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Paediatrics

High-dose *versus* low-dose tranexamic acid for paediatric craniosynostosis surgery: a double-blind randomised controlled non-inferiority trial

Susan M. Goobie[1,*], Steven J. Staffa[1], John G. Meara[2], Mark R. Proctor[3], Miriam Tumolo[4], Giuliana Cangemi[5] and Nicola Disma[4]

[1]Department of Anesthesiology, Critical Care and Pain Medicine, Boston Children's Hospital, Harvard Medical School, Boston, MA, USA, [2]Department of Plastic and Oral Surgery, Boston Children's Hospital, Harvard Medical School, Boston, MA, USA, [3]Department of Neurosurgery, Boston Children's Hospital, Harvard Medical School, Boston, MA, USA, [4]Department of Anaesthesia, IRCCS Istituto Giannina Gaslini, Genoa, Italy and [5]Central Laboratory of Analyses, IRCCS Istituto Giannina Gaslini, Genoa, Italy

*Corresponding author. E-mail: susan.goobie@childrens.harvard.edu

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Abstract

Background: Tranexamic acid (TXA) reduces blood loss and transfusion in paediatric craniosynostosis surgery. The hypothesis is that low-dose TXA, determined by pharmacokinetic modelling, is non-inferior to high-dose TXA in decreasing blood loss and transfusion in children.

Methods: Children undergoing craniosynostosis surgery were enrolled in a two-centre, prospective, double-blind, randomised, non-inferiority controlled trial to receive high TXA (50 mg kg^{-1} followed by 5 mg kg^{-1} h^{-1}) or low TXA (10 mg kg^{-1} followed by 5 mg kg^{-1} h^{-1}). Primary outcome was blood loss. Low dose was determined to be non-inferior to high dose if the 95% confidence interval (CI) for the mean difference in blood loss was above the non-inferiority margin of −20 ml kg^{-1}. Secondary outcomes were transfusion, TXA plasma concentrations, and biological markers of fibrinolysis and inflammation.

Results: Sixty-eight children were included. Values were non-inferior regarding blood loss (39.4 [4.4] *vs* 40.3 [6.2] ml kg^{-1} [difference=0.9; 95% CI: −14.2, 15.9]) and blood transfusion (21.3 [1.6] *vs* 23.6 [1.5] ml kg^{-1} [difference=2.3; 95% CI: −2.1, 6.7]) between high-dose (n=32) and low-dose (n=34) groups, respectively. The TXA plasma concentrations during surgery averaged 50.2 (8.0) and 29.6 (7.6) μg ml^{-1}. There was no difference in fibrinolytic and inflammatory biological marker concentrations. No adverse events were observed.

Conclusions: Tranexamic acid 10 mg kg^{-1} followed by 5 mg kg^{-1} h^{-1} is not less effective than a higher dose of 50 mg kg^{-1} and 5 mg kg^{-1} h^{-1} in reducing blood loss and transfusion in paediatric craniosynostosis surgery.

Clinical trial registration: NCT02188576.

Keywords: anti-fibrinolytics; blood loss; blood transfusion; craniosynostosis surgery; paediatric anaesthesia; pharmacokinetics; tranexamic acid

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Editor's key points

- Tranexamic acid can reduce blood loss and blood transfusion in paediatric craniosynostosis surgery.
- This study validates tranexamic acid dosage schemes that have been recommended based on pharmacokinetic modelling.
- Tranexamic acid at a loading dose of 10 mg kg^{-1} and maintenance dose of mg kg^{-1} h^{-1} is effective and safe in reducing blood loss and blood transfusion requirements in paediatric craniosynostosis surgery.

More than 90% of craniofacial surgical procedures performed in children worldwide are associated with transfusion of blood products.[1,2] Intraoperative bleeding, measuring half to a whole a blood volume, is attributed to numerous factors, including accelerated fibrinolysis.[3] Anti-fibrinolytic agents are the most common effective pharmaceutical patient blood management (PBM) intervention.[4] Tranexamic acid (TXA) is a lysine analogue that competitively inhibits the conversion of plasminogen to plasmin, which is responsible for degradation of the fibrin clot. Tranexamic acid is an anti-fibrinolytic agent with anti-inflammatory properties at higher doses.[5] In our previous paediatric craniosynostosis surgery trial, TXA in a loading dose (LD) of 50 mg kg^{-1} and a 5 mg kg^{-1} h^{-1} maintenance dose (MD) significantly reduced blood loss and blood transfusion by two-thirds compared with placebo.[6] However, high TXA dosing schemes are associated with neurological complications, such as seizures.[7–9] Alternatively, studies using lower-dosage schemes do not report seizures in paediatrics.[10,11] In addition, recent expert consensus suggests that trials are urgently needed to clarify the risk and appropriate indications, and provide proper TXA dosing guidelines as regimes based on pharmacokinetic (PK) target blood concentrations have not been validated.[12–14] Our previously published TXA population PK model simulated dose–response curves and predicted that an ideal dosage scheme of 10 mg kg^{-1} LD followed by 5 mg kg^{-1} h^{-1} MD maintains TXA plasma concentrations above the presumed accepted therapeutic concentration of 16 μg ml^{-1}.[6,14,15]

The primary aim of this trial is to test non-inferiority and validate this lower-dosage scheme in children undergoing craniosynostosis reconstruction surgery, and to demonstrate generalisability by including two tertiary care hospitals. The hypothesis is that this low-dosage TXA scheme (10 mg kg^{-1} LD and 5 mg kg^{-1} h^{-1} MD) is non-inferior to the high-dosage TXA scheme used in our previous study (50 mg kg^{-1} LD and 5 mg kg^{-1} h^{-1} MD) in decreasing intraoperative blood loss and blood transfusion in children undergoing craniosynostosis surgery.

Secondary aims include a determination and validation of the predicted TXA plasma concentrations with this lower-dosage scheme. In addition, to improve on the standard measurement of TXA efficacy (besides blood loss and transfusion, which are indirect outcome measures) and to define TXA efficacy in a direct manner, biological laboratory markers of fibrinolysis and inflammation are compared pre- and post-surgery between groups. Complications (seizures or thromboembolic events) and patient-centred outcomes (ICU and hospital length of stay) are also reported.

