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Efficacy and safety of tranexamic acid in pediatric patients with isolated traumatic brain injury: a randomized controlled trial

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Background: Tranexamic acid (TXA) is a hemostatic drug that has demonstrated benefits in adult traumatic brain injury (TBI). However, its efficacy and safety in pediatric TBI remain unclear and optimal dosing has not been established. This study aimed to investigate the potential benefits of TXA in children with isolated TBI.

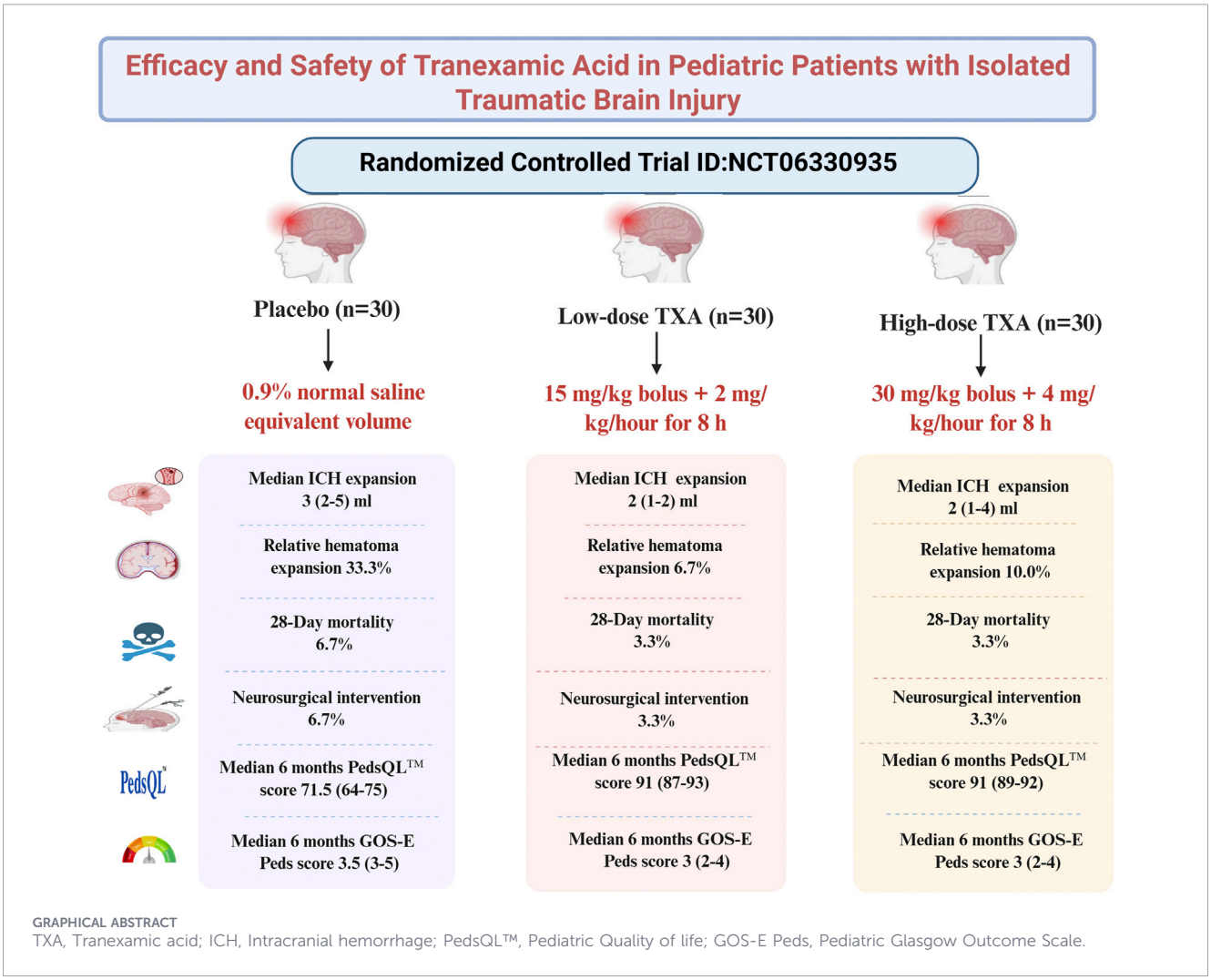
Methodology: This study was a randomized, double-blind, placebo controlled clinical trial that included ninety pediatric patients with TBI who were assigned, in 1: 1: 1 ratio, to receive low-dose TXA (15 mg/kg loading dose followed by a maintenance infusion of 2 mg/kg/hour for 8 h), high-dose TXA (30 mg/kg loading dose followed by a maintenance infusion of 4 mg/kg/hour for 8 h), or placebo (0.9% normal saline) along with conservative management with treatment initiated within 3 h of injury. The primary outcome was the measurement of intracranial hemorrhage (ICH) expansion after 48 h using ABC/2 method. Secondary outcomes included mortality, neurological impairment 6 months after injury, recovery and functional outcomes (Pediatric Glasgow Outcome Scale Extended (GOS-E Peds) score), and quality of life (Pediatric Quality of Life Inventory (PedsQL).

Results: Patients treated with TXA demonstrated a significant decrease in ICH expansion; median (IQR) hematoma volume at 48 h was 2 (1-2) mL in the low-dose (adjusted p = 0.0006) and 2 (1-4) mL in the high-dose group (adjusted p = 0.0015), compared with 3 (2-5) mL in the placebo group. No significant difference was observed between the low- and high-dose TXA groups (adjusted p = 0.32). The 28-day mortality was 3.3% in both treatment groups compared with 6.7% in the placebo group. At 6 months, GOS-E Peds scores showed that 30% of subjects in both TXA groups had significant functional deficits compared with 50% in the placebo group (P = 0.014).

Conclusion: The early administration of TXA, within 3 h of injury, at a low-dose regimen in pediatric patients with isolated TBI significantly reduced hematoma expansion compared with placebo. Administration of a higher-dose regimen did not provide additional benefit. However, further larger trials are warranted to validate these findings.

Clinical Trial Registration: The study was registered at https://clinicaltrials.gov/study/NCT06330935 (NCT06330935).

KEYWORDS
intracranial hemorrhage, pediatrics, RCT, tranexamic acid, traumatic brain injury



GRAPHICAL ABSTRACT
TXA, Tranexamic acid; ICH, Intracranial hemorrhage; PedsQL™, Pediatric Quality of life; GOS-E Peds, Pediatric Glasgow Outcome Scale.

