DOSE-RESPONSE RELATIONSHIP OF TRANEXAMIC ACID IN PEDIATRIC
SCOLIOSIS SURGERY

SM Goobie, MD, FRCPC\textsuperscript{1}, T Hresko, MD\textsuperscript{2}, ME McCann, MD, MPH\textsuperscript{1}, R
Brustowicz, MD\textsuperscript{1}, M Glotzbecker, MD\textsuperscript{2}, D Hedequist, MD\textsuperscript{2}, N Sethna, MD\textsuperscript{1},
L Karlin, MD\textsuperscript{2}, A Navedo, MD\textsuperscript{1}, J Emans, MD\textsuperscript{2}, E Dyer, RN\textsuperscript{1}, X Huang,
MS\textsuperscript{1}, J Dinardo MD\textsuperscript{1}, LM Pereira, PhD\textsuperscript{1}

\textsuperscript{1}Department of Anesthesiology, Critical Care, Perioperative and Pain Medicine, \textsuperscript{2}Department of
Orthopaedic Surgery,
Boston Children's Hospital and Harvard Medical School, Boston, MA.

Correspondence to:
Susan M. Goobie, MD, FRCPC
Department of Anesthesiology, Critical Care, Perioperative & Pain Medicine.
Boston Children's Hospital
300 Longwood Avenue
Boston, MA 02115
Phone  617 355 7737
Fax 617 730 0894
E-Mail: susan.goobie@childrens.harvard.edu

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Abstract

Background: Extensive blood loss causes significant healthcare costs and poses relevant morbidity and mortality risks. Tranexamic acid (TXA) has consistently been shown to reduce perioperative blood loss in various settings, from traumatic to surgical, both pediatric and adult. However, no consensual dose-response relationship has been identified to support an evidence-based dosing rationale. This study was conducted to fill that knowledge gap in a pediatric idiopathic scoliosis population.

Methods: Eighty children received either placebo or intravenous TXA in a dose of 50 mg.kg$^{-1}$ loading dose (LD) over 15 minutes and 10 mg.kg$^{-1}$.h$^{-1}$ maintenance dose (MD) thereafter until the end of idiopathic posterior scoliosis surgery. TXA plasma concentrations were measured throughout the procedure, concomitantly with hourly estimated blood volume loss (EBL). A pharmacokinetic/pharmacodynamic (PK/PD) modeling framework was developed to identify an in-vivo dose-response relationship for TXA.

Results: The pharmacokinetics of TXA was adequately described by a two-compartment open model with first order elimination. Patients’ body weight, centered on the mean, was identified as a significant covariate for systemic clearance. Cumulative EBL (cEBL) was assessed hourly, compared between placebo and TXA treated patient and the relative difference over time ($\Delta$EBL) was modelled as the PD variable. The overall average reduction in blood loss in the TXA group compared to the placebo group was 27%.

A sigmoid-Emax model with baseline effect was fitted to the $\Delta$EBL data with an estimated half maximal effective concentration (EC$_{50}$) calculated to be 73ug/mL.
Simulations were conducted with the final population PK/PD model to explore competing dosing regimens aiming at this concentration target.

**Conclusions:** TXA is effective in reducing perioperative blood loss in children undergoing Idiopathic scoliosis surgery. A therapeutic plasma steady-state concentration, sustained at 70±5 ug/mL during the surgery, was shown to elicit 50-90% of the maximum effect. Based on PK modeling and simulation, and considering the inherent high variability observed with tranexamic acid, a comprehensive dosing regimen in the range of 10-30 mg/kg LD and 5-0 mg/kg/h MD can be recommended to achieve that therapeutic target. More generous or sparing dosing regimens within this recommendation can be adopted in light of the perceived bleeding risk associated with the type of surgery, the inherent individual patients' risk associated with antifibrinolytic treatment, and the clinical teams' comfort level given the present risk-benefit ratio.
Introduction

Perioperative bleeding and the subsequent need for blood transfusion is known to have significant morbidity and mortality (1-4). Tranexamic acid (TXA, trans-4-aminomethyl cyclohexane carboxylic acid) is an antifibrinolytic that has been shown to have efficacy in pediatric cardiac, craniofacial, orthopedic and neuro surgery minimizing blood loss and blood transfusion requirements (1, 5-9). Antifibrinolytic treatment is recommended as an effective peri-operative blood management strategy in pediatric and adult surgery (6, 10). Less overall bleeding significantly correlates with reduced hospital costs and decreased morbidity and mortality (11, 12).

