

Impact of tranexamic acid use on blood loss and transfusion rates following femoral varus derotational osteotomy in children with cerebral palsy

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Abstract

Purpose Previous studies have established the safety and efficacy of tranexamic acid (TXA) in reducing blood loss after total joint arthroplasty and spinal fusion surgery; however, literature regarding the effectiveness of intraoperative TXA in children with cerebral palsy (CP) is limited. The aim of this study was to investigate the safety and efficacy of intraoperative TXA in reducing blood loss and transfusion requirements for children with CP undergoing a proximal femoral varus derotational osteotomy (VDRO).

Methods This is a retrospective review of 258 children with CP who underwent VDRO performed at the author's institution between 2004 and 2017. In all, 36 subjects underwent VDRO surgery with administration of intravenous TXA and 222 subjects underwent VDRO without administration of TXA. Outcome measures including blood loss, transfusion requirements and venous thromboembolic events were compared between groups using t-tests and chi-squared tests.

Results No significant differences were seen in the rates of transfusion between groups for the entire hospitalization (TXA group: 11.1% versus No TXA group: 19.8%), intraoperatively (TXA: 2.8% versus No TXA: 9.0%) or postoperatively (TXA: 8.3% versus No TXA: 14.4%). Intraoperative estimated blood loss (TXA: 144.4 mL versus No TXA: 159.0 mL) and percentage blood loss (TXA: 8.9% versus No TXA: 9.2%) were

similar between groups. No major thromboembolic complications events occurred in either group.

Conclusion The use of TXA was not associated with thromboembolic complications in this series of children with CP undergoing VDRO surgery. Though there was a trend toward lower rates of intraoperative and postoperative blood transfusion with TXA use in these patients, the differences were not significant, possibly due to low estimated blood loss in both groups and sample size.

Level of evidence III- retrospective comparative study

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Introduction

Cerebral palsy (CP) is a disorder of movement and posture resulting from a non-progressive injury during early brain development.¹ CP is the most common cause of persisting motor impairment in children, with an estimated prevalence of 3.3 per 1000 live births in the United States.² Bony and soft-tissue procedures including pelvic osteotomies, hip reconstructions and hamstring lengthenings are commonly performed in children with CP.³⁻⁵ CP patients may have a higher likelihood of major blood loss during surgery due to risk factors including seizure medications, poor nutritional status and depletion of clotting factors.^{6,7} Previous authors have reported high rates of transfusion in the range of 37% to 67% in children with CP undergoing hip reconstructive surgery.^{8,9}

Tranexamic acid (TXA) is a synthetic anti-fibrinolytic agent that works by reversibly blocking plasminogen and thereby promoting haemostasis through prevention of fibrin degradation.^{10,11} Previous studies have established the safety and efficacy of TXA in reducing blood loss after total joint arthroplasty and spinal fusion surgery.¹²⁻¹⁶ However, current literature investigating the safety and effectiveness of TXA in children with CP undergoing

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orthopaedic procedures is limited. Dhawale et al¹⁷ found in a retrospective study of 84 CP children with scoliosis that anti-fibrinolytics, including TXA, significantly reduced estimated blood loss during posterior spinal fusion. However, anti-fibrinolytic administration was not associated with a significant difference in total transfusion rates, except in cell salvage. A recent study by Majid et al⁸ of children with CP undergoing hip reconstruction found TXA to be significantly associated with higher transfusion rates, decreased postoperative haemoglobin levels and longer length of inpatient stay.⁸

The aim of this study was to investigate the safety and efficacy of intraoperative TXA administration in reducing blood loss and transfusion requirements for children with CP undergoing a proximal femoral varus derotational osteotomy (VDRO). Specifically, we sought to compare transfusion requirements, estimated blood loss during surgery, postoperative haemoglobin and haematocrit levels, length of inpatient stay and postoperative complication rates between CP patients treated with and without TXA during VDRO surgery. We hypothesized that patients treated with TXA would have reduced blood loss and transfusion requirements with similar postoperative complication rates compared with those whom did not receive TXA.

Patients and methods

Institutional review board approval was obtained for all study procedures before initiation of the study. Clinical data were retrospectively reviewed for children with CP (age < 18 years) who underwent VDRO performed at the Children's Hospital Los Angeles between 01 November 2004 and 02 February 2017. TXA use during VDRO surgery began at our institution in 2014 following reports of its use in the literature. Patients were eligible if they underwent a VRDO for CP within the study eligibility period. Patients with pre-existing bleeding or coagulation disorders and those without sufficient clinical data were excluded.

