:106–10

34. Fearon JA, Weinthal J: The use of recombinant erythropoietin in the reduction of blood transfusion rates in craniosynostosis repair in infants and children. Plast Reconstr Surg 2002; 109:2190–6

35. Meneghini L, Zadra N, Aneloni V, Metrangolo S, Faggin R, Giusti F: Erythropoietin therapy and acute preoperative normovolaemic haemodilution in infants undergoing craniosynostosis surgery. Paediatr Anaesth 2003; 13:392–6

36. Krajewski K, Ashley RK, Pung N, Wald S, Lazareff J, Kawamoto HK, Bradley JP: Successful blood conservation during cranio-

37. synostotic correction with dual therapy using procrit and cell saver. J Craniofac Surg 2008; 19:101–5

37. Przybylo HJ, Przybylo JH: The use of recombinant erythropoietin in the reduction of transfusion rates in craniosynostosis repair in infants and children. Plast Reconstr Surg 2003; 111:2485–6; author reply 2486–7

38. Velardi F, Di Chirico A, Di Rocco C, Fundaro C, Serafini R, Piastra M, Viola L, Pietrini D, Pusateri A, Stoppa F: "No allogeneic blood transfusion" protocol for the surgical correction of craniosynostoses. I. Rationale. Childs Nerv Syst 1998; 14:722–31; discussion 740–1

39. Jimenez DF, Barone CM: Intraoperative autologous blood transfusion in the surgical correction of craniosynostosis. Neurosurgery 1995; 37:1075–9

40. Dahmani S, Orliaguet GA, Meyer PG, Blanot S, Renier D, Carli PA: Perioperative blood salvage during surgical correction of craniosynostosis in infants. Br J Anaesth 2000; 85:550–5

41. Deva AK, Hopper RA, Landecker A, Flores R, Weiner H, McCarthy JG: The use of intraoperative autotransfusion during cranial vault remodeling for craniosynostosis. Plast Reconstr Surg 2002; 109:58–63

42. Hans P, Collin V, Bonhomme V, Damas F, Born JD, Lamy M: Evaluation of acute normovolemic hemodilution for surgical repair of craniosynostosis. J Neurosurg Anesthesiol 2000; 12:33–6

43. Diaz JH, Lockhart CH: Hypotensive anaesthesia for craniectomy in infancy. Br J Anaesth 1979; 51:233–5

44. Reid RW, Zimmerman AA, Laussen PC, Mayer JE, Gorlin JB, Burrows FA: The efficacy of tranexamic acid *versus* placebo in decreasing blood loss in pediatric patients undergoing repeat cardiac surgery. Anesth Analg 1997; 84:990–6

45. Gruber EM, Shukla AC, Reid RW, Hickey PR, Hansen DD: Synthetic antifibrinolytics are not associated with an increased incidence of baffle fenestration closure after the modified Fontan procedure. J Cardiothorac Vasc Anesth 2000; 14:257–9

46. Neilipovitz DT, Murto K, Hall L, Barrowman NJ, Splinter WM: A randomized trial of tranexamic acid to reduce blood transfusion for scoliosis surgery. Anesth Analg 2001; 93:82–7

47. Durán de la Fuente P, García-Fernández J, Pérez-López C, Carceller F, Gilsanz Rodríguez F: [Usefulness of tranexamic acid in cranial remodeling surgery]. Rev Esp Anestesiol Reanim 2003; 50:388–94

48. Breuer T, Martin K, Wilhelm M, Wiesner G, Schreiber C, Hess J, Lange R, Tassani P: The blood sparing effect and the safety of aprotinin compared to tranexamic acid in paediatric cardiac surgery. Eur J Cardiothorac Surg 2009; 35:167–71; author reply 171

49. Martin K, Wiesner G, Breuer T, Lange R, Tassani P: The risks of aprotinin and tranexamic acid in cardiac surgery: A one-year follow-up of 1188 consecutive patients. Anesth Analg 2008; 107:1783–90

50. Murkin JM, Falter F, Granton J, Young B, Burt C, Chu M: High-dose tranexamic Acid is associated with nonischemic clinical seizures in cardiac surgical patients. Anesth Analg 2010; 110:350–3

51. Chauhan S, Bisoi A, Modi R, Gharde P, Rajesh MR: Tranexamic acid in paediatric cardiac surgery. Indian J Med Res 2003; 118:86–9

52. Abrishami A, Chung F, Wong J: Topical application of antifibrinolytic drugs for on-pump cardiac surgery: A systematic review and meta-analysis. Can J Anaesth 2009; 56:202–12

53. Wong J, Abrishami A, El Beheiry H, Mahomed NN, Roderick Davey J, Gandhi R, Syed KA, Muhammad Ovais Hasan S, De Silva Y, Chung F: Topical application of tranexamic acid reduces postoperative blood loss in total knee arthroplasty: A randomized, controlled trial. J Bone Joint Surg Am 2010; 92:2503–13

Appendix

TXA HPLC Analysis

Reagents

Tranexamic acid for use as a standard was provided by Pharmacia/Upjohn, division of Pfizer Inc (New York, NY). Phenyl isothiocyanate and L-norleucine were of peptide sequencing grade. All organic chemicals and reagents used for HPLC were of HPLC grade or better.

Plasma Preparation and Derivatization

One hundred microliters plasma was mixed with an equivalent volume of 1 mM L-norleucine that had been prepared in 0.1 N HCl and then partially purified using Amicon Ultra/Ultracel 10K membrane filters (Millipore, Billerica, MA). After centrifugation at 6,400 revolutions per minute for 30 min, 50 μl filtrate was dried under vacuum and treated with 10 μl solution containing 1 M sodium acetate:tetraethylammonium:methanol (2:2:1 v/v). Samples were vacuum-dried and derivatization performed by adding 20 μl methanol:tetraethylammonium:water:phenyl isothiocyanate (7:1:1:1, v/v) for 20 min at room temperature. The derivatized samples were vacuum-dried, reconstituted in 100 μl solution containing 5 mM sodium phosphate, pH 7.4, and acetonitrile (950:50 v:v) and transferred to glass tubes for HPLC analysis.

HPLC

The chromatographic system was an Agilent 1200 Series (Santa Clara, CA) with equipment that included an autosampler, in-line degasser, binary pump, oven, and photodiode ultraviolet/visible light detector. The analytical column was a Nova-Pak C18 (4 μm;

Table 5. High-performance Liquid Chromatography Gradient for Tranexamic Acid

Time (min)	%B
0	3
13.5	9
20	30
30	30
35	100
45	100
52	3
54	3

%B = percentage of mobile phase B.

3.9 × 300 mm; Waters Corp, Milford, MA). Mobile phase A contained 70 mM sodium acetate, pH 6.5, and acetonitrile (975:25 v:v). Mobile phase B contained acetonitrile:water:methanol (450:400:150 v:v). The flow rate was 1 ml · min^{-1} using a gradient, as outlined in table 5 above; column temperature was maintained at 38°C. The elution of derivatized TXA and L-norleucine (internal standard) was monitored at 254 nm.

Assay Performance

Standard curves were linear over a TXA concentration range of 10–1,800 μg·ml^{-1}; the standard curve linear regression R^2 typically equaled 0.96–0.98. The lower limit of detection was 3–5 μg·ml^{-1}. The coefficient of variation for samples in the concentration range of 25–250 μg·ml^{-1} was 7.8% (SD increased proportionately with measured concentration). Assay accuracy and precision in plasma samples were 93% and 95%, respectively.