However, a still unanswered question pervasive among clinicians is ‘what is the therapeutic dose of TXA’? Several communications over the last fifteen years have argued for target TXA plasma concentrations ranging from 10ug/mL to 150ug/mL, with corresponding maintenance infusion doses ranging from 1mg/kg/h to 30mg/kg/h (5, 13). Whether observational, randomized or purely laboratorial, none of these recommendations are based on a formal in vivo dose-response relationship and corresponding therapeutic margin for TXA. With an established efficacy demonstrated above placebo in many clinical scenarios, a consensual pharmacokinetic and most efficacious clinical dosing regimen has not yet been well defined (14).

The primary aim of this portion of a larger prospective, randomized, double-blinded, placebo-controlled trial was to determine the pharmacokinetics (PK) of TXA in children and adolescents. Plasma TXA concentrations were obtained and blood volume lost over time was quantified in pediatric idiopathic scoliosis surgical patients, in order to explore a dose-response relationship for TXA. A second aim was to build a pharmacokinetic /
pharmacodynamic (PK/PD) model to identify in vivo, for the first time, an ideal therapeutic TXA target concentration. Linking the pharmacokinetics with the observed blood loss reduction we developed an evidence-based dosing regimen recommendation.

Materials and Methods

Patient subjects

With the approval of the Boston Children’s Hospital Institutional Review Board (BCH IRB), 80 children and adolescents undergoing idiopathic scoliosis surgery were enrolled in a prospective, placebo controlled, randomized, double-blinded study (clinicaltrials.gov NCT01813058). Total enrollment is projected to be 120 patients in a three-year period. With informed parental and patient consent subjects were randomly assigned to receive either intravenous TXA or 0.9% normal saline, according to a computer generated random number sequence. For this PK/PD analysis the first 80 patients enrolled were used in an interim analysis approved by the BCH IRB from the start of the study without unblinding the study investigators.

Children and adolescents were included when scheduled for elective idiopathic scoliosis corrective surgery, with posterior repair, age between 10 to 21 years. Exclusion criteria were a history of hematological abnormalities, coagulation, hepatic, renal, or vascular disorders, the administration of non-steroidal anti-inflammatory agents within 2 days prior to the surgery, or acetylsalicylic acid within the previous 14 days before the surgery.
Perioperative Management

After induction of anesthesia and before skin incision, patients received 50 mg.kg\(^{-1}\) of TXA (Cyclokapron\textsuperscript{®} Pharmacia and Upjohn Co, Pfizer Inc. NY, NY) diluted in normal saline (NS) to a volume of 1 mL.kg\(^{-1}\) infused over 15 minutes, followed by a maintenance infusion of 10 mg.kg\(^{-1}\).hr\(^{-1}\) (0.1 mL.kg\(^{-1}\).hr\(^{-1}\)). This TXA dosing was chosen based on our previous studies (15). Patients in the placebo group received 1 mL.kg\(^{-1}\) of 0.9% NS over 15 minutes followed by an infusion of NS at 0.1 mL.kg\(^{-1}\).hr\(^{-1}\). Both TXA and NS were infused for the duration of the surgery defined as the time from incision to the last stitch. All solutions were prepared in identical blinded 50 mL syringes by the hospital pharmacy. All anesthesiologists, operating room personnel and study staff were unaware of the study randomization.

Anesthetic management was standardized and consisted of an intravenous premedication of 2 mg midazolam and an intravenous induction with Fentanyl 5-10 µg/kg, Propofol 1-3 mg/kg, and Rocuronium 0.5 mg/kg. Maintenance infusions consisted of a Fentanyl infusion of 1-5 µg/kg/hr, Propofol infusion at 25-200 µg/kg/min titrated to MAP 65-75 mmHg. Anesthesia was also maintained using Isoflurane in oxygen/air, with an age-adjusted end tidal concentration of approximately 0.5 mean alveolar concentration. All patients were intubated and mechanically ventilated to maintain normocarbia. Each patient had at least two large-bore intravenous lines established, along with an arterial line and a urinary catheter. Esophageal temperature was maintained at 35.5 to 36.5\(^0\)C.