Introduction

Traumatic brain injury (TBI) remains a major global health issue among both children and adults [1, 2]. Intracranial hemorrhage (ICH) following TBI increases the probability of death and disability [3, 4] and the severity of this bleeding can be affected by both structural damages caused by the injury and the presence of trauma-induced coagulopathy (TIC) [5]. TIC is a complex condition characterized by abnormal coagulation, hyperfibrinolysis, and depletion of clotting factors, all resulting from the trauma itself [6].

Tranexamic Acid (TXA), an antifibrinolytic agent, inhibits the conversion of plasminogen to plasmin, a key enzyme involved in fibrin clot breakdown [7]. By blocking this process, TXA helps prevent excessive hemorrhage and preserves clot integrity [7]. The potential of TXA was demonstrated in the CRASH-2 trial, where early administration of TXA within 3 h of injury in adult trauma patients significantly reduced bleeding-related deaths [8]. TXA has also been shown to be cost-effective in treating these patients and to have a favourable safety profile [2, 9]. Moreover, adult patients with TBIs experienced slower progression of ICH when TXA was administered within 3 h of injury [10, 11]. This time-dependent effect may be partially explained by the dynamic changes in fibrinolytic activity following trauma, characterised by early hyperfibrinolysis, which may peak roughly 3 h after injury, followed in some cases by a transition toward fibrinolytic shutdown around 6 h [12]. However, data on TXA use in pediatric populations are limited and mainly restricted to specific contexts, such as cardiopulmonary bypass (CPB) surgery and orthopaedic procedures [13, 14].

To date, only one clinical trial, the Traumatic Head Injury Tranexamic Acid Pediatric Trial (TIC-TOC), has examined the effects of TXA in children with both torso and/or brain injuries [3]. However, this pilot feasibility study was not powered to detect clinically significant differences between pediatric patients treated with TXA and those receiving standard care only [15]. Additionally, a recent observational study on pediatric TBI conducted in Japan using data from the Trauma Data Bank found no association between TXA administration and death or poor neurologic outcomes [16]. The small sample and retrospective design with residual confounding may also have limited ability to detect an effect. Furthermore, hematoma expansion was not evaluated, and data on neurological outcomes and the timing of TXA administration were missing for approximately 40% of the patients [16]. Another significant gap in the literature is the

absence of standardized pediatric trauma-specific recommendations regarding the optimal dose and timing of TXA administration [14]. While the Royal College of Pediatrics has determined a TXA pediatric dose of 15 mg/kg [3, 17], the ATLS (Advanced Trauma Life Support) and the European Guidelines on Management of Major Bleeding and Coagulopathy Following Trauma do not recommend pediatric-specific dosing [3, 14].

Given the limited data and the urgent need to understand the impact of TXA in pediatric patients with isolated TBI, the current study assessed the effect of TXA on hematoma expansion and its impact on mortality, neurological outcomes, and optimal dosing in pediatric patients with TBI.

Materials and methods

Study design

This was a randomized, placebo-controlled, double-blind, parallel group study. The trial was conducted at Al-Azhar University Hospital, New Damietta, Egypt. The study protocol was approved by the Ethics Committee of the Faculty of Pharmacy, Mansoura University (approval number: 2023-192), and was registered on ClinicalTrials.gov (NCT06330935) before patient enrolment. The study was performed according to the Declaration of Helsinki.

Given the narrow therapeutic window for TXA administration (within 3 h of injury) [10]. Federal Exception from Informed Consent procedures were implemented, and the written informed consent was signed at the time when parents or guardians were available and able to provide informed consent [18].

Patient population

Patients presented to the emergency department were screened for eligibility. Included patients were children aged younger than 18 years who had isolated TBI, defined as the presence of ICH on cranial CT, with no clinically significant extracranial injuries (head Abbreviated Injury Score (AIS) ≥ 3 and all other body regions AIS <3) [6]. Eligible patients exhibited moderate to severe injury, indicated by a Glasgow Coma Scale (GCS) score ≤12, and presented to the hospital and initiated the study intervention within 3 h of injury. Patients were excluded if they had a known hypersensitivity or contraindications to TXA; a history of thromboembolic events (e.g., deep vein thrombosis or pulmonary embolism); severe renal impairment; congenital or acquired coagulation disorders; seizure disorders; significant extracranial bleeding; unknown time of injury.

Randomization, study interventions, and blinding

Upon arrival at the emergency department, eligible patients were simply randomized in a 1:1:1 ratio using a computerized random sequence generator to one of three treatment groups: (i) low-dose TXA (15 mg/kg bolus followed by a maintenance infusion of 2 mg/kg/hour for 8 h) where the maximum loading dose was 1,000 mg, the maximum infusion rate was 50 mg/min, and the maximum total maintenance dose was 1,000 mg, (ii) high-dose TXA (30 mg/kg bolus followed by a maintenance infusion of 4 mg/kg/hour for 8 h) where the maximum loading dose was 2000 mg, the maximum infusion rate was 100 mg/min, and the maximum total maintenance dose was 2000 mg, or (iii) placebo (a loading dose of an equivalent volume of 0.9% normal saline) [15, 19]. Study interventions were prepared as identical-appearing solutions of equal volume in indistinguishable syringes labelled only with the participant number, so that neither the drug nor its dose could be identified by inspection. The treatment assignments remained blind to participants/caregivers and the outcome investigators; (the clinician, the radiologist measuring hematoma volume, and the investigator assessing functional outcomes).

Study endpoints

Primary endpoint

The primary endpoint of this study was the difference in ICH expansion between groups, defined as the change in the total intracranial bleeding volume (measured in mL) between the baseline and 48 h follow-up cranial computed tomography (CT) scans. The total hemorrhage volume included all types of intracranial hemorrhage, namely intraparenchymal hematoma, hemorrhagic contusion, subdural hematoma, and epidural hematoma [10]. Two non-contrast cranial CT scans were evaluated for each patient: the baseline scan, performed upon hospital admission, and a follow-up scan, obtained 48 h later. Hemorrhage volumes were estimated using the validated ABC/2 method where: A represents the greatest hemorrhage diameter on axial slices (in cm), B is the maximum width perpendicular to A on the same slice, and C denotes the approximate number of slices with visible hemorrhage multiplied by slice thickness (in cm) [20].