Patients underwent proximal femoral VDRO, with concomitant bony and soft-tissue procedure performed as indicated during the same surgical session.¹⁸ Subjects were divided into two groups: those whom received intraoperative TXA (TXA group, n = 36) and those whom did not receive intraoperative TXA (No TXA group, n = 222). TXA was administered at a loading dose of 50 mg/kg and a maintenance dose of 5 mg/kg/hour to 10 mg/kg/hour at the discretion of the anaesthesiologist. The majority of patients underwent a combination of general and spinal anaesthesia. Postoperative drains were not routinely placed.

Demographic data including age, gender, weight and height, date of comorbid conditions, Gross Motor

Functional Classification System (GMFCS),¹⁹ American Society of Anesthesiologists²⁰ physical status, feeding method and outpatient medications were collected. Surgical variables collected were length of surgery and anaesthesia, fluid administration, blood products transfusion, urine output and tourniquet time. At the conclusion of each surgery, anaesthesiologist and surgeon agreed upon an estimated blood loss by inspecting surgical sponges and suction. Preoperative haemoglobin and haematocrits were measured in all patients within 30 days of the procedure. Postoperative blood lab monitoring was left to surgeon discretion and, therefore, not all patients had postoperative haemoglobin and haematocrit levels measured. Postoperative blood product transfusions and complications were recorded in all patients from surgery to time of discharge. Final follow-up was defined as the most recent documented clinic visit.

Continuous outcome variables were analyzed using unpaired *t*-tests and categorical variables were analyzed using Fisher's exact test and chi-squared tests. Variables from the univariate analysis that differed significantly between groups were included in the multiple regression analysis as co-variables. All statistical analyses were performed in STATA (version 14.0; StataCorp LP, College Station, Texas).

Results

Similar baseline characteristics were seen between the TXA and No TXA groups. Age at time of surgery, concomitant surgeries, preoperative seizure medication use and distribution of GMFCS and ASA were similar between groups (Table 1). Baseline preoperative haemoglobin and haematocrit values were not significantly different between groups (Table 2). Patients in the TXA group tended to weigh less (22.2 kg (8.7 to 92.0) *versus* 26.5 kg (8.8 to 124.0), *p* = 0.31), have a higher proportion of gastrostomy (g)-tube dependency (47% *versus* 23%, *p* = 0.18) and have fewer procedures performed (5.8 (2 to 14, SD 2.5) *versus* 6.5 (1 to 16, SD 2.9), *p* = 0.09).

No significant differences in total transfusion rates over the peri- and postoperative period were seen between groups (TXA: 11.1 % *versus* No TXA: 19.8%, *p* = 0.21; Table 2). Intraoperative (TXA: 2.8% *versus* No TXA: 9.0%, *p* = 0.20) and postoperative blood product transfusion rates were not statistically different between groups (TXA: 8.3% *versus* No TXA: 14.4 %, *p* = 0.32) (Figs 1 and 2). There was no statistical difference in estimated blood loss (TXA: 144.4 mL (25 to 400, SD 102.2) *versus* No TXA: 159.0 mL (10 to 850, SD 144.8), *p* = 0.58) or percentage blood loss based on total body weight (TXA: 8.9% *versus* No TXA: 9.2%, *p* = 0.83). Postoperative haemoglobin difference (TXA: -3.6 g/dL (-7.2 to -0.4, SD 1.5) *versus* No TXA: -3.8

Table 1 Similar baseline characteristics were seen between patients with cerebral palsy undergoing proximal femoral varus derotational osteotomy (VDRO) surgery with and without tranexamic acid (TXA). Age at time of surgery, concomitant surgeries, preoperative seizure medication use and distribution of gross motor functional classification system (GMFCS) and American Society of Anesthesiologists classification were similar between groups. Data are presented as mean (SD) (g-tube, gastrostomy tube; GJ tube, gastro-jejunal tube)