Methods

Trial design

With internal research board and ethics board approval from two participating hospitals (Boston Children's Hospital: BCH IRB-P00008434; Gaslini Children's Hospital: GCH Ethic 2013-001056-35) and with informed consent, children were randomised with a 1:1 allocation in a prospective double-blind non-inferiority trial (ClinicalTrials.gov identifier: NCT02188576) according to an investigator-blinded computer-generated random number sequence.

Participants

Children aged between 3 months and 2 yr of age undergoing cranial remodelling surgery for craniosynostosis (fronto-orbital advancement surgery, and posterior and total calvarial remodelling procedures) at BCH and GCH were eligible for inclusion. Exclusion criteria were a pre-existing active haematological abnormality (defined as an active genetic or acquired bleeding disorder/coagulation defect), pre-existing active coagulation defect (defined as prothrombin time, partial thromboplastin time, or international normalised ratio >1.5 times normal), or acetylsalicylate ingestion within 4 days or nonsteroidal anti-inflammatory ingestion within 2 days of the surgery.

Intervention

Children were allocated to receive an i.v. TXA dose (50 mg kg^{-1} over 15 min LD followed by a maintenance infusion of 5 mg kg^{-1} h^{-1}) or a lower TXA dose (10 mg kg^{-1} over 15 min LD followed by a maintenance infusion of 5 mg kg^{-1} h^{-1}) until the end of surgery. A standardised anaesthetic management and transfusion plan was followed with improved modifications from our previous protocol[6] (Supplementary Appendix 1). Consolidated Standards of Reporting Trials guidelines were followed (Supplementary Appendix 2). A blood loss volume of 20 ml kg^{-1} was defined as clinically significant as it is the volume that typically is associated with clinically significant haemodynamic compromise (hypotension ≥20% from baseline and tachycardia if left untreated [treatment being i.v. crystalloid or colloid bolus or vasopressors]).

A baseline blood sample before the start of surgery and another at the end of surgery were drawn for TXA plasma concentrations and the following biological markers of fibrinolysis: fibrinogen, D-dimer, plasminogen activator inhibitor-1 (PAI-1), alpha 2-antiplasmin, plasminogen, tissue plasminogen activator (TPA), and plasmin-antiplasmin complex (PAPC). Inflammatory markers assayed include interleukin-6 (IL-6), interleukin-10 (IL-10), and tumour necrosis factor (TNF).

Additional intraoperative blood samples (each 0.5 ml and up to 10 per patient) were drawn for TXA analysis utilising four different sampling schemes randomly assigned, designed to capture a variety of time points. Samples were anticoagulated with ethylenediamine tetra-acetic acid (EDTA) and stored on ice. Plasma was separated by centrifugation (1000 $g \times 10$ min at 4°C) and stored at −80°C pending analysis. Tranexamic acid concentrations were measured in duplicate by an improved method from our previous work using liquid chromatography with mass spectrometry detection with pre-processing by solid-state extraction.[6]

For PAI-1 protein analysis, IL-6, IL-10, and TNF, 2 ml whole blood was collected in EDTA tubes and centrifuged for platelet-

poor plasma within 30 min of collection. Platelet-poor plasma was frozen at −20°C; PAI-1 concentrations measured in duplicate using DSE100 Human Serpin E1/PAI-1 Quantikine ELISA kit (BCH Core Laboratory); and markers of inflammation TNF-RII, IL-10, and IL-6 measured in duplicate using Spacesrl R&D Systems kit's (DRT200, D1000B, and HS600−B) (GCH Core Laboratory). Alpha 2-antiplasmin, plasminogen, TPA, and PAPC analysis was conducted by the BCH Core Laboratory.

Outcomes

Outcomes were pre-specified. The primary outcome variable was intraoperative blood loss calculated with a previously validated formula (Supplementary Appendix 1).[6] Secondary outcomes were blood product transfusion, biological markers of fibrinolysis and inflammation, and TXA plasma concentrations. Complications (seizures or thromboembolic events) and patient-centred outcomes (ICU and hospital length of stay) are also reported.

Statistical analysis

An *a priori* power analysis indicated that 56 children (28 randomised per group) would provide 80% statistical power (α=0.05; β=0.20) to test whether the difference in average calculated blood loss (CBL) is equivalent to within 20 ml kg^{-1}, assuming an approximated pooled standard deviation of 25 ml kg^{-1} (moderate effect size=0.80) (nQuery Advisor, version 7.0; Statistical Solutions, Saugus, MA). A conservative pooled standard deviation of 25 ml kg^{-1} was estimated because our previous study showed a standard deviation for blood loss in the TXA group of 22 ml kg^{-1}.[6] Sixty-six patients were randomised to ensure sample size requirements were met whilst accounting for a potential 15% dropout. A single randomisation list was used for both sites with stratification per site.

An *a priori* non-inferiority margin of −20 ml kg^{-1} was set in the analysis for the difference in means between the two groups (high-dose TXA minus low-dose TXA) for the primary outcome of blood loss as a clinically relevant difference between the groups to represent a reasonably small difference in CBL. The low-dosage TXA scheme was determined non-inferior as compared with the high-dosage scheme if the 95% confidence interval (CI) for the mean difference in blood loss (high-dose TXA minus low-dose TXA) was above the non-inferiority margin of −20 ml kg^{-1}. A sample size of 40 children (20 randomised per group) will produce a two-sided 95% CI for the difference in mean CBL between the two groups (high-dose TXA minus low-dose TXA) within the non-inferiority limit of −20 ml kg^{-1}, assuming a standard deviation of 25 ml kg^{-1} and equal average CBL in the two groups. A conservative pooled standard deviation of 25 ml kg^{-1} was estimated because a previous study showed a standard deviation for blood loss in the TXA group of 22 ml kg^{-1}. The targeted total sample size of 56 children (28 per randomised