Secondary endpoint

Relative hematoma expansion

To determine the proportion of patients with clinically significant hematoma expansion, defined as an increase in ICH volume ≥33% compared to baseline imaging within 48 h [21, 22].

Mortality

The incidence of early mortality within 24 h of admission was compared among study groups [1]. Additionally, differences in the incidence of all-cause mortality within 28 days of hospital admission were also compared.

The requirement for neurosurgical intervention

The requirement for neurosurgical intervention, defined as the need for any surgical procedure to alleviate elevated intracranial pressure or mass effect, including decompressive craniectomy (DC) and craniotomy [23] was assessed throughout the index of hospitalization period and compared between the TXA and placebo groups.

Pediatric glasgow outcome scale extended (GOS-E peds)

The GOS-E Peds is the pediatric adaptation of the GOS-E; the gold standard outcome measure of adults TBI; it was designed as a structured interview completed with parents and/or guardians to

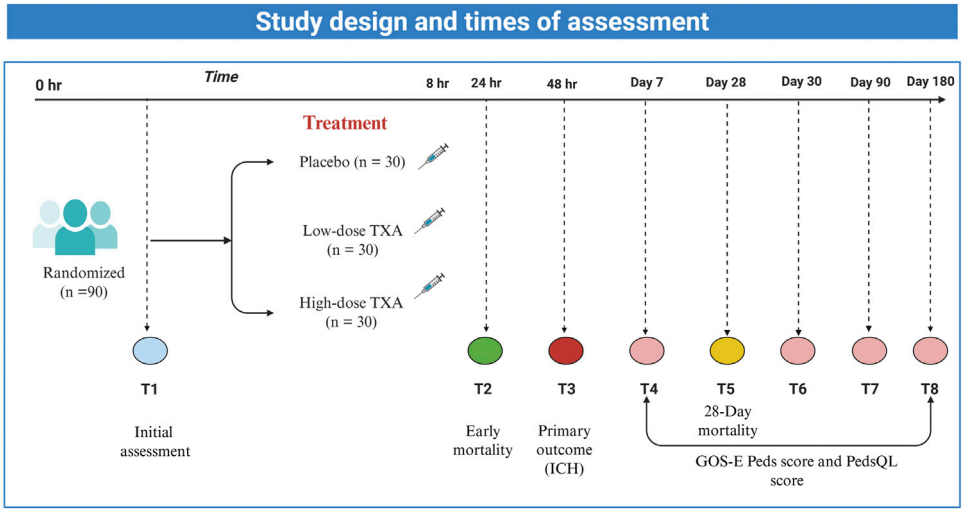


FIGURE 1
Study design and times of assessment. TXA: Tranexamic acid; hr: hour; T: time point, ICH: intracranial hemorrhage, GOS-E Peds: Pediatric Glasgow Outcome Scale Extended score, PedsQL: Pediatric Quality of Life Inventory.

assess changes in function of children and adolescents following injury across seven areas: consciousness, independence at home, independence outside the home, school/work, social and leisure activities, family and friendships, and return to normal life [24]. The GOS-E Peds is an eight-point scale, with higher scores reflect greater disability. Outcomes are categorizing as upper good recovery, lower good recovery, upper moderate disability, lower moderate disability, upper severe disability, lower severe disability, vegetative state and death [25]. The scale was administered to all enrolled patients at 1 week, 1 month, 3 months, and 6 months post-injury (Figure 1). After hospital discharge, assessments were conducted during the follow-up clinic visits or via telephone for all enrolled subjects.

Pediatric quality of life inventory

To evaluate the longitudinal impact of TBI on pediatric health-related quality of life, the Pediatric Quality of Life Inventory (PedsQL 4.0 Generic Core Scales) were administered using age-specific forms tailored to toddlers aged 2–4 years, young children aged 5–7 years, children aged 8–12 years, and adolescents aged 13–18 years at predefined post-injury intervals [26]. The PedsQL is a validated, multidimensional instrument comprising 23 items that assess the child's quality of life across four core domains: physical functioning, emotional functioning, social functioning, and school functioning [27]. Each item is rated on a 5-point Likert scale (0 = Never; 4 = Almost Always). Responses are reverse-scored and linearly transformed to a 0–100 scale, where higher scores reflect better functioning. The scale was conducted for all enrolled children at various intervals: 1 week, 1 month, 3 months, and 6 months post-injury.

ICU stay and hospitalization index

The length of ICU stays, and the total hospital length of stay were recorded for all participants and compared between the study groups. The ICU stay is defined as the number of consecutive calendar days from ICU admission to ICU discharge. Hospitalization index was calculated as the number of consecutive calendar days from hospital admission to discharge or death.

Safety endpoints

The incidence of thromboembolic events, including deep vein thrombosis (DVT), pulmonary embolism (PE), arterial thrombosis, ischemic stroke, and myocardial infarction (MI) was evaluated and confirmed through clinical assessment and appropriate imaging (Doppler ultrasound, CT angiography, or MRI) [28]. During the first 24 h after initiation of study interventions, all participants underwent seizure surveillance via clinical observation and, when indicated, electroencephalography. If anaphylaxis or severe hypersensitivity was suspected during drug infusion, the drug was immediately discontinued and was not restarted. All study patients were followed for 180 days after randomization or until death, whichever occurred first.

Sample size calculation

A priori sample size was calculated using G*Power software (version 3.1) for the primary continuous outcome across the three arms. A sample size of 84 participants (28 per treatment arm) was estimated to provide a power of 90%, α level of 0.05 and an effect size (Cohen's f = 0.40) for ICH haemorrhage growth after TBI between the three groups. In the absence of pediatric data, f = 0.40 was adopted as a feasibility-oriented assumption for a radiographic endpoint. To account for possible dropouts, 6 participants were added, resulting in a total sample size of 90 patients. A *post hoc* power analysis was performed using G*Power software (version 3.1) to evaluate the statistical power achieved of the study. The significance level (α) was set at 0.05. The pooled within-group standard deviation was calculated from the standard deviations of the primary outcome (2.02541, 1.42595, and 1.62205), yielding a