Fluid therapy and blood loss were managed by a standardized protocol (Appendix) ie. the administration of crystalloid solutions, 5% human albumin, and blood products. Decisions regarding replacement and maintenance of intravascular volume were at the
discretion of the individual anesthesiologist, according to the guidelines set in the protocol and guided by monitoring arterial blood pressure, urinary output (≥ 1 mL.kg⁻¹.h⁻¹), hematocrit (Hct), and arterial blood gas measurements performed every thirty minutes. Intraoperative cell salvage was used and all recovered autologous red cells were transfused intraoperatively at the anesthesiologist discretion prior to considering allogeneic transfusion and routinely at the end of the case. The decision to transfuse allogenic packed red blood cells (PRBC) was triggered by a hematocrit ≤ 22%.

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(10). PRBC were transfused at 10-15 mL.kg⁻¹ increments to increase the hematocrit by approximately 7-10% and to achieve a target 25-30% at the end of the surgery.

Arterial blood samples were analyzed for hematocrit, electrolytes, prothrombin time, partial thromboplastin time, platelet count, and fibrinogen concentration before the administration of the study drug, at regular hourly intervals during the surgery, and at 24 hours postoperatively.

At the end of the surgery, the trachea was extubated successfully in all patients and patients were transferred to the postoperative recovery room. All surgical procedures were performed by one of five orthopedic surgeons. Anesthesia management was provided by one of five anesthesiologists.
**Assay of TXA Concentrations**

Arterial blood samples for the measurement of TXA (0.2 mL) were drawn at specific time points during the intraoperative period according to one of 4 randomly assigned sampling schemes to ensure an adequate distribution of the sampling time points. They consisted of a baseline sample before the loading infusion, a sample 15 minutes later at the end of it, i.e. at the start of the maintenance infusion, and further samples at intervals throughout the infusion until the end of the surgery; at 15-minute intervals for the first hour, 30-minute intervals for the second hour, and at 60-minute intervals for the remainder of the operation. Once TXA administration was completed at the last surgical stich, further blood samples were drawn over the next 2 hours post infusion to characterize the elimination phase.

Each blood sample was immediately anticoagulated with ethylene diamine tetra-acetic acid (EDTA) and kept on ice. Plasma was separated by centrifugation (1000g x 10 min at 4°C) and stored at -80°C until the time for batch analysis. TXA plasma concentrations were measured by ultra-high performance liquid chromatography (UPLC) with mass spectrometry detection (LC/MS/MS). All TXA samples were analyzed in triplicate along with freshly made daily calibrators and quality control (QC) samples to determine precision and accuracy. The chromatographic method was developed and validated in a Acquity UPLC UPLC (Waters Co.) consisting of a thermostatic auto-injector, a binary pump, a temperature-controlled column compartment and a diode array detector. The mobile phase consisted of acetonitrile as component A and 0.01% formic acid in ultrapure water as component B, with a gradient of 0% to 50% of A in 5 minutes.
Assessment of Blood Volume Loss

The total volume of intraoperative blood loss per hour was determined (estimated blood loss; EBL) by accurately weighing all sponges using a standard analytical scale, measuring the amount of blood collected in the cell salvage volumetric suction canister and subtracting irrigation fluid used (including irrigation in the surgical field and the volume of heparin diluant used in the cell saver). EBL was determined by the same research team consisting of a trained research nurse and research administrator, while confirming with the anesthesiologist. Also recorded were the total volumes of crystalloid and colloid agents administered to the patient per hour, hemodynamic parameters, mean arterial blood pressure and heart rate, total urine output, total surgical time, and number spinal levels involved. Total volumes and units of blood products administered and total volume of autologous cell salvage blood recovered and administered were also recorded. Postoperative data collection included blood transfusion requirement in the first 24 hours after surgery (administered based on a target postoperative Hct > 22%), amount of blood collected in the surgical drains for the first 24 hours postoperatively, the occurrence of any postoperative complications and the duration of hospital stay.

