

Comparison of Two Tranexamic Acid Dosage Regimes for Craniosynostosis Surgery.

A Multi-center Randomized Controlled Equivalency Trial.

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Introduction: Tranexamic acid (TXA) in a dose of 50 mg/kg loading dose followed by 5 mg/kg/h infusion significantly reduced blood loss in pediatric open craniosynostosis surgery as well as the overall exposure of children to donor PRBC, compared with placebo¹. TXA plasma concentrations with this high dosing regimen were shown to exceed the accepted therapeutic level by over 10 fold; Figure 1. From pharmacokinetic modeling, we predicted that reducing the loading dose to 10 mg/kg is adequate to maintain plasma concentrations above the presumed accepted therapeutic level of 20 mcg/mL; Figure 2². This may be safer in terms of side effect profile.

The hypothesis of this study is to validate our TXA pharmacokinetic model and determine if the lower dosage scheme is as effective as the higher dosage scheme in decreasing blood loss and transfusion requirements in pediatric craniosynostosis surgery.

Methods: With IRB (BCH IRB-P00008434) and Ethic (2013-001056-35) approval, patients were consented and enrolled in a multicenter, prospective, double-blind equivalence randomized controlled trial to compare high TXA dose (50mg/kg/15min and 5mg/kg/h) vs a low TXA dose (10 mg/kg/15min and 5 mg/kg/h) regime. Standardized anesthetic, fluid, blood and blood product management protocols were followed. TXA analysis was performed by BCH PKLab using liquid chromatography with mass spectrometry detection (LC/MS). The two participating hospitals were: Boston Children's Hospital, Boston USA, and Istituto Gaslini, Genoa, Italy. ClinicalTrials.gov identifier: NCT02188576.

Results: Sixty-eight children, 3 mos to 2 yrs scheduled for open craniosynostosis surgery were included. Demographics were comparable between groups (Table). **There was no significant difference in blood loss (32.1 vs 32.4 mL/kg) or blood product transfusion (PRBC 19.6 vs 22.5 mL/kg) between the high and low dose groups respectively.** TXA plasma levels at steady state averaged 50 mcg/mL in the high dose group vs 25 mcg/mL the low dose group; both above the presumed therapeutic threshold. Blood loss and blood product transfusion were also less than our previous study by two fold(1). No adverse events such as seizures or thromboembolic events were observed in either group.

Conclusion: A tranexamic acid low dose regimen of 10 mg/kg loading dose and 5 mg/kg/h maintenance dose is as effective as a high dose regime of 50 mg/kg loading dose and 5 mg/kg/h maintenance dose in reducing blood loss and transfusion requirements in pediatric craniosynostosis reconstruction surgery.

	Low Dosage Scheme (n=34)	High Dosage Scheme (n=32)	P Value
Age (months)	8.5 (5-16)	8 (4-13.5)	0.442
Weight (kg)	8.3 (7.1-10.6)	8.5 (6.5-9.7)	0.496
Gender			0.843
Male	21 (62%)	19 (59%)	
Female	13 (38%)	13 (41%)	
ASA physical status			0.892
I	13 (38%)	11 (34%)	
II	15 (44%)	16 (50%)	
III	6 (18%)	5 (16%)	
Presence of craniosynostosis syndrome	7 (21%)	7 (22%)	0.898
Duration of surgery (min)	144 (108-190)	170 (125-199)	0.253
Preoperative hematocrit (%)	35.8 ± 3.7	34.9 ± 2.1	0.239
Preoperative hemoglobin (%)	12.1 ± 1.2	14.3 ± 14.2	0.368
Preoperative platelets (10 ³ cells/μl)	382 ± 149.3	375.2 ± 99.4	0.833
Calculated blood loss (ml/kg)	32.1 (26.8-48.1)	32.4 (22.1-42.9)	0.538
24 hour blood loss in drain (ml/kg)	17.4 (12.9-20)	14.3 (8.7-19.7)	0.423
PRBC transfused (ml/kg)	19.6 (14.8-26.8)	22.5 (17.7-29.5)	0.154
Total blood products transfused (ml/kg)	19.7 (16.1-26.9)	22.5 (17.7-30.6)	0.202
Length of stay (days)			
ICU	1.9 (0.9-3.1)	1.4 (1-4.8)	0.928
In hospital	8 (4-13)	10 (5-15)	0.205
Total crystalloid (ml/kg)	41.2 (28.5-49.5)	42.7 (31.7-52.8)	0.254
Total 5% albumin (ml/kg)	11.7 (9.1-19.7)	15.4 (10-27.6)	0.148
Use of cryoprecipitate	1 (3%)	2 (6%)	0.608
Cryoprecipitate (ml/kg)	0.09 ± 0.56	0.64 ± 3.1	0.319
Use of FFP	2 (6%)	1 (3%)	0.591
FFP (ml/kg)	0.70 ± 2.9	0.87 ± 4.91	0.859
Use of platelets	0 (0%)	0 (0%)	-