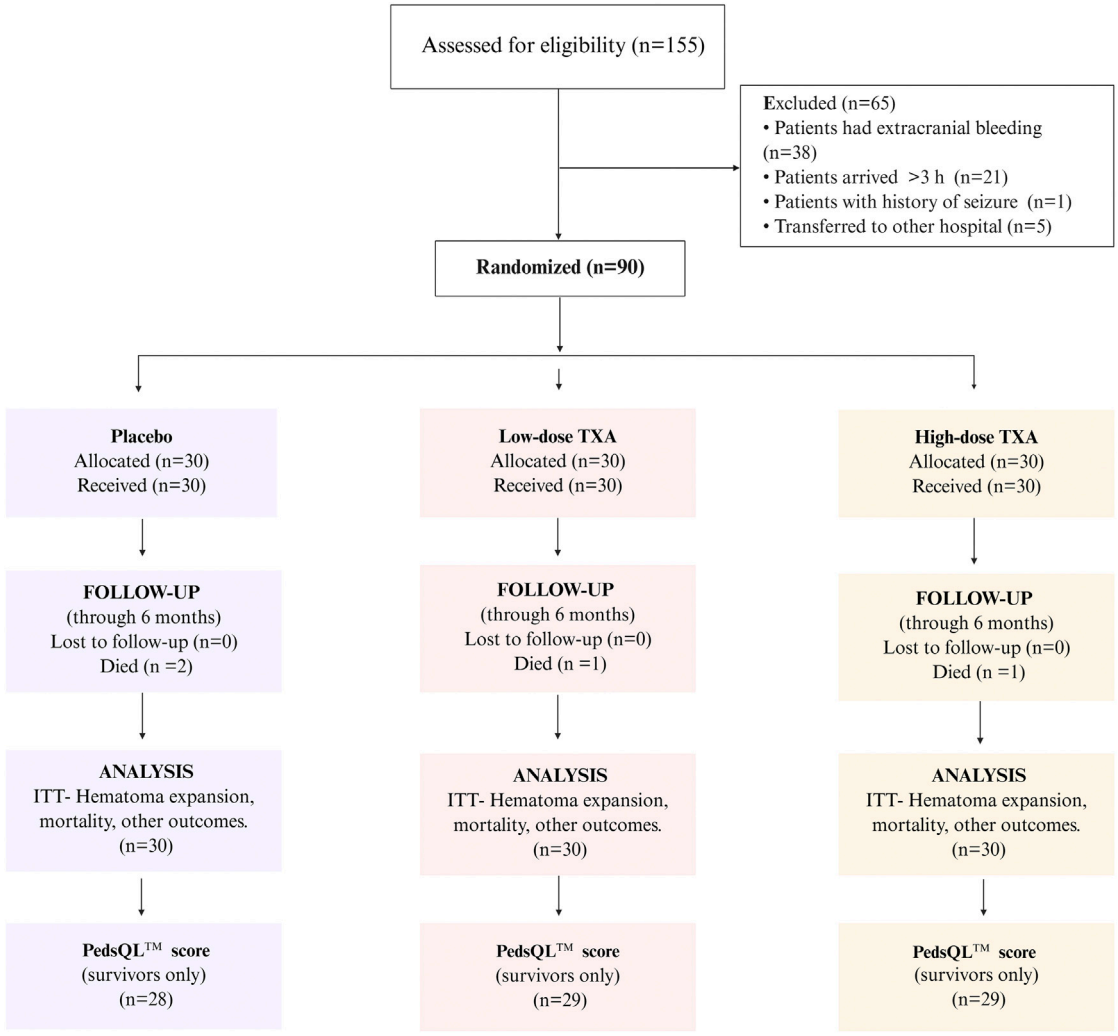


FIGURE 2
CONSORT flow chart TXA: Tranexamic acid, ITT: intention to treat, PedsQL: Pediatric Quality of life, GOS-E Peds: Pediatric Glasgow Outcome Scale.

pooled standard deviation of approximately 1.709. The calculated effect size was Cohen's f = 0.4114. Based on these parameters, the achieved statistical power (1 − β) was 0.9398 (93.98%).

Statistical analysis

Data were fed to the computer and analyzed using IBM SPSS, Version 27.0. Numerical continuous variables were reported as median and interquartile range (IQR) for non-normally distributed data. Normality assessment was done using the Shapiro-Wilk test. Data from three groups were compared using Kruskal-Walli's test for non-normally distributed numerical variables with Dunn's test to detect pair-wise comparison and the resulting p-values were adjusted for multiple comparisons using the Benjamini–Hochberg false discovery rate (FDR) procedure. For the Kruskal–Wallis omnibus test, epsilon-squared (ε^2) is reported as a measure of effect size and the rank-transformation ANCOVA was performed as a prespecified sensitivity analysis for the primary outcome. Categorical variables were expressed as frequency and percentage and were compared across the three groups using the chi-square test. Statistical significance was set at $p < 0.05$.

Results

Baseline patient characteristics

From April 2024 to February 2025, 155 patients were screened, of whom 90 were randomized. Of these individuals, 30 were assigned to each study arm. The CONSORT flow diagram appears in Figure 2. All randomized patients were included in the primary outcome analysis.

The median age was 6 years (IQR 4-10), and 53 (58.9%) participants were male. Median baseline systolic blood pressure

TABLE 1 Baseline patient characteristics.

Characteristics	Placebo (n = 30)	Low-dose TXA (n = 30)	High-dose TXA (n = 30)	*P* value
Age (years), median (IQR)	7.5 (5.0–10.0)	5.8 (4.0–10.0)	5.0 (3.0–10.0)	0.32[a]
Age group, n (%)				
<3 years	2 (6.7)	2 (6.7)	6 (20.0)	0.46[b]
3–9 years	19 (63.3)	19 (63.3)	16 (53.3)	
>9 years	9 (30.0)	9 (30.0)	8 (26.7)	
Gender, n (%)				
Male	13 (43.3)	19 (63.3)	21 (70.0)	0.09[b]
Female	17 (56.7)	11 (36.7)	9 (30.0)	
Primary mechanism of injury, n (%)				
Fall from height	12 (40.0)	16 (53.3)	19 (63.3)	0.19[b]
Road traffic accident	18 (60.0)	14 (46.7)	11 (36.7)	
Time from injury to ED admission (hour), median (IQR)	1 (1.0–2.5)	1 (0.5–2.0)	1 (0.5–2.0)	0.20[a]
ICH baseline volume (mL), median (IQR)	12 (8–20)	9.5 (7–16)	10 (7–18)	0.66[a]
Vital signs				
Temperature (°C), median (IQR)	36.3 (36.0–36.5)	36.5 (36.0–36.5)	36.5 (36.5–36.5)	0.34[a]
Systolic blood pressure (mmHg), median (IQR)	95 (90–110)	97.5 (90–105)	95 (90–100)	0.63[a]
Diastolic blood pressure (mmHg), median (IQR)	65 (65–70)	65 (60–70)	65 (60–70)	0.58[a]
Heart rate (beat/minute), median (IQR)	110 (90–122)	110 (90–114)	110 (90–112)	0.32[a]
Respiratory rate (breath/minute), median (IQR)	26.5 (24–29)	28 (26–30)	28 (24–30)	0.39[a]
Neurological status				
Initial GCS total score, median (IQR)	10 (8–12)	10 (9–12)	11 (9–12)	0.91[a]
Injury severity				
Injury severity scale score, median (IQR)	13 (10–17)	13 (10–13)	13 (10–17)	0.56[a]
Baseline labs				
INR, median (IQR)	1.1 (1.0–1.3)	1.1 (1.1–1.2)	1.1 (1.0–1.2)	0.14[a]
Platelets (10^3/μL), median (IQR)	356.5 (255–397)	345 (248–368)	292 (248–377)	0.64[a]
Glomerular filtration rate (mL/min/1.73 m^2), median (IQR)	95 (93–95)	94.5 (91–100)	93 (90–102)	0.80[a]