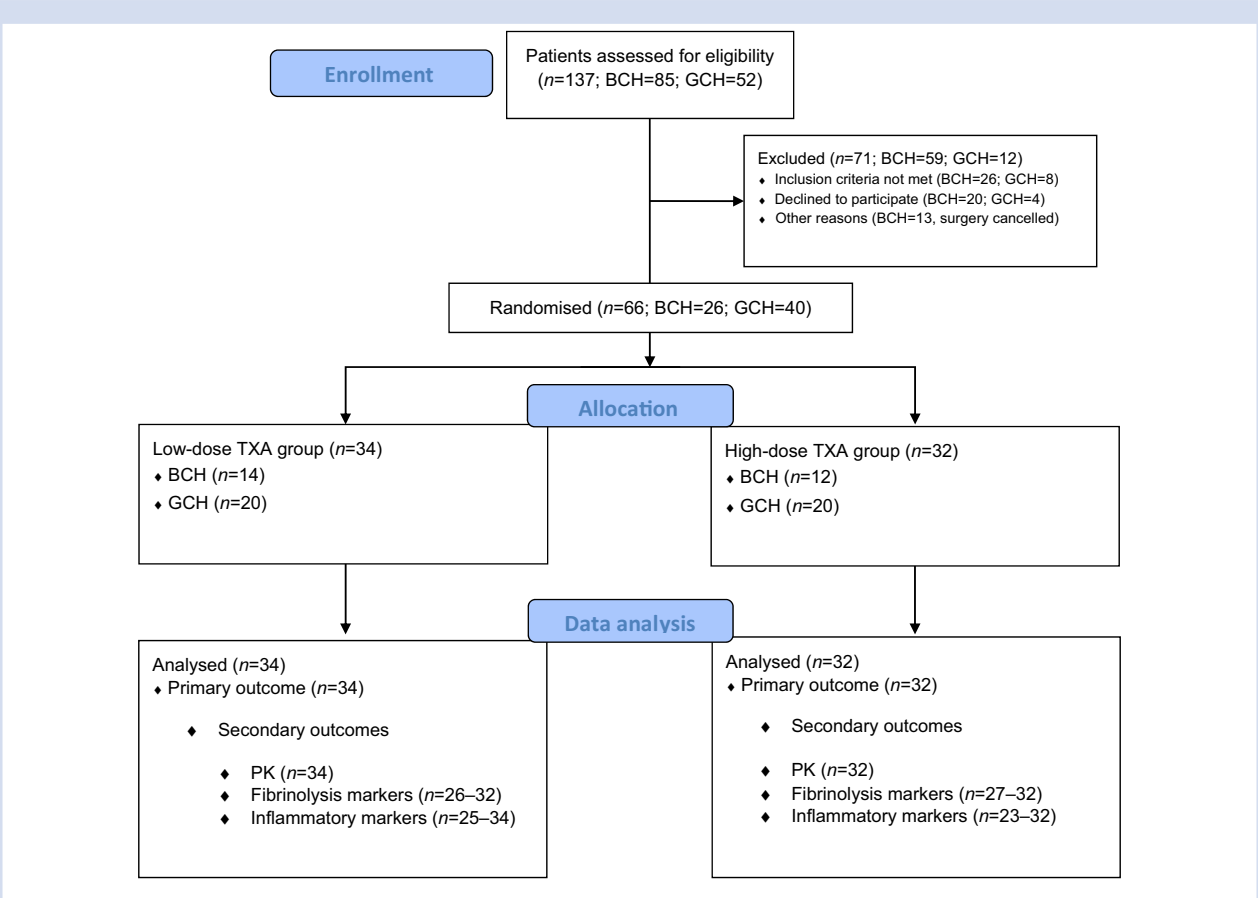

Fig 1. Study recruitment flow chart. BCH, Boston Children's Hospital; GCH, Gaslini Children's Hospital; PK, pharmacokinetic; TXA, tranexamic acid.

group) will ensure this non-inferiority margin. Similarly, an *a priori* non-inferiority margin of −10 ml kg^{-1} was set in the analysis of packed red blood cell (PRBC) transfusion to reflect a reasonably small difference in mean transfusion between the groups. Here, again, the low-dosage TXA scheme was determined as non-inferior to the high-dosage scheme if the 95% CI for the mean difference in PRBC transfusion was above the non-inferiority margin of −10 ml kg^{-1}.

The low-dose and high-dose TXA groups were compared with respect to patient characteristics, baseline characteristics, laboratory values, and intraoperative and postoperative outcomes. Continuous data are presented as mean and standard error of the mean (SEM) or median and inter-quartile range (IQR) with comparisons performed using Student's *t*-test or the Wilcoxon rank-sum test as appropriate. Medians and IQRs are presented where the data deviate from normality, including age, weight, length of stay, CBL, and PRBC transfused. Categorical data are presented as frequency and percentage with comparisons made by Fisher's exact test. Mean differences between the groups are presented with 95% CIs. For data presented with median and IQR, a 95% CI estimate for the difference between comparison groups was obtained using 1000 bootstrap resamples. Statistical analyses were performed using Stata (version 15.0; StataCorp, College Station, TX, USA). A two-sided alpha of 0.05 was used to determine statistical significance.

Results

Blood loss and transfusion outcomes

Sixty-six children, 3 months to 2 yr scheduled for craniosynostosis reconstruction surgery, were included during a 3 year time period: August 2014 until July 2017 (Fig. 1). Patient characteristics were comparable between the TXA groups. Median age (IQR) was 8.5 months (5–16) and 8 months (4–13.5) with more males in both groups; 62% *vs* 59%, for the high- and low-dose groups, respectively (Table 1).

