ASWAN UNIVERSITY

Faculty of Medicine

Cover Page

Study Title:

Evaluating the Efficacy and Safety of Tranexamic Acid in Reducing Perioperative Bleeding During Recurrent Hypospadias Repair – A Randomized Controlled Trial

Date:

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1. (Introduction):

Hypospadias is a prevalent congenital anomaly of the male genitalia, with an incidence as high as 71.6 per 10,000 births in some regions (Lavoie et al., 2025). While surgical correction is typically performed in infancy to restore function and appearance (Keays & Dave, 2017; Baskin, 2006), the procedure is prone to complications such as fistulas and strictures, with failure rates reaching over 50% in severe cases (Wu et al., 2020; Bhat, 2008).

The management of recurrent or "redo" hypospadias is even more complex, as previous surgeries leave behind dense, fibrotic scar tissue and compromised vascular patterns (Mushtaq & Wood, 2014). This distorted anatomy doubles the risk of complications compared to primary repairs (Emeka et al., 2023). A major obstacle in these revision surgeries is intraoperative hemorrhage from fibrotic tissues, which obscures the surgical field and leads to imprecise reconstruction and postoperative hematomas (Zhao et al., 2024; Bhat, 2008).

While traditional hemostatic methods like penile tourniquets pose risks of tissue ischemia, Tranexamic Acid (TXA) offers a systemic pharmacological alternative. TXA works by competitively inhibiting plasminogen activation, thereby stabilizing fibrin clots and reducing bleeding (Chauncey & Wieters, 2023). Although TXA has a well-established safety and efficacy profile in cardiac, orthopedic, and pediatric trauma surgeries (Zhang et al., 2019; Ker et al., 2015; Wei et al., 2021), its application in pediatric urology remains largely under-researched. Recent evidence suggests TXA may benefit primary hypospadias repairs (Zhao et al., 2024), but there is a distinct lack of high-quality, double-blind randomized controlled trials focusing on the high-risk recurrent population.

This study aims to fill that gap by evaluating the efficacy and safety of intravenous TXA in children undergoing redo hypospadias surgery, potentially establishing a new standard of care (Goobie & Faraoni, 2019).

2. Objectives (Aim):

Primary Objective

To evaluate whether a 15 mg/kg intravenous bolus of TXA significantly reduces measured intraoperative blood loss in pediatric patients compared to a placebo group receiving normal saline.

Secondary Objectives

1. Surgical Field Clarity: Quantitatively assess if TXA improves visibility for the surgeon by reducing active bleeding during dissection.
2. Operative Efficiency: Determine if the use of TXA results in a shorter total operative time.
3. Postoperative Complications: Evaluate the incidence and severity of bleeding-related issues after surgery, specifically the formation of clinically significant hematomas.
4. Safety Monitoring: Meticulously document the safety profile of the 15 mg/kg dosing regimen to ensure there are no adverse events specific to this pediatric population

3. Study Design:

- Experimental: - **Randomized Clinical Trial**

4. Study Methods

- **Population of study:**

Target Population: The study will enroll male children, aged between 1 and 10 years, who are scheduled to undergo surgical repair for recurrent hypospadias. Recurrent hypospadias is defined as requiring surgical intervention following at least one previous unsuccessful repair attempt. All participants must be classified as American Society of Anesthesiologists (ASA) physical status I or II.

- **Study Location:**

The study will be conducted at Aswan University Hospital, a tertiary care center with expertise in pediatric urological surgery. After ethical committee approval no (1218-2-26).

- **Inclusion criteria:**
  1. Male children aged 1 year to 10 years, inclusive.
  2. Scheduled for surgical repair of recurrent hypospadias.
  3. Classified as ASA physical status I or II.

- **Exclusion criteria:**
  1. Known personal or family history of bleeding disorders or thrombophilia.
  2. Documented history of seizures or epilepsy.
  3. Known allergy or hypersensitivity to tranexamic acid.
  4. Concurrent use of anticoagulant medications or other antifibrinolytics.
  5. Significant renal impairment (eGFR < 60 mL/min/1.73m²).

- **Methodology in detail:**

Eligible participants will be randomly assigned in a 1:1 ratio to either the TXA group or the placebo group. The randomization sequence will be generated by a computer and stratified by age (1-5 years vs. 6-10 years) to ensure a balanced distribution of younger and older children in each group. Allocation concealment will be maintained using sequentially numbered, opaque, sealed envelopes (SNOSE) prepared by the hospital pharmacy, which is not involved in patient recruitment or care. This ensures that the investigators enrolling patients cannot predict the next treatment allocation.
The study will be double-blinded: the participants and their guardians, the clinical care team (including surgeons and anesthesiologists), and the outcome assessors will all be unaware of the treatment group assignment until the study is completed and the data are locked.

a. Intervention and Control

Intervention Group (TXA):
Participants randomized to the intervention group will receive a single intravenous (IV) bolus dose of tranexamic acid (TXA) at 15 mg/kg (maximum dose 1000 mg). The dose will be diluted in a standardized volume of normal saline (20 cc) and administered slowly over 10-15 minutes, approximately 15-20 minutes prior to the surgical incision.