Results are presented as n (%) or median (IQR).
TXA, tranexamic acid; ED, emergency department; GCS, glasgow coma scale; INR, international normalised ratio; IQR, interquartile range.
[a]Kurskal-Walli's test.
[b]Pearson chi-square test.

was 95 mm Hg (IQR 90-105), and diastolic blood pressure was 65 mm Hg (IQR 60-70). The median time from trauma to randomization was 1 h (IQR 0.5–2). Baseline demographic characteristics were well balanced between the two treatment groups and the placebo group as described in Table 1.

Efficacy measures

Primary outcome

At baseline, the median hematoma volume was 10 mL (IQR 7–17) and it was comparable across the three groups (Table 2). Forty-eight hours post injury, the median ICH expansion differed significantly across groups (P = 0.001). Dunn's Pairwise comparison test and BH correction showed that both low-dose TXA (2 [1, 2] mL, adjusted p = 0.0006) and high-dose TXA (2 [1–4] mL, adjusted p = 0.0015) showed less expansion in ICH than that seen in placebo group (3 [2–5] mL). In addition, no significant difference was observed between the low and high-dose TXA groups (adjusted p = 0.32, Table 2). Beyond statistical significance, the effect size for the primary outcome was medium-to-large (ε^2 = 0.16).

Table 3 displays the Rank-transformation ANCOVA with 48-h hematoma expansion as the dependent variable and baseline hematoma volume as a continuous covariate. The

TABLE 2 Absolute ICH expansion by treatment arm, with between-group effect sizes and unadjusted versus multiplicity-adjusted p-values.

Group	ICH volume (mL), median (IQR)		
	Baseline	After 48 h	ICH expansion
Placebo	12 (8–20)	14 (11–25)	3 (2–5)
Low-dose TXA	9.5 (7–16)	11 (8–18)	2 (1–2)
High-dose TXA	10 (7–18)	12.5 (9–21)	2 (1–4)
P value	0.66[a]	0.25[a]	<0.001[a]
ICH expansion pairwise contrasts			
Group	Dunn's test unadjusted *p* value	BH-adjusted *p* value	Effect size ε^2
Placebo vs. low-dose TXA	*P= 0.0002*	*P = 0.0006*	$\boldsymbol{\varepsilon^2}$ = 0.16
Placebo vs. high-dose TXA	*P = 0.001*	*P = 0.0015*	
Low- vs. high-dose TXA	*P = 0.32*	*P = 0.32*	

TXA, tranexamic acid; ICH, intracranial hemorrhage; IQR, interquartile range.
[a]Kruskal–Wallis test, ε2; epsilon-squared, BH; Benjamini–Hochberg adjustment.

treatment-group effect F (2, 86) = 6.0, p = 0.003. The baseline-volume covariate was strongly associated with the outcome F (1, 86) = 1,609.9, p < 0.001, partial η^2 = 0.126), confirming that the between-group difference persists after adjustment for baseline volume.

TABLE 3 Rank-transformation ANCOVA for 48-h hematoma expansion volume, adjusted for baseline hematoma volume.

Effect	F (df)	P	Partial η^2
The treatment-group effect (adjusted)	6.185 (2, 86)	0.003[a]	0.126
Baseline hematoma volume (covariate)	1,609.94 (1, 86)	<0.001[a]	0.949

[a]ANCOVA, analysis of covariance, F = F-ratio (ratio of between-group to within-group variance); df = degrees of freedom, partial η2 (partial eta-squared).

Secondary outcomes

Relative hematoma expansion

The effects of TXA on relative hematoma expansion of more than 33% is presented in Table 4. Percent of patients having relative hematoma expansion of more than 33% after 2 days was significantly lower in low-dose TXA group (6.66%), and high-dose TXA (10%) than that in placebo group, *P* = 0.01). Bonferroni pairwise testing and BH correction showed no significant difference was observed between the low-dose vs. high-dose, adjusted *P* = 0.64).

Mortality

There was no significant difference in mortality across the three study groups. There were no cases of early mortality within 24 h of admission. The 28-day mortality was 3.3% (n = 1) in the two treatment groups and 6.7% (n = 2) in the placebo group (*P* = 1.00). All mortalities occurred within the first week after treatment and were directly attributable to the primary brain injury and its sequelae (progressive intracranial hypertension and herniation), rather than to extracranial causes.

The requirement for neurosurgical intervention

During the intervention period, no significant difference in the need for neurosurgery was observed between the study groups: two patients (6.7%) in the placebo group compared to one patient (3.3%) in both TXA-treated groups (*P* = 1.00).

Pediatric Glasgow Outcome Scale Extended (GOS-E peds) score

Table 5 illustrates the GOS-E Peds scale, which assessed the effect of TXA administration on recovery and long-term disabilities. Three months after treatment, both low and high-dose TXA groups showed significantly lower disability than the placebo group. This was also maintained after 6 months.

At the end of 6-month follow-up period, 30% of subjects in both low and high-dose TXA groups had significant functional deficit compared with 50% in the placebo group (*P* = 0.014, Table 6).