Pharmacokinetic analysis

TXA plasma concentrations were determined in triplicate and mean results were plotted and modelled as a function of time. A preliminary nonlinear regression was conducted in WinNonlin (Pharsight Co., Cary, NC), on individual and pooled data, to obtain initial estimates of the adjustable parameters. Both single and two compartment models with dual input, i.e. loading injection and constant rate maintenance infusion, and first order
elimination, were fitted to the data. Goodness of fit criteria based on residuals analysis, parameters reliability and information criteria such as Akaike (AIC) and Schwarz (BIC), were used in the model selection process. A subsequent mixed effects analysis was performed with Nonmem7 (ICON/Globomax, Hanover, MD) and Monolix 3.1 (MONOLIX Group, http://software.monolix.org/) to refine the parameter estimates, construct diagnostic plots, and conduct a covariate analysis (16, 17).

A Bayesian objective function was then minimized with a proportional error model and different schemes of covariates. A visual predictive check was conducted superimposing a 90% confidence region around the pooled observed concentration.

The typical values of the systemic clearance and the steady-state volume of distribution were modeled as,

\[
TVCL = CL + \theta_{CL,WT} \times \text{weight}
\]

\[
TVV_{ss} = V_{ss} + \theta_{V1,Agg} \times \text{age} + \theta_{V1,WT} \times \text{weight}
\]

where \(\theta\)'s are the numerical coefficients associated to the respective covariates (in subscript), and \(V_{ss}\) is defined as the sum of the volumes of distribution of central and peripheral compartments once the distribution steady state is established. TXA concentrations were calculated (\(\bar{C}\)) with a proportional error as,

\[
C_{ij} = \bar{C}_{ij} \times \varepsilon_{ij}
\]

for the \(i^{th}\) subject at the \(j^{th}\) time point being \(\varepsilon\) the residual random error.

**Pharmacodynamic analysis**

Given the relative and variable nature of ongoing surgical and nonsurgical blood loss, maximum TXA efficacy does not correspond to the total absence of bleeding, but rather a
reduction in bleeding relative to no treatment. Therefore, the cumulative hourly bleeding observed in the TXA treated group was subtracted from the correspondent observed on the NS placebo group to obtain a relative drop in cumulative hourly bleeding (AE/BL) better suited as a pharmacodynamic variable. The asymptotic TXA steady-state concentrations established by the maintenance infusion, were taken as the pharmacokinetic variable in the establishment of a dose-response relationship. A sigmoid Emax model was used to model this PK/PD relationship.

**Results**

Patients’ demographics are depicted for both TXA and placebo groups in Table 1. The higher frequency of female patients, albeit comparable in both groups, is characteristic of the underlying population, as it has been described in the literature (18). No patients had any complications intraoperatively or postoperative while in hospital such as seizures or thromboembolic events.

**Pharmacokinetic Profile**

Following the initial peak TXA concentrations resulting from the loading dose, they decayed to level off at a steady-state sustained by the maintenance infusion for the duration of the surgery. Plasma TXA concentrations ($\mu$/mL; mean ± SEM) were 214.2 ± 96.3 after the loading dose, 158.2 ± 13.4 at 30 minutes, 133.1 ± 13.0 at 60 minutes, 104.9 ± 15.6 at 120 minutes and 86.5 ± 19.0 at 240 minutes (Figure 1). At the end of the infusion (i.e. last stitch at end of surgery) patients reached an average plasma concentration of 81.5 ± 18.2 $\mu$/mL.
Predicted versus observed TXA concentrations are shown in Figure 2, according to the best fit PK model and respective individual parameters, indicating a good capture of the underlying variability. Furthermore, the agreement of a regression line with the identity line in this representation attests the absence of bias and good reliability of the model.

The pharmacokinetics of TXA was adequately described by a two-compartment open model with first order elimination. Patients’ body weight, centered on the mean, was identified as a significant covariate for systemic clearance. Pharmacokinetic parameters, as well as significant covariates affecting systemic clearance and steady-state volume of distribution, are reported in Table 2.

**Effect of TXA on Blood Loss**

Intraoperative cumulative estimated blood loss (cEBL) was significantly lower in the TXA group compared to the placebo group (Figure 4). The hourly percentage of blood loss lower than placebo was 22%, 25%, 25%, 19%, 31%, 33%, 31% at the same time points, with an overall average of 27% reduction in blood loss in the TXA group compared to the placebo group.