The lower dose was not less effective than the higher dose regarding the primary outcome, mean (SEM) intraoperative blood loss (CBL 39.4 [4.4] *vs* 40.3 [6.2] ml kg^{-1} [95% CI: −14.2, 15.9]) within the 20 ml kg^{-1} non-inferiority margin. The lower dose was not less effective than the higher dose regarding the secondary outcome, mean (SEM) PRBC transfusion (PRBC 21.3 [1.6] *vs* 23.6 [1.5] ml kg^{-1} [95% CI: −2.1, 6.7]) within the 10 ml kg^{-1} non-inferiority margin (Table 2). Similarly, comparable values are reported for the haemostatic blood products (fresh frozen plasma, cryoprecipitate, or platelets) transfused intra- and postoperatively between groups, in postoperative 24 h blood loss in the surgical drain (Table 2), and in postoperative PRBC transfusion (4.1 [1.2] *vs* 8.6 [2.1] ml kg^{-1} [95% CI: −0.3, 8.8] for the high- and low-dose groups, respectively) (see Fig. 2 for group comparison of perioperative CBL and PRBC transfusion). There was also no difference between the intraoperative or postoperative laboratory values, except for the fibrinogen concentration, which increased in both, with a significantly larger increase from baseline in the low-dose group (Table 2). There was no difference in the postoperative haemoglobin (Hb) (haematocrit [Hct]) in the high- and low-dose groups: Hb 10.8 (0.4)% (Hct 31.3 [1.1] g dl^{-1}) and Hb 10.1 (0.3)% (Hct 29.4 [0.9] g dl^{-1}), respectively. Supplementary Table S1 reports the outcomes for the two centres combined and for each centre independently. Blood loss and blood component transfusion values were not different between BCH and GCH.

No adverse events, such as seizures or thromboembolic events, were reported or observed in either group during the hospital stay, and both groups had comparable length of stay in ICU and in hospital (Table 1).

Table 1 Patient and baseline characteristics of the two treatment groups. Continuous data are presented as mean (standard error of the mean) or median (inter-quartile range), with groups compared by the Student's *t*-test or the non-parametric Wilcoxon rank-sum test, as appropriate; 95% confidence intervals (CIs) for difference in medians were obtained using 1000 bootstrap samples. Categorical data are presented as *n* (%) with groups compared by the χ^2 test. *Duration of surgery is from incision to last stitch. BCH, Boston Children's Hospital; GCH, Gaslini Children's Hospital; INR, international normalised ratio; PT, prothrombin time; PTT, partial thromboplastin time.

	Low-dose scheme (*n*=34)	High-dose scheme (*n*=32)	Difference	95% CI	P-value
Age (months)	8.5 (5–16)	8 (4–13.5)	−0.5	(−6.1, 4.1)	0.442
Weight (kg)	8.3 (7–10.6)	8.5 (6.5–9.7)	0.2	(−1.5, 1.7)	0.877
Gender					0.843
Male	21 (62%)	19 (59%)	—	—	
Female	13 (38%)	13 (41%)	—	—	
ASA physical status					0.892
1	13 (38%)	11 (34%)	—	—	
2	15 (44%)	16 (50%)	—	—	
3	6 (18%)	5 (16%)	—	—	
Presence of craniosynostosis syndrome	7 (21%)	7 (22%)	—	—	0.898
Duration of surgery* (min)	151.2 (8.8)	167.8 (10.2)	16.6	(−10.3, 43.5)	0.222
Preoperative laboratory values					
Haemoglobin (%)	12.1 (0.2)	14.3 (2.5)	2.2	(−2.7, 7.1)	0.368
Haematocrit	35.8 (0.6)	34.9 (0.4)	−0.9	(−2.4, 0.6)	0.239
Platelets (10^3 cell μg^{-1} L^{-1})	382 (25.6)	375 (17.9)	−6.7	(−70.2, 56.8)	0.833
PT (s): BCH	12.8 (0.4)	12.5 (0.4)	−0.3	(−1.4, 0.7)	0.527
PT (s): GCH	87.7 (2.7)	87.2 (2.7)	−0.6	(−8.3, 7.2)	0.884
PTT (s)	29.6 (0.6)	29.6 (0.7)	−0.02	(−1.8, 1.8)	0.980
INR	1.1 (0.02)	1.0 (0.02)	−0.03	(−0.08, 0.03)	0.371
Fibrinogen	224.5 (13.4)	242.5 (12.5)	17.9	(−18.9, 54.9)	0.332

Table 2 Intraoperative and postoperative clinical outcomes and laboratory values in low- and high-dose tranexamic acid groups. Continuous data are presented as mean (standard error of the mean) or median (inter-quartile range), with groups compared by the Student's *t*-test or the non-parametric Wilcoxon rank-sum test, as appropriate. Categorical data are presented as *n* (%) with groups compared by the χ^2 test. *Total intraoperative and postoperative RBC transfusion at 24 h. †Statistically significant. BCH, Boston Children's Hospital; CI, confidence interval; GCH, Gaslini Children's Hospital; INR, international normalised ratio; POD, postoperative day; PT, prothrombin time; PTT, partial thromboplastin time; RBC, red blood cell.