GOSE-Peds was analyzed across all four timepoints using a cumulative-logit ordinal mixed model with patient as a random effect. There were significant main effects of treatment group (F (2, 328) = 5.670, p = 0.004) and time (F (3, 328) = 62.647, p < 0.001), and a significant Group × Time interaction (F (6, 328) = 3.157, p = 0.005), indicating that between-group differences in functional outcome varied over the follow-up period. In between-group contrasts versus placebo, the low-dose TXA arm differed significantly (OR = 19.3, 95% CI 1.49–250; p = 0.024), whereas the high-dose arm did not (OR = 1.10, 95% CI 0.10–12.4; p = 0.940).

Pediatric quality of life inventory (PedsQL)

The impact of TXA on children's quality of life, as measured by the Pediatric Quality of Life scale, was similar between groups at baseline (*P* = 0.4). However, over the 6-month follow-up period, the total AUC of the PedsQL score was significantly higher in both the low- and high-dose TXA groups (13579, 13743, respectively) compared to the placebo group (11329; *P* < 0.001), with no

TABLE 4 Relative hematoma expansion by treatment arm, with between-group comparison.

Group	Relative hematoma expansion of more than 33%, *n* (%)	*P value*
Placebo	10 (33.3%)	0.01[b]
Low-dose TXA	2 (6.7%)	
High-dose TXA	3 (10.0%)	
Relative hematoma expansion pairwise contrasts		
Group	Bonferroni unadjusted *p* value	BH-adjusted *p* value
Placebo vs. low-dose TXA	*P = 0.01*	*P = 0.03*
Placebo vs. high-dose TXA	*P* = 0.03	*P* = 0.045
Low- vs. high-dose TXA	*P* = 0.64	*P = 0.64*

TXA, tranexamic acid; ICH, intracranial hemorrhage.
[b]Pearson chi-square test, BH; Benjamini–Hochberg adjustment.

TABLE 5 Pediatric Glasgow Outcome Scale Extended (GOS-E Peds) score by treatment arm, with between-group comparison.

Variable	Groups	Median (IQR)	*P* value	Dunn's test pairwise comparison	BH-adj *p* value
GOS-E peds score after 1 week	Placebo	6 (5–6)	0.43[a]	P_1 = 0.49 P_2 = 0.13 P_3 = 0.13	P_1 = 0.49 P_2 = 0.195 P_3 = 0.195
	Low-dose TXA	6 (5–6)			
	High-dose TXA	6 (5–6)			
GOS-E peds score after 1 month	Placebo	5 (5–6)	0.0001[a]	P_1 = 0.10 P_2 = 0.0000 P_3 = 0.0002	P_1 = 0.10 P_2 < 0.0001 P_3 = 0.0003
	Low-dose TXA	5 (4–5)			
	High-dose TXA	5 (4–5)			
GOS-E peds score after 3 months	Placebo	4 (4–5)	0.0001[a]	P_1 < 0.0001 P_2 < 0.0001 *P3* = 0.41	P_1 < 0.001 P_2 < 0.001 *P3* = 0.41
	Low-dose TXA	4 (3–5)			
	High-dose TXA	4 (3–5)			
GOS-E peds score after 6 months	Placebo	3.5 (3–5)	0.0001[a]	P_1 < 0.0001 P_2 < 0.0001 P_3 = 0.40	P_1 < 0.001 P_2 < 0.001 P_3 = 0.40
	Low-dose TXA	3 (2–4)			
	High-dose TXA	3 (2–4)			

Data are reported as Median (IQR). TXA, tranexamic acid; GOS-E, peds, Pediatric Glasgow Outcome Scale Extended; IQR, interquartile range.
[a]Kruskal Walli's test with Dunn's pairwise testing and BH, correction where P_1, difference between placebo versus low-dose TXA; P_2, difference between placebo versus high-dose TXA; P_3, difference between low-dose versus high-dose TXA.

significant difference between the low- and high-dose TXA groups. Figure 3 shows an area graph of the PedsQL AUC over time for the three groups.

ICU stay and hospitalization index

The analysis of ICU and hospital lengths of stay was restricted to patients who survived until hospital discharge. Statistically significant overall differences were observed among the study groups in both ICU length of stay (P = 0.031) and total hospital length of stay (P = 0.013). However, subsequent pairwise comparisons revealed that these differences were statistically significant only the placebo-versus-low-dose (adjusted P =0.03 and adjusted P =0.009, respectively) whereas no statistically significant differences were observed between the remaining groups as presented in Table 7.

Safety and adverse events

Of the 90 enrolled patients, one patient in the placebo group developed a seizure (3.3%) within the first 7 days after randomization. No seizures were observed in the two TXA treatment groups, the difference was not significant (P = 0.36). Throughout the study, no acute thromboembolic events were identified after randomization in any of the three study groups. No allergic or hypersensitivity reactions were observed in any patient during the study period.

Discussion

This study is the first randomized controlled trial to evaluate the efficacy of TXA in pediatric patients with TBI. The primary outcome

TABLE 6 Categories of Pediatric Glasgow Outcome Scale Extended score 6 months post injury.

GOSE-P categories	Restriction	Placebo (n = 30)	Low-dose TXA (n = 30)	High-dose TXA (n = 30)	*P* value
1) Upper good recovery	No functional deficit	0 (0)	0 (0)	0 (0)	0.014[c]
2) Lower good recovery	Mild functional deficit	0 (0)	10 (33.3)	11 (36.7)	
3) Upper moderate disability		15 (50)	11 (36.7)	10 (33.3)	
4) Lower moderate disability	Significant functional deficit	7 (23.3)	5 (16.7)	6 (20)	
5) Upper severe disability		5 (16.7)	3 (10)	2 (6.7)	
6) Lower severe disability		1 (3.3)	0 (0)	0 (0)	
7) Vegetative state		0 (0)	0 (0)	0 (0)	
8) Dead		2 (6.7)	1 (3.3)	1 (3.3)	

Results are presented as n (%). TXA: tranexamic acid, GOS-E, Peds: Pediatric Glasgow Outcome Scale Extended.
[c]Fisher- Exact test.