As expected, from an ongoing surgery, blood loss increased over time. Compared to placebo, the TXA treated group exhibited a slower rate of increase in cumulative bleeding, noticeable right after the first hour of administration. On average the TXA group had a 213 mL/h bleeding rate, compared to 321mL/h for the placebo group (Figure 4). The hourly differences between placebo and TXA treated patients increased over time up to an estimated 600mL of cumulative blood loss observed in surgical times lasting 6 hours or more. For the mean surgical duration of 4.5h, the corresponding difference in cEBL was on average 300mL.
Pharmacokinetic- Pharmacodynamic Simulation and Modeling

Linking the pharmacokinetics with the observed blood loss reduction we developed an evidence-based dosing regimen rationale. Defining cumulative EBL in relative terms (ΔEBL) as the difference at the same time between the expected cEBL for no treatment, from the placebo group, and that observed under a TXA steady-state concentration, a clear maximum efficacy is evident at a concentration close to 70±5ug/mL (Figure 5). These data were adequately described by a sigmoid Emax model with an inflection point at 73ug/mL.

Based on the population model estimated from the PK/PD data, several dosing regimens could be simulated to explore their corresponding concentrations versus time profiles (Figure 6). Changes in loading dose for the same maintenance infusion rate affect mostly the peak concentrations achieved, as expected, and incrementally less the plateau concentrations approached at the end of surgery (Figure 7).

Discussion

This is the first report to determine the population pharmacokinetic/pharmacodynamic profile and dose response relationship of TXA in adolescents and children undergoing idiopathic scoliosis surgery. Furthermore, this is the first report to define the optimum therapeutic and effective TXA plasma concentration based on in-vivo patient data. The most significant finding of this report is that a TXA dosing regimen of 50mg/kg loading dose with 10mg/kg/h maintenance dose reached a target TXA plasma concentration of 81.5 ug/mL, which was effective in reducing blood loss in children and adolescents
undergoing idiopathic scoliosis surgery. An additional finding is that we first report, using PK simulation and modeling, a most efficacious dosage recommendation for TXA administration in scoliosis surgery directly based on blood loss data. TXA has been used in wide dosing ranges (from loading doses of 10 to 100 mg/kg and maintenance infusion rates from 1 to 10 mg/kg/h) and in patients of different ages and surgical procedures. While there are no studies to unequivocally justify high dosing regimens as initially suggested, others have demonstrated that low doses may offer unsatisfactory results (19-21). Various in-vitro reports focusing on inhibition of fibrinolysis, platelet activation inhibition and enhanced thrombin generation have argued for target TXA plasma concentrations ranging from 10 \( \mu \text{g/mL} \) to 150 \( \mu \text{g/mL} \) (5, 13). Yee et al (22) reported that TXA inhibits fibrinolysis at a plasma concentration of 6.54 \( \mu \text{g/mL} \) in neonates and 17.5 \( \mu \text{g/mL} \) in adults, while Sosslau et al.(23) found that plasmin-induced platelet activation seems to be reduced by 50% when platelet-rich plasma is incubated with 16 \( \mu \text{g/ml} \) of TXA. To date, it's still unclear which TXA therapeutic plasma concentrations are required in children to optimally inhibit fibrinolysis. Indeed, recent pediatric cardiac anesthesia literature recommends three potential targets; 20 \( \mu \text{g/mL} \), 60 \( \mu \text{g/mL} \) and 150 \( \mu \text{g/mL} \) for consideration as therapeutic plasma concentration targets (13). In this study, the individual plasma concentrations of TXA across all patients and at all times intraoperatively, were always above the 20ug/mL threshold. We firstly report here using in-vivo blood loss data that the most adequate therapeutic TXA concentration target is around 70±5ug/mL.

Given that side effects, such as seizures are likely dose-related, it is important to recommend the lower bound effective therapeutic plasma concentration (24, 25). In a
recent communication, Lecker et al. (21) reported that 314ug/mL (2mM) peak plasma concentrations, equating to 31ug/mL (200uM) in the cerebral spinal fluid, are enough to cause hyperexcitability and seizure-like events in the neocortex. Although all patients in our study were under this threshold, lower loading doses as necessary just to achieve the target concentration as quickly as possible, will reduce this risk of toxicity and potential seizures.