Variable	Low dose (*n*=34)	High dose (*n*=32)	Difference	95% CI	*P*-value
Clinical outcomes					
Blood loss (ml kg^{-1})					
Intraoperative	39.4 (4.4)	40.3 (6.2)	0.9	(−14.2, 15.9)	0.909
Postoperative surgical drain loss	16.5 (1.4)	15.6 (1.6)	−0.9	(−5.1, 3.3)	0.672
RBCs transfused (ml kg^{-1})					
Intraoperative use of RBC	30 (88%)	29 (91%)	3%	(−14%, 18%)	0.753
Intraoperative RBC transfused (ml kg^{-1})	21.3 (1.6)	23.6 (1.5)	2.3	(−2.1, 6.7)	0.306
Total RBC transfused (ml kg^{-1})*	23.3 (1.9)	29.9 (2.9)	6.6	(−0.3, 13.7)	0.06
Yellow blood products transfused					
Total cryoprecipitate (ml kg^{-1})	0.1 (0.1)	0.6 (0.5)	0.5	(−0.5, 1.6)	0.319
Use of cryoprecipitate (no. of patients)	1 (3%)	2 (6%)	3%	(−9.5%, 17%)	0.608
Total fresh frozen plasma (ml kg^{-1})	0.7 (0.5)	0.9 (0.8)	0.2	(−1.8, 2.1)	0.859
Use of fresh frozen plasma (no. of patients)	2 (6%)	1 (3%)	−3%	(−16%, 11%)	0.591
Total use of platelets	0 (0%)	0 (0%)	0%	(−10%, 10%)	0.999
Intraoperative fluids					
Total crystalloid (ml kg^{-1})	44.1 (4.9)	45.7 (3.2)	1.5	(−10.4, 13.5)	0.796
Total albumin 5% (ml kg^{-1})	15.4 (2.5)	19.7 (3.1)	4.3	(−3.7, 12.5)	0.29
Use of albumin	15 (47%)	23 (68%)	—	—	0.027†
Use of albumin (BCH)	13 (100%)	11 (92%)	—	—	0.48
Use of albumin (GCH)	9 (45%)	4 (20%)	—	—	0.176
Length of stay (days)					
ICU	1.9 (1.0–3.1)	1.4 (1.0–3.4)	−0.5	(−1.4, 0.7)	0.928
In hospital	8 (4–13)	10 (5–15)	2	(−2.1, 6.1)	0.205
Laboratory values					
Intraoperative					
Haemoglobin (%)	10.4 (0.3)	10.0 (0.2)	−0.4	(−1.0, 0.3)	0.238
Haematocrit	32.2 (0.7)	31.0 (0.5)	−1.2	(−2.9, 0.5)	0.168
Platelets (10^3 cell μg^{-1} L^{-1})	367 (49)	415 (46)	48	(−119, 217)	0.537
PT (s): BCH	13.3 (0.3)	13.3 (0.4)	0	(−0.9, 1)	0.937
PT (s): GCH	78.1 (3.1)	76.6 (1.8)	−1.6	(−8.9, 5.7)	0.659
PTT (s)	30.5 (0.5)	32.3 (1.9)	1.9	(−2.2, 5.9)	0.359
INR	1.1 (0.02)	1.1 (0.02)	0	(−0.05, 0.06)	0.879
Fibrinogen	184.8 (7.7)	202.7 (8.7)	17.8	(−5.5, 41.1)	0.131
POD 1					
Haemoglobin (%)	10.8 (0.4)	10.1 (0.3)	−0.7	(−1.6, 0.4)	0.218
Haematocrit	31.3 (1.1)	29.4 (0.9)	−1.9	(−4.7, 0.9)	0.185
Platelets (10^3 cell μg^{-1} L^{-1})	241 (20)	224 (17)	−17	(−69, 36)	0.526
PT (s): BCH	15.1 (0.4)	15.3 (0.5)	0.2	(−1.9, 2.3)	0.833
PT (s): GCH	69.5 (4.1)	66.8 (2.4)	−2.7	(−12.8, 7.3)	0.578
PTT (s)	29.6 (1.3)	36.2 (5.8)	6.6	(−6.9, 20.1)	0.328
INR	1.2 (0.04)	1.3 (0.03)	0.1	(−0.04, 0.15)	0.216
Fibrinogen	297.3 (23.7)	249.1 (13.9)	−48.2	(−102.7, 6.3)	0.081
Delta (preoperative to POD 1)					
Haemoglobin (%)	−1.3 (0.5)	−4.2 (2.6)	−2.9	(−8.5, 2.5)	0.281
Haematocrit	−4.4 (1.4)	−5.6 (0.9)	−1.2	(−4.5, 2.2)	0.481
Platelets (10^3 cell μg^{-1} L^{-1})	−157 (23)	−153 (16)	4	(−50, 58)	0.897
PT (s): BCH	2.4 (0.2)	2.4 (0.3)	0	(−0.9, 1)	0.889
PT (s): GCH	−19.3 (3.4)	−22.1 (4.8)	−2.8	(−14.9, 9.2)	0.63
PTT (s)	0.7 (1.2)	6.7 (6.0)	6	(−7.7, 19.7)	0.377
INR	0.18 (0.04)	0.21 (0.04)	0.03	(−0.09, 0.15)	0.639
Fibrinogen	98.2 (30.5)	46.7 (24.8)	−51.5	(−171.9, −11.1)	0.027†

Non-inferiority graphs of the 95% CIs for low-dosage TXA scheme compared with high-dosage scheme for average CBL and PRBC transfusion are presented in Fig. 3a and b, with the non-inferiority margin (delta) defined as 20% for CBL and 10% for PRBC transfusion. These graphs show that the low-dosage TXA scheme is non-inferior to the high-dose scheme regarding CBL and PRBC within the respective 20 and 10 ml kg^{-1} non-inferiority margins.

Tranexamic acid plasma concentrations

Following the initial peak TXA plasma concentrations resulting from the LD (mean [SEM] 199.4 [10.6] μg ml^{-1} in the high-dose group [50 mg kg^{-1} LD and 5 mg kg^{-1} h^{-1} MD] and 67.5 [14.0] μg ml^{-1} in the low-dose group [10 mg kg^{-1} LD and 5 mg kg^{-1} h^{-1} MD]), the TXA concentrations decreased to a maintenance level during the surgery. The TXA plasma