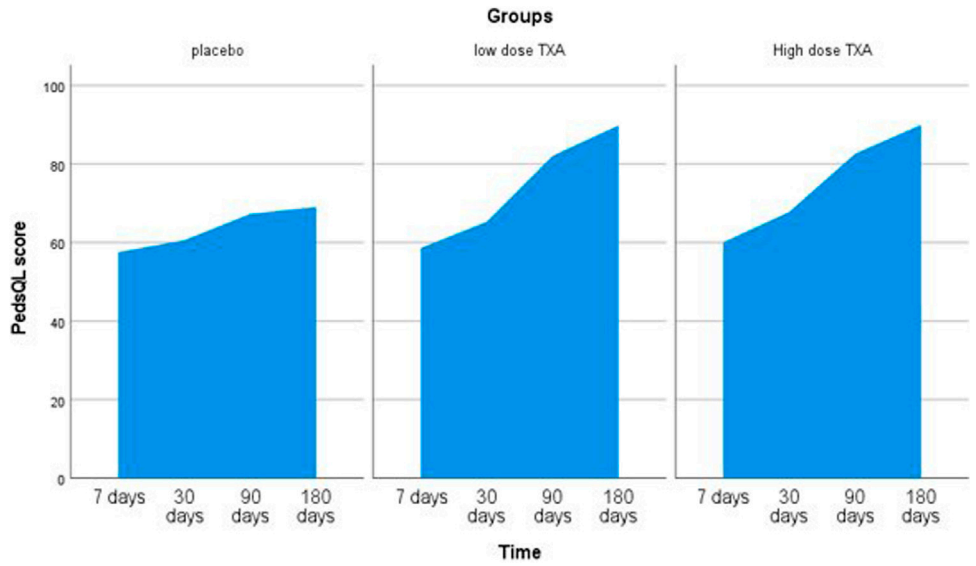


FIGURE 3
Area graph of the Pediatric Quality of Life Inventory (PedsQL) score over 6 months of follow-up in the three study group.

TABLE 7 Comparison of ICU length of stay and Hospital Index between groups among survivors only.

Variable	Groups	Median (IQR)	*P* value	Dunn's test pairwise comparison	BH-adj *p* value
ICU length of stay (days)	Placebo (n = 28)	4 (2–6)	0.031[a]	P_1 = 0.01	P_1 = 0.03
	Low-dose TXA (n = 29)	2 (2–3)		P_2 = 0.075	P_2 = 0.11
	High-dose TXA (n = 29)	3 (2–3)		P_3 = 0.417	P_3 = 0.417
Hospital length of stay (days)	Placebo (n = 28)	5 (4–8)	0.013[a]	P_1 = 0.003	P_1 = 0.009
	Low-dose TXA (n = 29)	4 (4–5)		P_2 = 0.067	P_2 = 0.10
	High-dose TXA (n = 29)	5 (4–5)		P_3 = 0.268	P_3 = 0.268

Data are reported as Median (IQR).
TXA, tranexamic acid; ICU, intensive care unit; IQR, interquartile range.
[a]Kruskal -Walli's test with Dunn's pairwise testing and BH, correction where P_1, difference between placebo versus low-dose TXA; P_2, difference between placebo versus high-dose TXA; P_3, difference between low-dose versus high-dose TXA.

was hemorrhage growth, defined as hematoma expansion over 48 h and calculated using the validated ABC/2 method which is originated in adults and has been independently validated in children with intracranial hemorrhage, with high accuracy against volumetric segmentation (R^2 = 0.93–0.97) and excellent interrater reliability (ICC 0.94), supporting its geometric validity in the smaller pediatric brain [29].

In the present study, TXA significantly reduced hemorrhage expansion compared with placebo. The median hematoma expansion was 3 mL (IQR, 2–5 mL) in the placebo group, compared with 2 mL (IQR, 1–2 mL) in the low-dose TXA group and 2 mL (IQR, 1–4 mL) in the high-dose TXA group (overall P = 0.001). Pairwise comparisons demonstrated significantly less hemorrhage expansion in both the low-dose (adjusted P = 0.0006) and high-dose TXA groups (adjusted P = 0.0015) than in the placebo group, whereas no significant difference was observed between the two TXA dosing regimens (adjusted P = 0.32). These findings are consistent with evidence from adult TBI. A recent meta-analysis of randomized controlled trials demonstrated that TXA significantly reduced mean hemorrhage volume compared with placebo (SMD −0.39, 95% CI −0.60 to −0.18; $P < 0.001$) and reduced the risk of hemorrhagic expansion (RR 0.83, 95% CI 0.70–0.99; P = 0.03) [30]. Furthermore, subgroup analysis showed that administration of TXA within 3 h of injury was associated with an even greater reduction in mean hemorrhage volume (SMD −0.51, 95% CI −0.81 to −0.20; P = 0.001) [30]. The observed reduction in hemorrhage expansion supports the antifibrinolytic mechanism of TXA, whereby inhibition of plasminogen activation limits hematoma progression following TBI [2].

The timing of TXA administration in the present study may have contributed to the observed efficacy. Treatment was started within 3 h of injury in all patients, consistent with the previously established time-dependent effect of TXA. In CRASH-3 study, early treatment was more effective than later treatment in patients with mild-to-moderate TBI, whereas time to treatment had no evident effect in severe TBI [2]. Biologically, hyperfibrinolysis after TBI peaks approximately 3 h after injury and is followed by a shift toward fibrinolysis shutdown [12]. Hematoma expansion also occurs mainly early after injury [31], so early TXA is most likely to limit hemorrhage growth. Restricting enrollment to the early window may therefore have favored the observed reduction in hematoma expansion. However, because time from injury to treatment was not analyzed as an effect modifier, the influence of timing within the 3-h window could not be determined.

Although both TXA regimens significantly reduced hematoma expansion compared with placebo, no significant difference was observed between the low-dose and high-dose TXA groups, indicating that increasing the dose did not provide additional efficacy in limiting hemorrhage growth. The absence of an observable dose–response relationship may reflect a ceiling effect of TXA on fibrinolysis inhibition. Pharmacodynamic studies have shown that substantial inhibition of fibrinolysis is achieved at relatively low plasma TXA concentrations (10–15 mg/L), suggesting that higher concentrations provide little additional antifibrinolytic activity. Consistent with this hypothesis, clinical studies in TBI have similarly reported no significant differences in outcomes across different TXA dosing regimens [32]. In contrast, the TRACES trial in postpartum hemorrhage demonstrated greater efficacy with a 1-g dose than with a 0.5-g dose [33], suggesting that the presence and magnitude of a dose–response relationship may depend on the clinical setting and the dose range evaluated.