In addition, with our fixed dosing regimen, longitudinal plasma concentrations revealed a variability of 20-30%, with peaks ranging between 118-310 ug/mL and plateau concentrations of 63-100 ug/mL. By current standards, the Federal Drug Administration has coined the term ‘Highly Variable Drugs’, albeit for bioequivalence purposes, as those exhibiting a within-subject (same as intra-subject) variability of at least 30% relative to peak concentrations (Cmax) and area under the curve (AUC)(26). Based on ours and previous studies it seems like TXA is a drug that at least borderlines that definition, which makes it much harder to narrowly establish a target concentration or therapeutic margin. This pharmacokinetic variability, albeit minimized by the inclusion of body weight and age as covariates for the clearance and volume of distribution, is indicative of other sources of variability still latent and perhaps requiring further scrutiny.

Furthermore, we identify a possible misunderstanding in the discussion of optimal target concentrations and respective doses. Although one might refer to a target concentration as the mean, naturally bounded by a plausible plus and minus margin of expected variability, in the context of intraoperative blood loss we have preferred in the past to choose as the target the lower bound of such margin. For instance, with our current data we can argue for an optimal target of about 20ug/mL, meaning the lowest admissible
concentration for any patient, corresponding to a median concentration of about 70ug/mL, as per the 10 and 50 percentiles in Figure 1, respectively. On the other hand, choosing to identify the latter as the target, one must acknowledge that with 90% confidence actual concentrations are expected to vary between 20 ug/mL and 110ug/mL. This possible confusion about defining a target must not cloud the choice of a dosing regimen for TXA aimed at maximizing its therapeutic effect.

Based on our TXA PK/PD analysis we can recommend optimal dosage regimens for TXA using the PK model derived and computer simulations. Figure 6 shows simulated concentrations vs. time profiles for different loading (mg/kg) & maintenance (mg/h/kg) doses of TXA. Considering 70 ug/mL as the target therapeutic TXA plasma concentration, with a 90% confidence interval above this threshold, we can recommend a ‘generous’ dosing regimen of 50mg/kg LD and 10mg/kg/h MD, as depicted in Figure 6A. However, with a 90% CI centered around this threshold, then we would recommend a ‘sparing’ dosing regimen of 30mg/kg LD and 10mg/kg/h MD (Fig. 6B).

For completion sake, we also include 20 ug/mL as a possible lowest therapeutic TXA plasma concentration, since this has been reported in previous in vitro reports as the minimum plasma concentration to inhibit fibrinolysis. Should this plasma concentration be shown in future in vivo PK studies to be indeed adequate, then these simulations may help with dosing guidelines. Considering this lower target, with a 90% confidence interval above this threshold we recommend a ‘generous’ dosing regimen of 15mg/kg LD and 10mg/kg/h MD, as depicted in Figure 6D. However, willing to choose 20ug/mL as a central target, with a 90% CI around it instead, then we would recommend a sparing dosing regimen of 10mg/kg LD and 5mg/kg/h (Fig. 6F).
All these choices must reside with the clinical team while identifying the bleeding risk of the surgery, the characteristics of the patient and the perceived efficacy and safety of the drug. For example, for a high risk surgery for bleeding such as scoliosis surgery and a low-risk patients such as an adolescent, then perhaps the clinician might choose a generous and higher dosing regimen. However, with a moderate risk surgery such as neurosurgery and a high-risk patient (with a seizure or thromboembolic risk), the clinician may choose a more sparing dosing regimen. Comprehensively, all recommendations above will achieve a therapeutic margin between 20 ug/mL and 70 ug/mL identified in the dose-response relationship of TXA found in this study. In a recent communication, Johnson et al. (21) compared 10 mg/kg loading and 1 mg/kg/h maintenance doses with 50 mg/kg loading and 5 mg/kg/h maintenance doses, which they defined as low-dose and high-dose, respectively. Their conclusion that “high-dose TXA is more effective than low-dose TXA in reducing blood loss and transfusion requirements in pediatric idiopathic scoliosis patients undergoing surgery” is in agreement with our findings. Their “high-dose” corresponds in terms of the maintenance dose to our sparing regimen recommendation, which we concur to achieve therapeutic concentrations for the duration of the surgery. It’s just important to separate the discussion of the loading dose from that relative to the maintenance one. Clearly a 1 mg/kg/h maintenance infusion lasting the entire surgery is not enough (Figure 7C). In this case plateau concentrations will be significantly lower than the lowest admissible target, i.e. the lower limit of the 20-70 ug/mL therapeutic margin.