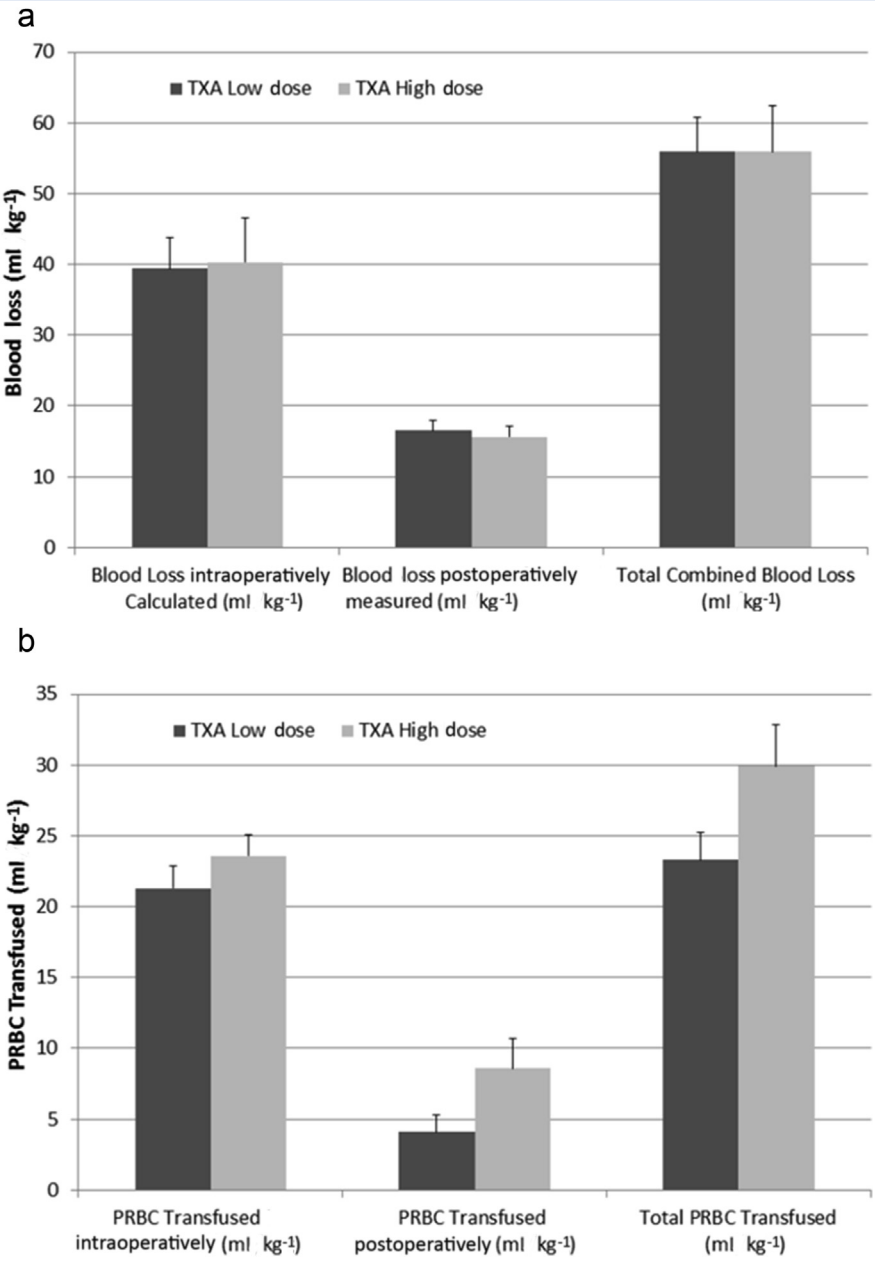

Fig 2. Comparison of (a) blood loss and (b) blood transfusion across the perioperative course in tranexamic acid (TXA) groups. PRBC, packed red blood cell.

concentrations during the maintenance phase of the surgery at 2.5 h (~80% steady state) were 50.2 (8.0) μg ml^{-1} in the high-dose group and 29.6 (7.6) μg ml^{-1} in the low-dose group, both above the presumed therapeutic plasma concentration of 16 μg ml^{-1}. The TXA plasma concentrations at the end of surgery were 40.0 (6.0) μg ml^{-1} for the high-dose group (surgery duration: 3.6 [0.2] h) and 27.8 (5.0) μg ml^{-1} for the low-dose group (surgery duration: 3.5 [0.18] h). In patients whose surgeries lasted more than 4 h, the TXA plasma concentration at 4.5 h (which is ~94–97% steady state assuming the TXA elimination half-life is ~1 h in children undergoing craniofacial surgery[15]) measured 17.8 (5.9) and 16.1 (10.6) μg ml^{-1} for the high-dose (n=3) and low-dose (n=6) groups, respectively.

Tranexamic acid biomarkers

The measured fibrinolysis and inflammatory biological biomarker concentrations pre- and post-surgery are compared within each group (Table 3). There is no difference in the change between the TXA dosage schemes in these biomarker concentrations before or after surgery (delta). The concentrations of the biomarkers IL-6, IL10, TPA, PAI-1, and D-dimer all

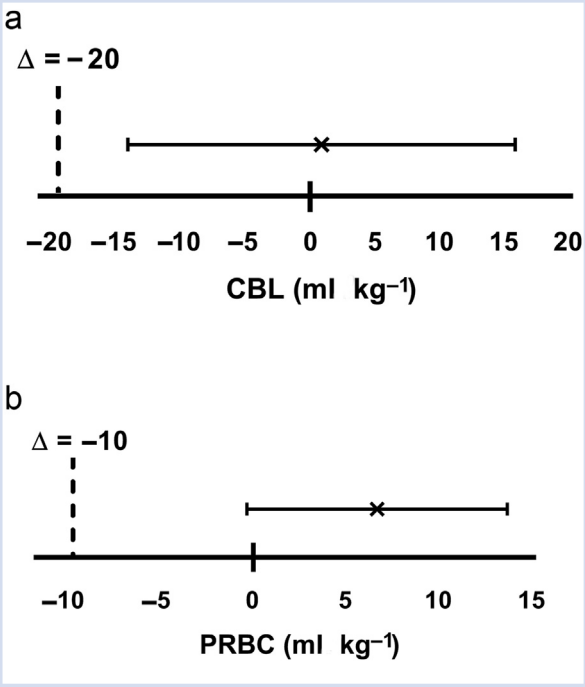

Fig 3. Non-inferiority graphs for (a) calculated blood loss (CBL, ml kg^{-1}) and (b) packed red blood cell (PRBC) transfusion (ml kg^{-1}).

increased significantly between pre- and post-surgery in both groups combined (Table 3). Whilst the trend was an increase, the change in TNF was not significantly different. Plasminogen concentrations decreased significantly when comparing pre-levels to post-levels in both groups combined.