Characteristic	No TXA (n = 222)	TXA (n = 36)	p-value
Gender, n (%)			
Male	133 (60)	21 (58)	0.56
Female	89 (40)	15 (42)	
Weight at surgery (kg)	26.5 (14.5)	22.2 (11.1)	0.31
Height at surgery (cm)	118.0 (26.3)	109.1 (18.7)	0.08
GMFCS	II: 26 III: 34 IV: 106 V: 56	II: 2 III: 4 IV: 19 V: 11	0.72
ASA Classification	I: 3 II: 72 III: 147	I: 0 II: 7 III: 29	0.17
Preoperative feeding status	Oral: 171 G-tube: 45 GJ-tube: 1 Combined Oral/G-tube: 5	Oral: 19 G-tube: 17 GJ-tube: 0 Combined Oral/G-tube: 5	0.06
Preoperative seizure medication use	Yes: 82 No: 140	Yes: 16 No: 20	0.18
VDRO side	Bilateral: 164 Unilateral: 58	Bilateral: 27 Unilateral: 9	0.78
Pelvic osteotomy	Yes: 34 No: 188	Yes: 4 No: 32	0.39
Mean procedures performed (sd)	6.5 (2.9)	5.8 (2.5)	0.09

P-values were determined using unpaired t-tests and Fishers exact test for continuous and categorical variables, respectively

Table 2 In patients with cerebral palsy undergoing proximal femoral varus derotational osteotomy (VDRO) surgery with and without tranexamic acid (TXA), there were no significant differences in total transfusion rates over the peri- and postoperative period were seen between groups. Data are presented as mean (SD) (Hb, haemoglobin; Hct, haematocrit; TBW, total body weight)

Characteristic	No TXA (n = 222)	TXA (n = 36)	p-value
Preoperative Hb (g/dL)	13.5 (1.2)	13.4 (1.2)	0.62
Preoperative Hct (g/dL)	39.7 (3.1)	39.7 (2.9)	0.97
Initial postoperative Hb (g/dL)	9.5 (1.6)	9.6 (1.4)	0.73
Initial postoperative Hct (g/dL)	27.8 (4.5)	28.7 (4.2)	0.50
Change pre- to postoperative Hb (g/dL)	-3.8 (2.2)	-3.6 (1.5)	0.76
Change pre- to postoperative Hct (g/dL)	-11.4 (5.0)	-10.7 (3.9)	0.51
Overall transfusion rate	44/222 (19.8)	4/36 (11.1)	0.21
Intraoperative transfusion rate	20/222 (9.0)	1/36 (2.8)	0.20
Postoperative transfusion rate	32/222 (14.4)	3/36 (8.3)	0.32
Estimated blood loss (cc)	159.0 (144.8)	144.4 (102.2)	0.58
Percentage blood loss based on TBW	9.2 (8.7)	8.9 (7.7)	0.83
Length of stay (days)	2.7 (2.4)	3.0 (3.2)	0.47

P-values were determined using unpaired t-tests and Fishers exact test for continuous and categorical variables, respectively

g/dL -8.8 to -0.2, SD 2.2), p = 0.76) and haematocrit difference (TXA: -10.7 (-20.5 to -0.3, SD 3.9) versus No TXA: -11.4 (-25.6 to 0.8, SD 5.0), p = 0.51) from baseline were similar between groups. Length of inpatient hospital stay was not significantly differently between groups (TXA: 3.0 days (1 to 17, SD 3.2), No TXA: 2.7 days 1 to 19, SD 2.4), p = 0.47). No adverse events associated with TXA administration (e.g. stroke or deep vein thrombosis) occurred within the follow-up period. Average follow-up for TXA group was 11.6 months (0.8 to 48.9) and for No TXA group was 33.9 months (0.9 to 145.5).

Discussion

We found that intraoperative administration of TXA was not associated with thromboembolic complications in

patients with CP undergoing VDRO surgery at an average follow-up of approximately one year. The TXA treatment group showed a trend toward lower blood transfusion rates over the peri- and postoperative period, though it did not reach statistical significance. There was no significant difference in surgical estimated blood loss, postoperative haemoglobin levels and length of inpatient hospital stay between those treated with or without TXA.