A separate but relevant discussion pertains to the choice of the loading dose. As with all constant rate infusion administrations alone, drug concentrations rise from zero towards a
plateau, defined as the steady-state concentration. The time to reach that asymptotic level depends mostly on the elimination half-life of the drug. In many cases it may just be too long for a patient to sustain sub-therapeutic concentrations. That’s the main reason for a concomitant administration of a bolus or rapid infusion at time zero for the concentrations to rise more rapidly, usually approaching thereafter steady-state from above. Therefore, as illustrated in Figure 8, the repercussions of the loading dose affect mostly the first couple of hours of the TXA administration, and not so much the later steady-state concentration governed by the maintenance infusion. As pointed above, under the assumption that plasma concentrations above 200 μg/mL, eliciting CSF concentrations higher than 30 μg/mL, are the culprit of seizure-like events in the neocortex, the most rapid attainment of the desired steady-state concentration, to maximize efficacy, should be balanced with the lowest peak plasma concentrations possible, in order to prevent toxicity. Our dosing recommendations above are intended to achieve this desideratum.

A final consideration is due about the particular clinical efficacy of TXA. Although it has been shown by many independent authors that the anti-fibrinolytic action of TXA has a significant lowering effect on perioperative bleeding, this is in fact a dynamic and kinetic phenomenon. As shown in Figure 4A, early on not only there’s yet not enough bleeding to assess drug efficacy, but also there is not enough time for the drug to exert its full effect. In other words, as the surgery progresses and an increase in cumulative blood loss occurs, that’s when comparing to placebo, TXA treated patients exhibit lesser and lesser bleeding towards maximum drug efficacy. This crucial aspect must be considered when interpreting literature data about total estimated blood loss without a time tag. Averaging
for instance surgeries that lasted just 3h with others that lasted more than 6h creates a
significant bias in defining and comparing blood loss. A lesser volume for the former
may not be at all different from a larger one with the latter, just because extra time always
implies added bleeding. As we’re reporting, our TXA treated patients bled at a rate of
213 mL/h versus 321 mL/h for the placebo group. Furthermore, the longer the surgery the
higher the benefit of TXA translated in perioperative bleeding lowering.
In this study we also encountered pertinent inter-patient variations relative to estimated
blood loss. These are most plausibly due to a multitude of factors from surgical teams and
techniques to underlying orthopedics such as the Cobb angle, the number of levels and
the duration of surgery. A recent meta-analysis published by the Cochrane Library (9)
refers a 681.8mL lower mean total blood loss between placebo (1149.1mL) and TXA
treated (214.5mL) intervention groups, which is in agreement with our findings. They
concluded that “more than a 20% reduction in blood loss” resulted from the
administration of antifibrinolytic drugs. We found it to be 27% on average, between 19
and 33%. However, they also state that “the quality of the evidence for all of these
findings (is) low... because of the small numbers of participants, some concerns about
study designs and imprecision in study findings”. They call for larger trials and dosing
and safety recommendations. Our findings corroborate this assessment, providing
pharmacokinetic evidence and dosing guidelines based on maximum TXA efficacy and
minimal side effects.
Conclusion

A tranexamic acid dose-response relationship was established based on a dosing regimen of 50 mg.kg\(^{-1}\) over 15 minutes followed by a 10 mg.kg\(^{-1}\).hr\(^{-1}\) infusion, which was effective in reducing blood loss in children and adolescents undergoing idiopathic scoliosis surgery. The EC\(_{50}\) was estimated to be 73 ug/mL. Maintained over the entirety of the surgical procedure, with a rapid onset provided by a loading dose, this target concentration may serve as the basis for clinicians to choose maximally effective TXA dosing regimens. Based on these findings and using a pharmacokinetics modeling and simulation approach, we report a comprehensive dosing regimen ranging from 10-30 mg/kg loading dose (LD) and 5-10 mg/kg/h maintenance dose (MD) to maintain plasma concentrations in the 20-70 ug/mL target range. At the discretion of the clinical team, considering the risk-benefit ratio, to target 70±5ug/mL TXA therapeutic plasma concentration a TXA dosing regimen of 30 mg/kg loading dose and 10 mg/kg/h maintenance infusion should be administered in pediatric scoliosis surgery for optimal efficacy.
Table 1 – Patients’ demographics and clinical data (# or mean +/- SEM)