Discussion

This randomised controlled non-inferiority trial from two tertiary care centres found that a TXA dosage scheme of 10 mg kg^{-1} LD and 5 mg kg^{-1} h^{-1} MD is non-inferior to a high-dose scheme of 50 mg kg^{-1} LD and 5 mg kg^{-1} h^{-1} MD in reducing blood loss and transfusion requirements in paediatric craniosynostosis reconstruction surgery when used as part of a multimodal PBM protocol. This low-dosage scheme maintains average TXA plasma concentrations at 29 (7.6) μg ml^{-1} for the maintenance duration of the surgery, which is within the presumed therapeutic range. This report validates current TXA dosage schemes for paediatric craniosynostosis reconstruction surgery, which have been recommended based on PK modelling.[14 15]

Furthermore, this report validates the TXA recommendations published as expert consensus guidelines in paediatric surgery, which have been extrapolated from TXA PK modelling work.[16–18] The Australian National Government PBM guidelines on TXA dosing in surgical paediatric patients at bleeding risk (craniofacial and other than cardiac) recommend a TXA dose of 10 mg kg^{-1} LD followed by an infusion of 5 mg kg^{-1} h^{-1} MD.[16] The 2017 European Society of Anaesthesiology management of severe perioperative bleeding guidelines state, 'Based on TXA pharmacokinetic data, a LD of 10 mg kg^{-1} followed by 5 mg kg^{-1} h^{-1} MD may be sufficient to maintain adequate plasma concentrations during craniosynostosis surgery. However, further randomised controlled trials (RCTs) are needed to assess the efficacy of this dose regimen'.[17] This recommendation is based on our previous report using PK computer simulation and modelling; to sustain a therapeutic plasma TXA concentration, a TXA dose of 10 mg kg^{-1} LD and 5 mg kg^{-1} h^{-1} MD is recommended.[15] Other RCTs have used higher doses and shown efficacy: Goobie and colleagues[6] with 50 mg kg^{-1} LD and 10 mg kg^{-1} h^{-1} MD, and Dadure and colleagues[18] with 15 mg kg^{-1} LD and 10 mg kg^{-1} h^{-1} MD. Herein, we provide this RCT to validate this lower and potentially safer TXA dosage scheme: 10 mg kg^{-1} LD and 5 mg kg^{-1} h^{-1} MD.

It should be emphasised that TXA is one modality to be used as part of multimodal paediatric PBM strategies.[19,20] In this current study, we used a standardised protocol consisting of careful haemodynamic control, a fluid management strategy to avoid haemodilution, meticulous surgical technique with experienced surgeons using haemostasis, and blood loss and blood product transfusion algorithms. Calculated blood loss and PRBC transfusion were less than our previous study by two-fold using blood conservation techniques, including a transfusion target of Hct <25% (whilst also considering the patient's clinical status, such as maintaining haemodynamic stability and end-organ perfusion), which was agreed on by the two centres before the start of the study.[6]

Our secondary analysis focused on attempting to quantify the anti-fibrinolytic and anti-inflammatory properties of TXA as blood loss, whilst a standard and accepted measurement of efficacy is a secondary consequence (and potentially imprecise) of its biological properties. The rationale for investigating the inflammatory biomarkers is that recent reports have highlighted the role of TXA not only as inhibiting fibrinolysis but also as an anti-inflammatory agent.[21] Regarding these secondary outcomes, we did not find a quantitative difference in concentrations of markers of fibrinolysis or inflammation between the high-dosage and low-dosage TXA schemes when comparing preoperative *vs* postoperative.

Limitations

A limitation of this report is inherent with a two-centre study. The sample size, whilst powered appropriately, was small, and therefore, the external validity is limited. In addition, generalisability to other centres, with different patient populations, and anaesthetic, perioperative, and surgical practices cannot be assumed. A larger multicentre trial could provide external validation, including a diverse range of study participants from a variety of practice settings. In addition, whilst no thromboembolic events or seizures were observed, the study was not powered to make any conclusions on safety. This would require a larger trial similar in scope to the Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage-2 or 3 and World Maternal Antifibrinolytic Trial, which confirmed the efficacy and safety of TXA in the adult population.[22–25] Also, given the postoperative Hb (Hct) values in the high- and low-dose groups were Hb 10.8 (0.4)% and Hb 10.1 (0.3)%, respectively, the use of a restrictive transfusion strategy targeting an Hb of 7–8 g dl^{-1}, as current PBM guidelines recommend,[21] may have reduced transfusion by up to ~25%. In addition, whilst this study had defined specific guidelines regarding transfusion of the haemostatic blood products, more current restrictive guidelines could have been followed.[26]

Table 3 Markers of fibrinolysis and inflammation. Values are mean (standard error of the mean). *P*-values are obtained using Student's *t*-test. *Statistically significant. CI, confidence interval; IL-6, interleukin-6; IL-10, interleukin-10; nH, sample size in the high-dose group; nL, sample size in the low-dose group; PAI-1, plasminogen activator inhibitor-1; TNF, tumour necrosis factor; TPA, tissue plasminogen activator.

Overall changes

Variable	Pre	Post	Delta	95% CI for delta	*P*-value
IL-6 (*n*=61)	2.37 (0.64)	17.5 (1.2)	15.1	(12.6, 17.6)	<0.001*
IL-10 (*n*=45)	9.9 (0.9)	31.6 (8.2)	21.7	(5.1, 38.1)	0.012*
TNF (*n*=60)	920 (36)	924 (37)	4	(−76.5, 87.8)	0.891
TPA (*n*=54)	1141 (54)	1694 (124)	553	(374, 787)	<0.001*
PAI-1 (*n*=52)	24.0 (2.32)	30.3 (2.9)	6.3	(0.3, 12.9)	0.039*
D-dimer (*n*=53)	0.22 (0.01)	0.28 (0.02)	0.06	(0.03, 0.09)	<0.001*
Plasminogen (*n*=54)	542 316 (27 542)	465 775 (29 202)	−76 541	(−103 069, −50 013)	<0.001*