Dose Rationale: The 15 mg/kg loading dose is well-supported by pediatric literature. It falls within the recommended range of 10-30 mg/kg for a loading dose in pediatric surgery and trauma (Faraoni & Goobie, 2014). The TIC-TOC trial for pediatric trauma evaluated a 15 mg/kg bolus as its low-dose arm (Nishijima et al., 2022), and a survey of US children's hospitals found it to be the most common initial dose for pediatric trauma (Cornelius et al., 2021). This dose is considered effective for hemostasis while minimizing the risk of side effects associated with higher doses.

Control Group (Placebo):

Participants in the control group will receive an equivalent volume (20cc) of 0.9% normal saline solution, prepared in an identical syringe by the pharmacy. It will be administered intravenously in the same manner and over the same duration as the intervention drug to maintain blinding.

b. Data Collection and Management

Data will be collected prospectively by trained research personnel who are blinded to the treatment allocation. Standardized Case Report Forms (CRFs) will be used to ensure consistency. All collected data will be entered into a secure, password-protected electronic database.

The following data points will be collected:

• *Baseline Data*: Demographics (age, weight), ASA status, baseline hemoglobin (Hb) and hematocrit (Hct), details of previous hypospadias repairs.

• *Intraoperative Data:* Total intraoperative blood loss (gravimetric method), surgical field visibility score (Fromme scale), total operative time, use of electrocautery, and any intraoperative adverse events.

• *Postoperative Data:* Incidence and size of hematoma, drain output (if used), wound complications (infection, dehiscence), and any adverse events (thrombotic events, seizures, allergic reactions) up to day 7 or hospital discharge, whichever comes first.

- **Potential risks:**
  1- Thrombotic events
  2- Seizures,
  3- Allergic reactions

Confidentiality of data:

To protect participant confidentiality, all collected data will be anonymized. Each participant will be assigned a unique study identification code.

5. Study outcomes

- **Primary outcomes**

  Total intraoperative blood loss: This will be quantified using the gravimetric method. All surgical sponges and gauzes will be weighed before use and after being soaked with blood. The difference in weight (1 gram = 1 mL of blood) will be summed to calculate the total blood loss. Suctioned fluids will be measured, and the amount of irrigation fluid used will be subtracted to determine the volume of blood loss collected via suction.

- **Secondary outcome parameters**

  1. Surgical field visibility: Assessed intraoperatively by the primary surgeon at predefined intervals using the Fromme scale (also known as the Boezaart scale), a validated 5-point scale ranging from 0 (no bleeding) to 4 (severe bleeding, surgery not possible).
  2. Surgeon satisfaction with the surgical field visibility: To be assessed post-operatively using a 5-point Likert scale (1=Very Dissatisfied, 2=Dissatisfied, 3=Neutral, 4=Satisfied, 5=Very Satisfied).
  3. Total operative time: Measured in minutes from the time of skin incision to the application of the final dressing.
  4. Incidence of postoperative bleeding complications: Defined as the occurrence of a clinically significant hematoma (requiring drainage or causing wound compromise) or other bleeding event requiring intervention within 7 days of surgery.

6. Sample size

The sample size was determined based on the primary outcome of total intraoperative blood loss. Based on institutional preliminary data and literature review, we assume a mean blood loss of 50 mL with a standard deviation (SD) of 15 mL in the placebo group. We aim to detect a clinically meaningful reduction of 30% (i.e., 15 mL) in the TXA group.

Using a two-sample t-test framework, with a two-sided significance level (α) of 0.05 and a desired statistical power ($1-\beta$) of 80%, the calculated required sample size is 17 participants per group. This corresponds to a large effect size (Cohen's $d = 1.0$).

To account for a potential dropout or protocol violation rate of approximately 20%, the sample size will be inflated. Therefore, we will recruit a total of 44 participants, with 22 participants allocated to each arm (TXA and placebo). This calculation was performed using the stats model's library in Python.

7. Statistical analysis

Data analysis for this study will be conducted using statistical software like SPSS or R, primarily following the intention-to-treat (ITT) principle to maintain the integrity of the original randomization, supplemented by a per-protocol sensitivity analysis. Baseline characteristics and outcomes will be reported using descriptive statistics, including means and standard deviations for normal data or medians and interquartile ranges for skewed data. The primary outcome—total intraoperative blood loss—will be evaluated for normality via the Shapiro-Wilk test and visual inspection; comparison between the TXA and placebo groups will then be performed using either an independent samples t-test or a Mann-Whitney U test.

Secondary outcomes will be analyzed based on their data type, with continuous variables like operative time and Fromme scale scores undergoing t-tests or Mann-Whitney U tests, while categorical variables such as hematoma incidence and complications will be assessed using Chi-square or Fisher's exact tests, reporting odds ratios and 95% confidence intervals. Finally, safety data will be summarized descriptively, with a p-value of less than 0.05 defining statistical significance across all tests.

8. Source of funding:

NONE

9. References:

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