Intraoperative estimated blood loss was not significantly different between the TXA and No TXA groups. Interestingly, we found a much larger number of outliers in terms of intraoperative estimated blood loss greater than approximately 400 mL in the No TXA compared with the TXA group. It is possible that intraoperative TXA administration may reduce the incidence of major blood losses while not having a significant effect on cases with

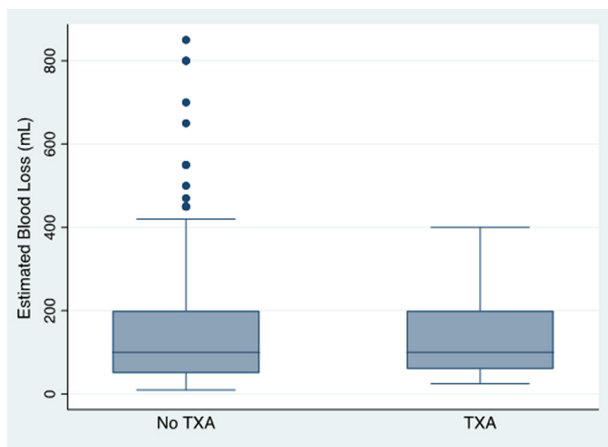


Fig. 1 Box-and-whiskers plots of intraoperative estimated blood loss in children with cerebral palsy undergoing proximal femoral varus derotational osteotomy (VDRO) surgery with and without tranexamic acid (TXA). Reproduced with permission from the Children's Orthopaedic Center, Los Angeles.

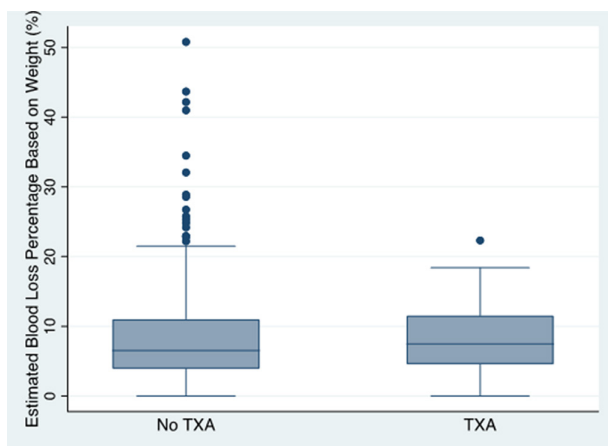


Fig. 2 Box-and-whiskers plots of intraoperative estimated blood loss percentage based on weight in children with cerebral palsy undergoing proximal femoral varus derotational osteotomy (VDRO) surgery with and without tranexamic acid (TXA). Reproduced with permission from the Children's Orthopaedic Center, Los Angeles.

relatively minor blood loss. This may contribute to the differing results regarding TXA efficacy found in our study compared with previous studies investigating TXA administration in spinal surgery where average blood loss was much higher.^{17,21} However, the disproportionate number of outliers between the TXA and No TXA groups may also be a result of the unbalanced cohort sizes between groups.

Part of the difficulty in detecting differences in blood transfusion in the TXA and No TXA groups in our study is likely due to the low rates of intraoperative blood loss and transfusion rates in our non-TXA patients. In the current study, the two groups had intraoperative estimated blood

loss (EBL) of 6 cc/kg to 6.5 cc/kg, which is less than half the mean EBL of 15.4 cc/kg reported by McNerney et al.⁹ The intraoperative EBL of 159 cc in our No TXA group is roughly half the 300 cc EBL reported by Kjeldgaard Pedersen et al.²² Finally, the total rate of transfusion in our non-TXA patients of 19.8% during their intra- and postoperative courses contrasts with transfusion rates of 37% to 67% reported in two previous studies.^{8,9}

Another factor limiting our ability to detect potential differences between the TXA and No TXA groups is the study's power. The current study is significantly larger than the only previously reported study of TXA use in children with CP undergoing hip reconstruction (258 total patients versus 51, including 36 versus 17 treated with TXA) but remains underpowered due to its retrospective nature, sample sizes and unbalanced cohort population sizes. Intraoperative TXA use began at our institution relatively recently in the hip surgery patients, resulting in the disproportionately smaller TXA cohort size. *Post hoc* power analysis of total transfusion rates between groups with the current sample was powered at 19.8% and 312 subjects per group would have been needed to reach a power of 80%. Because our study was considerably underpowered, it is difficult to ascertain whether the lack of significance found between the TXA and No TXA groups in transfusion rates and haemoglobin levels can be extrapolated to the entire patient population or is secondary to an inadequate sample size.