Table: Comparison of Two Tranexamic Acid Dosage Regimes for Craniosynostosis Surgery.

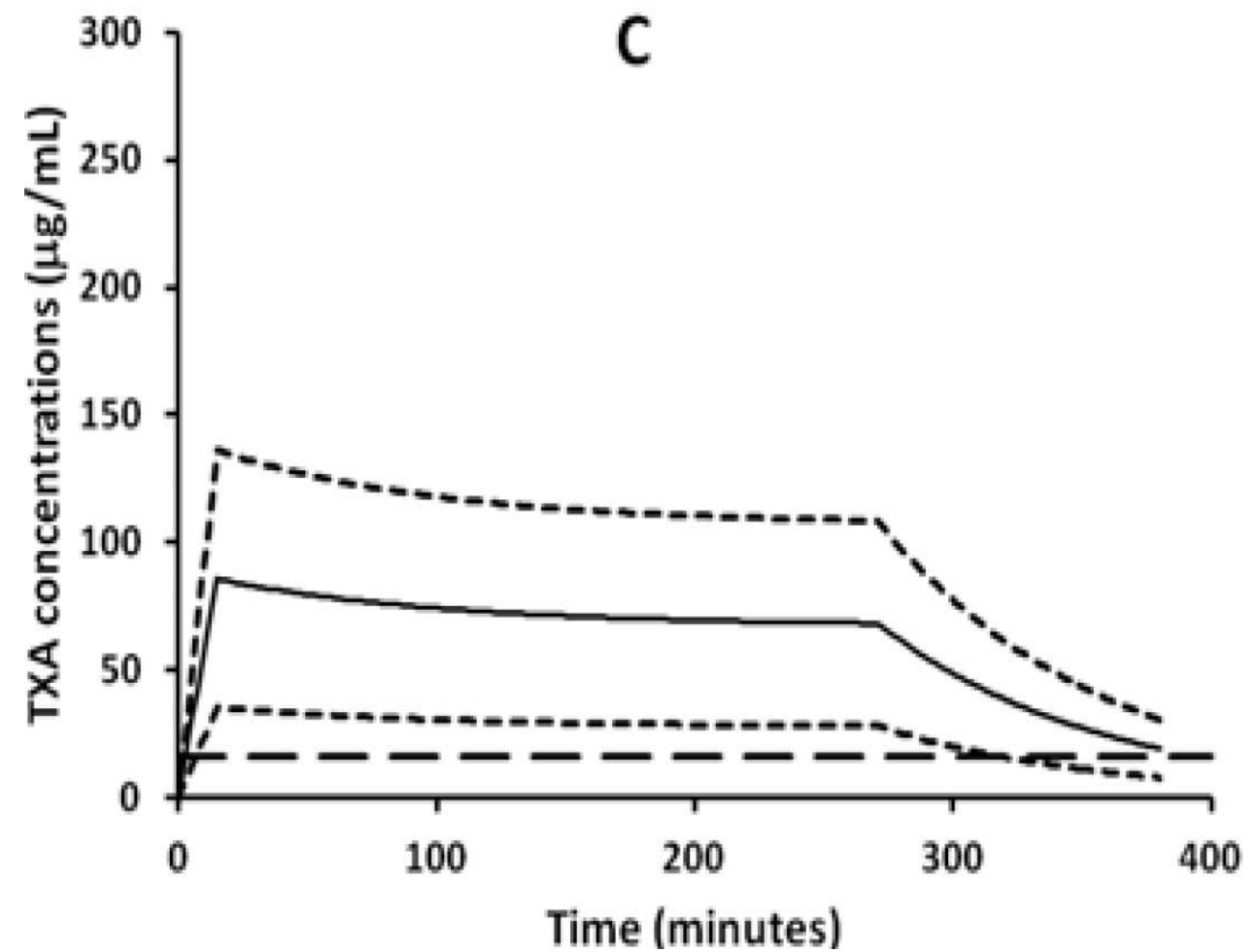
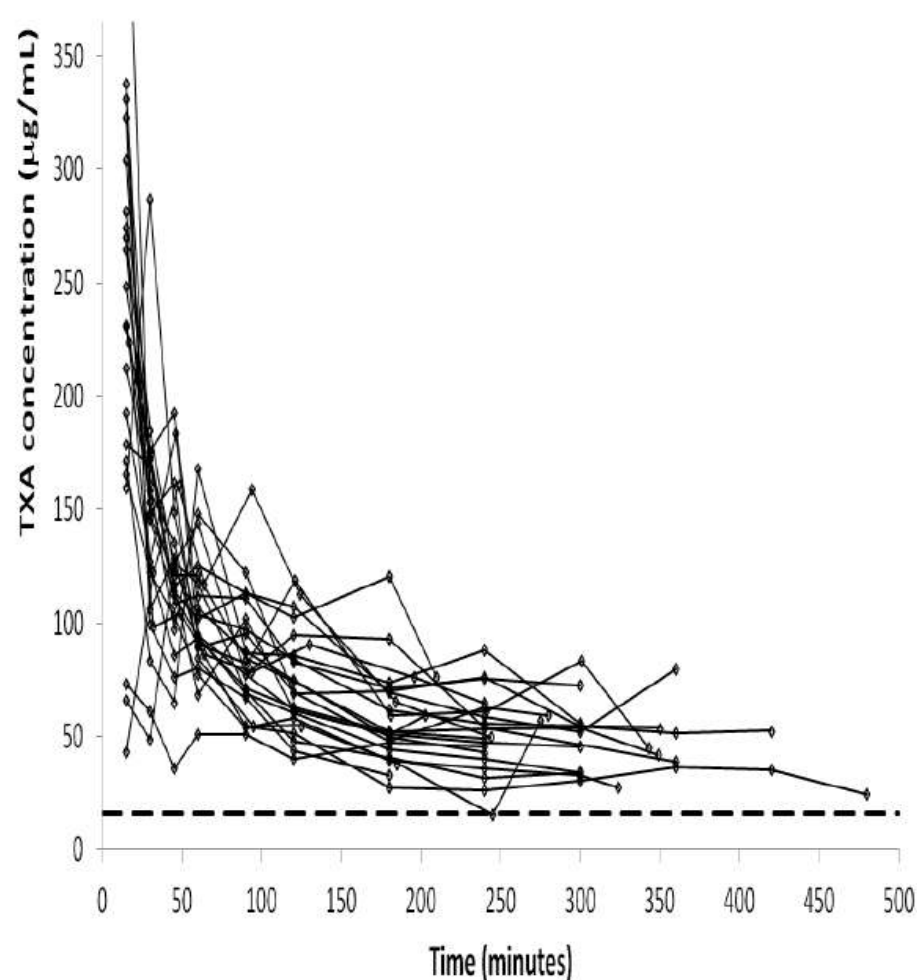


Figure:
A. Actual TXA plasma ccn vs time curve for 50 mg/kg loading dose and 5 mg/kg/h.¹
B. Simulated TXA plasma vs time ccn curve for 10 mg/kg loading dose and 5 mg/kg/hour.²
Dashed line is perceived therapeutic concentration of 16 ug/mL.
Dotted lines indicate 95% CI for an interpatient variability of 30% coefficient of variation.

Reference(s):
1. Goobie et al. *The Efficacy of Tranexamic Acid in Pediatric Craniofacial Surgery: A Double Blind Placebo Controlled Study* Anesth. 2011;114(4):862-71.
2. Goobie et al. *Population Pharmacokinetics of Tranexamic Acid in Pediatric Patients Undergoing Craniosynostosis Surgery.* Clin Pharmacokin. 2013;52(4):267-76.