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<tr>
<th></th>
<th>TXA</th>
<th>Placebo</th>
<th>P-value</th>
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<tbody>
<tr>
<td>N</td>
<td>40</td>
<td>40</td>
<td>-</td>
</tr>
<tr>
<td>Age at surgery (yrs)</td>
<td>14.9 +/- 0.357</td>
<td>14.7 +/- 0.273</td>
<td>0.299</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>54.6 +/- 2.08</td>
<td>58.0 +/- 205</td>
<td>0.129</td>
</tr>
<tr>
<td>BMI (kg/m2)</td>
<td>21.2 +/- 0.812</td>
<td>22.6 +/- 0.776</td>
<td>0.114</td>
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<tr>
<td>Gender (M:F)</td>
<td>6:34</td>
<td>9:31</td>
<td>-</td>
</tr>
<tr>
<td>ASA level (1;2;3)</td>
<td>16;23;0</td>
<td>11;27;2</td>
<td>-</td>
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<tr>
<td>Cobb Angle (degree)</td>
<td>58.9 +/- 1.53</td>
<td>60.0 +/- 1.65</td>
<td>0.321</td>
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<tr>
<td>Surgical Time (h)</td>
<td>4.41 +/- 1.79</td>
<td>4.66 +/- 1.24</td>
<td>0.196</td>
</tr>
<tr>
<td>Total cumulative EBL (mL)</td>
<td>833 +/- 72.7</td>
<td>1110 +/- 79.8</td>
<td>0.006</td>
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Table 2 – Population pharmacokinetic parameters next to literature references with respective body weights

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate (%RSE)</th>
<th>Goobie (11Kg)</th>
<th>Wesley (12.3Kg pre-PCB)</th>
<th>Grassi-Delyle (70Kg)</th>
<th>Dowd (80Kg)</th>
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<tbody>
<tr>
<td>Systemic clearance (L/h)</td>
<td>7.44 (+4.54)</td>
<td>1.63</td>
<td>10.0</td>
<td>4.8</td>
<td>9</td>
</tr>
<tr>
<td>Distribution clearance (L/h)</td>
<td>19.4 (+9.82)</td>
<td>2.28</td>
<td>87</td>
<td>32.2</td>
<td>10.8</td>
</tr>
<tr>
<td>Central volume of distribution (L)</td>
<td>5.55 (+7.65)</td>
<td>2.35</td>
<td>0.568</td>
<td>6.6</td>
<td>10.3</td>
</tr>
<tr>
<td>Peripheral volume of distribution (L)</td>
<td>7.87 (+8.11)</td>
<td>2.04</td>
<td>16.3</td>
<td>10.8</td>
<td>8.5</td>
</tr>
<tr>
<td>Elimination half-life (h)</td>
<td>1.34 (+4)</td>
<td>0.762</td>
<td>1.19</td>
<td>2.7</td>
<td>0.82</td>
</tr>
</tbody>
</table>

a-from Ref.(27); b-from Ref.(13); c-from Ref.(28); d-from Ref.(29).
Figure 1 – TXA plasma concentrations versus time up to the end of surgery (n=40)

Figure 2 – TXA concentrations: observed versus predicted by the final model
Figure 3 – Typical individual TXA concentrations (solid circles) and cumulative EBL (open diamonds) profiles
Figure 4 – Cumulative estimated blood loss (cEBL) vs. time for both placebo and TXA treated groups (A); and net cEBL difference between groups (B). Dotted lines in A represent linear regression fits with error bars corresponding to standard error of the mean. Dotted line in B represents a power function curve fit.

Figure 5 - Drop in EBL relative to placebo as a function of TXA steady-state concentrations
Figure 6 – Simulated concentrations vs. time profiles for different loading (mg/kg) & maintenance (mg/h/kg) doses: A - 50&10; B - 30&10; C - 30&5; D - 15&10; E - 15&5; F - 10&5. Solid line represents the mean and dotted lines its 90% confidence region. Two dashed lines represent 70ug/mL and 20ug/mL reference concentrations.
Figure 7 – Simulated concentrations vs. time profiles for different loading doses and two different maintenance dose of 10mg/h/kg (A) and 5mg/h/kg (B), respectively.
REFERENCES