Despite being well studied in the adult population, there is a paucity of literature investigating intraoperative treatment with TXA in patients with CP undergoing orthopaedic procedures. Majid et al⁸ found in a retrospective study of 51 patients with CP undergoing hip reconstructive surgery that TXA use was associated with higher transfusion rates, lower postoperative haemoglobin values and longer hospital length of stays. However, patients who received TXA were more disabled based on the GMFCS and had twice as many bilateral hip reconstructions performed. Authors concluded that these factors resulted in significant selection bias that likely confounded results. Similarly, patients in the TXA group in our study trended towards lower body weight and higher rate of g-tube dependency possibly representative of more severe underlying condition. Both low body weight and g-tube dependency have been found to be risk factors for increased blood loss and poorer outcomes after surgery.⁷ Thus, it is likely that the therapeutic effect of TXA may have been partially masked by the increased severity of disease and preoperative risk factors in two cohorts. Dhawale et al¹⁷ found intraoperative TXA to decrease estimated blood loss and cell salvage transfusion, but not to have a significant effect on total transfusions in patients with CP undergoing scoliosis surgery. Heterogeneity in patient cohorts, perioperative management and underpowered sample

sizes likely contributed to the contrasting results found when comparing these studies. Nonetheless, our studies further validate that TXA can be administered with a low risk of thromboembolic complication in patients with CP undergoing orthopaedic procedures and emphasize the need for more prospective research to determine the efficacy of TXA in this patient population.

The average dose of intraoperative TXA given in our study was 98.2 mg/kg. Dhawale et al¹⁷ reported a TXA dosage of 40.8 mg/kg in their cohort of patients with CP undergoing scoliosis surgery. A previous database study on TXA use in 36 children's hospitals found a median weight-based TXA dose of 22.4 mg/kg most commonly prescribed in trauma cases, congenital heart surgery or scoliosis surgery.²³ TXA dosing in our study was considerably higher than reported in previous studies and, therefore, we believe that it is unlikely that the lack of significant differences in transfusion and blood loss between TXA and control groups was a result of low dosing. It is possible given that our average TXA dose was significantly higher than previously reported that our high dosing may have resulted in suboptimal dosing. However, there are no reports in the literature that have found high dosage to be correlated with decreased efficacy of TXA. We were unable to assess the optimal regiment, dosage and timing of intraoperative TXA in this patient population due to the retrospective nature of this study. However, these should be further investigated in an adequately powered and high-quality randomized controlled trial.

Additionally, data was retrospectively collected from medical records and laboratory reports. Although this may reduce the accuracy of our data, primary outcome variables (transfusion rates, complication rates, haemoglobin levels) are accurately and independently recorded at our centre. The anaesthesia team will often try to minimize blood loss by relative induced hypotension intraoperatively and may also use haemodilution. However, these techniques were used as part of the anaesthesiologists' routine practice and not systematically applied differently between cohort groups and were unlikely to affect the study results. Also, there may have been changes in surgery and anaesthesia practice over the long study period that cannot be controlled for. Postoperative blood loss was not measured because surgeons at our institution do not routinely place wound drains for VDRO surgery. Given the safety of TXA use in CP patients, future studies are needed to determine the effect of TXA use on postoperative outcomes in CP patients undergoing VDRO surgery.

In conclusion, the use of TXA was not associated with thromboembolic complications in this series of children with CP undergoing VDRO surgery. Though there was a trend toward lower rates of intraoperative and postoperative blood transfusion with TXA use in these patients, the differences were not significant, likely due to the low

blood loss in both groups and possibly also due to sample size. Intraoperative TXA use in children with CP undergoing VDRO should be considered in small patients due to their low blood volume and in larger patients expected to have significant blood loss.

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COMPLIANCE WITH ETHICAL STANDARDS

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OA LICENCE TEXT

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ETHICAL STATEMENT

Ethical approval: This study has been carried out with approval from the institutional review board (IRB) at Children's Hospital Los Angeles (CHLA).

Informed consent: A waiver of informed consent has been granted from the CHLA IRB as this is a retrospective study.

ICMJE CONFLICT OF INTEREST STATEMENT

LA reports stock or stock options in Eli Lilly.

RMK reports: Biomet: stock or stock options; Commission for Motion Lab Accreditation: board or committee member; Johnson & Johnson: stock or stock options; Journal of Pediatric Orthopedics: editorial or governing board; Medtronic: stock or stock options; Pfizer: stock or stock options; Zimmer: stock or stock options.

All other authors declare that they have no conflict of interest.

AUTHOR CONTRIBUTIONS

AN: Data collection, data analysis, manuscript preparation and review, final manuscript approval.

SJS: Data collection, data analysis, manuscript review, final manuscript approval.

LA: Study design, manuscript review, final manuscript approval.

RYG: Study design, manuscript review, final manuscript approval.

RMK: Study idea/design, manuscript review, final manuscript approval.

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