Comparison of low- *vs* high-dose TXA

Variable	Low dose	High dose	Difference	95% CI for difference	*P*-value
Pre					
IL-6 (nL=32; nH=31)	2.0 (0.83)	2.75 (0.98)	0.75	(−1.83, 3.31)	0.568
IL-10 (nL=25; nH=23)	9.7 (1.2)	10.3 (1.3)	0.6	(−2.9, 4.2)	0.707
TNF (nL=32; nH=30)	927 (50)	911 (53)	−16	(−162, 129)	0.822
TPA (nL=26; nH=29)	1154 (79)	1129 (76)	−25	(−245, 195)	0.821
PAI-1 (nL=27; nH=27)	24.7 (2.43)	23.3 (3.99)	−1.4	(−10.8, 7.9)	0.765
D-dimer (nL=26; nH=28)	0.21 (0.02)	0.24 (0.02)	0.03	(−0.03, 0.08)	0.331
Plasminogen (nL=27; nH=29)	557 710 (39 540)	532 910 (36 590)	−24 800	(−132 645, 83 041)	0.647
Post					
IL-6 (nL=31; nH=32)	17.1 (1.8)	17.8 (1.6)	0.7	(−4.1, 5.5)	0.773
IL-10 (nL=25; nH=28)	32.9 (10.4)	42.8 (12.7)	9.9	(−23.6, 43.3)	0.556
TNF (nL=31; nH=32)	958 (48)	891 (57)	−67	(−217, 82)	0.374
TPA (nL=27; nH=28)	1603 (162)	1782 (189)	179	(−323, 680)	0.479
PAI-1 (nL=27; nH=26)	28.8 (3.3)	31.7 (4.8)	2.9	(−8.8, 14.7)	0.616
D-dimer (nL=26; nH=27)	0.30 (0.02)	0.27 (0.02)	−0.03	(−0.09, 0.04)	0.392
Plasminogen (nL=27; nH=28)	481 781 (43 409)	449 678 (39 653)	−32 103	(−150 171, 85 785)	0.586
Delta (post−pre)					
IL-6 (nL=31; nH=30)	15.1 (1.8)	15.2 (1.7)	0.1	(−4.82, 5.12)	0.952
IL-10 (nL=23; nH=22)	21.4 (11.2)	21.8 (12.3)	0.4	(−33.1, 33.9)	0.981
TNF (nL=31; nH=29)	23.9 (61.2)	−13.8 (55.1)	−37.7	(−203, 128)	0.65
TPA (nL=26; nH=28)	487 (115)	668 (168)	181	(−234, 594)	0.387
PAI-1 (nL=26; nH=26)	4.0 (3.5)	9.2 (5.3)	5.2	(−7.5, 17.9)	0.412
D-dimer (nL=26; nH=27)	0.08 (0.02)	0.04 (0.03)	−0.04	(−0.11, 0.02)	0.182
Plasminogen (nL=27; nH=27)	−75 838 (22 872)	−77 244 (13 784)	−1406	(−54 991, 52 180)	0.958

Another limitation is that this study did not include a placebo group, as TXA is now a recommended standard of care in craniosynostosis reconstruction surgery at both centres (and worldwide).[3,4,14,16,17] Therefore, our chosen markers of fibrinolysis and inflammation could not be measured and compared in treatment *vs* non-treatment groups. Hence, this limits the utility of drawing conclusions as to the biological effect of TXA. An increase in inflammatory markers is expected when comparing preoperative values with postoperative values as a result of activation of the inflammatory cascade and physiological stress induced by surgery. Comparing inflammatory biomarkers to a population of surgical children who did not receive the drug therefore remains critical to determining whether TXA reduces or dampens the inflammatory response at all. Reporting these anti-fibrinolytic and anti-inflammatory levels in surgical children given TXA, however, may be helpful in designing future trials to analyse the biological mechanism of action of TXA. Furthermore, perhaps the report could have been enhanced by also utilising other measures of fibrinolysis, such as viscoelastic testing, plasma turbidity methods, and plasmin concentrations; however, this was not within the scope of design.

Goobie and Faraoni[14] recently recommended a paediatric noncardiac surgery TXA dosing range of LD 30–10 mg kg^{-1} followed by a maintenance infusion of 5–10 mg kg^{-1} h^{-1} based on PK modelling work given that the variability of TXA may be as high as 25%. Our current study tested the lower range (10 mg kg^{-1} LD and 5 mg kg^{-1} h^{-1} MD); however, higher-dosage schemes (up to 30 mg kg^{-1} LD and 10 mg kg^{-1} h^{-1} MD) are still justified, and institutions should make decisions based on the individual clinical experience (e.g. the Dadure and colleagues[18] TXA dosage scheme of 15 mg kg^{-1} LD and 10 mg kg^{-1} h^{-1} MD, which is certainly quite valid). Note that our study did not address the issue that, for longer surgeries (more than 4.5 h), TXA plasma concentrations may dip below the presumed accepted therapeutic concentration of 16 μg ml^{-1}. These higher-dosage schemes may be indicated for surgeries with higher expected blood loss or lasting longer than 4 h.[18] The authors do not recommend a TXA dosage regime higher than 30 LD/10 MD, but most importantly not lower than 10 LD/5 MD.

A final limitation is that TXA has ~25% inter-patient variability for effect and plasma concentrations for a given dose and that the ideal therapeutic plasma concentration of TXA to inhibit fibrinolysis and inflammation is not yet known.[14] It is

speculated that the anti-inflammatory effects of TXA and its direct action to inhibit plasmin, and therefore reduce platelet activation, may require higher levels than the anti-fibrinolytic effects.[22] Also, genetic variability may play a role as 5G polymorphism of the *PAI-1* gene (prevalence: 16–23%), and low PAI-1 concentrations have been implicated in increased fibrinolysis, operative bleeding, and increased response to TXA.[27,28] Large-scale multicentre trials in paediatric major surgery should be designed to validate this TXA dosage scheme, and report on safety, the biological mechanism regarding its anti-inflammatory and anti-fibrinolytic properties and patient-centred outcomes, such as length of stay, morbidity, and mortality.

A low-dose TXA scheme of 10 mg kg^{-1} LD and 5 mg kg^{-1} h^{-1} MD is non-inferior to a high-dose scheme of 50 mg kg^{-1} LD and 5 mg kg^{-1} h^{-1} MD in reducing blood loss and blood transfusion requirements in paediatric craniosynostosis reconstruction surgery. This report validates our previous TXA work and shows that this reduced dosage regime is not less effective than the high-dosage regimen at reducing blood loss (using a threshold difference of 20 ml kg^{-1}) and blood transfusion (using a threshold difference of 10 ml kg^{-1}) in paediatric craniosynostosis reconstruction surgery.

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Authors' contributions

Study conception/design: all authors
Data acquisition: SMG, ND
Data analysis/interpretation: SMG, SS, ND
Writing/revision of paper: all authors
Approval of final version: all authors

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Declarations of interest

The authors declare that they have no conflicts of interest.

Appendix A. Supplementary data

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