A potential concern in any hematoma-expansion trial is that 48-h volume is heavily determined by baseline volume, such that an apparent treatment effect could instead reflect chance baseline imbalance across arms. To address this, a pre-specified rank-transformation ANCOVA was performed as a sensitivity analysis, adjusting 48-h hematoma volume for baseline volume as a continuous covariate. As expected, baseline volume was by far the strongest determinant of 48-h volume; nevertheless, treatment arm remained independently and significantly associated with 48-h volume after this adjustment (F (2, 86) = 6.0, p = 0.003, partial η^2 = 0.126). The direction, magnitude, and pairwise pattern of the adjusted effect was concordant with the primary Kruskal–Wallis analysis, including the loss of significance for the placebo-versus-high-dose contrast after multiplicity correction. The agreement between the unadjusted nonparametric test and the baseline-adjusted model indicates that the observed group differences are not an artifact of baseline volume distribution and strengthens confidence in the primary finding.

Several definitions of clinically significant hematoma expansion have been proposed in the literature [34, 35]. Although a relative increase of more than 33% is one of the most frequently used thresholds in clinical trials [36]. These thresholds have consistently been associated with worse clinical outcomes in adults. However, evidence supporting the clinical relevance of hematoma expansion in pediatrics is limited. Boulouis *et al.* applied the adult-derived definition of significant hemorrhage expansion (>6 mL or >33% increase from baseline) to pediatrics with intracerebral hemorrhage and found that 15% of pediatric patients with intracerebral hemorrhage experience significant expansion, which independently leads to worse long-term neurological outcomes at 12 months [37]. In the current study, 33.3% of patients in the placebo group experienced clinically significant hematoma expansion, compared with only 6.7% and 10.0% in the low-dose and high-dose TXA groups, respectively (overall P = 0.01). Pairwise analyses confirmed significant reductions in both TXA groups compared with placebo (low-dose vs. placebo, (adjusted P = 0.03; high-dose vs. placebo, (adjusted P = 0.045), whereas no significant difference was observed between the two TXA dosing regimens (adjusted P = 0.64).

The median absolute difference in hematoma expansion between TXA and placebo was about 1 mL (2 vs. 3 mL). Although this appears modest effect, several considerations suggest it is clinically meaningful. In a cohort of adults with moderate-to-severe TBI, hematoma expansion showed a graded relationship with 12-month outcome: each 1-mL increase was independently associated with a 6% higher risk of a 1-point deterioration on the Glasgow Outcome Scale [31]. Also, considering that intracranial compliance is reduced in pediatrics, small volume increases can produce marked rises in the intracranial pressure [38]. Small hematoma increments may therefore carry proportionally greater consequences in those patients.

Despite these favorable radiological findings, there was no significant difference in 28-day mortality among the three study groups. Mortality was 6.7% in the placebo group compared with

3.3% in both the low-dose and high-dose TXA groups (P = 1.00). Evidence regarding the mortality effect of TXA in pediatric trauma remains limited and inconsistent. A recent meta-analysis by Lin et al. [3] reported a significant reduction in mortality associated with TXA administration (OR 0.58, 95% CI 0.38–0.89). Conversely, an earlier meta-analysis by Kornelsen et al. [39] did not demonstrate a significant association between TXA use and improved survival in pediatric trauma (adjusted OR 0.61, 95% CI 0.30–1.22). In adult TBI, the CRASH-3 trial demonstrated that the mortality benefit of TXA depends on injury severity. TXA significantly reduced head injury-related mortality among patients with mild-to-moderate TBI (RR 0.78, 95% CI 0.64–0.95), whereas no benefit was observed in patients with severe TBI [2]. The discrepancy between the present findings and those of the CRASH-3 trial may be explained by several factors. First, the present study enrolled a pediatric population consisting predominantly of patients with moderate TBI, whereas the CRASH-3 trial included adults with both mild and moderate TBI. Second, the substantially smaller sample size and the low number of mortality events in the present study might limit the statistical power to detect a survival benefit.

In the present study, TXA was associated with a modest decrease in the need for neurosurgical intervention compared with placebo; however, this difference was not statistically significant (P = 1.00). These findings are consistent with the meta-analysis by Weng et al. [40] which reported no significant difference in surgical intervention rates between TXA and control groups, despite reduced hematoma expansion. Despite the significant median reduction in hemorrhage volume of approximately 2 mL with TXA, this did not translate into a reduction in neurosurgical intervention. This may be explained by several factors; neurosurgical evacuation is generally reserved for patients with large hematomas causing significant mass effect or neurological deterioration [36]. Furthermore, TXA primarily prevents ongoing hemorrhagic progression rather than reversing an already established hematoma; therefore, patients presenting with lesions requiring surgical management are likely to undergo intervention regardless of TXA administration [41, 42].

Beyond its effect on hematoma progression, the present study demonstrated that TXA was associated with improved long-term functional recovery and health-related quality of life. At 6 months, children treated with TXA had significantly better functional outcomes compared with placebo, reflected by lower median GOS-E Peds scores and a lower proportion of patients with significant functional deficits (30% in both TXA groups vs. 50% in the placebo group; $P = 0.014$), however no participant in the three groups reached upper good recovery at 6 months, consistent with the substantial acute morbidity of this population and with the well-documented observation that good recovery in pediatric TBI accrues predominantly after 6 months [43].

Similarly, longitudinal assessment of quality of life demonstrated a significantly greater cumulative PedsQL score over the 6-month follow-up period in both TXA groups compared with placebo (AUC: 13,579 and 13,743 vs. 11,329; $P < 0.001$). No significant differences were observed between the low-dose and high-dose TXA groups for either functional outcome or quality of life, suggesting that the lower dose may provide comparable long-term clinical benefits while minimizing drug exposure.

These findings are notable because previous clinical studies have not consistently demonstrated that TXA improves long-term functional recovery after TBI. In adults, the prehospital TXA for TBI trial by Rowell et al. [42] reported no significant difference in 6-month favorable GOSE outcomes between TXA and placebo $P = 0.16$). Similarly, the CRASH-3 trial did not establish an improvement in functional recovery. Consistently, a systematic review by Al Lawati et al. [44] concluded that TXA probably has no effect on disability outcomes (mean difference in Disability Rating Scale score −0.18, 95% CI −0.43 to 0.08). Several factors may explain why the present trial demonstrated functional benefits despite the neutral findings of many adult studies. First, pediatric patients exhibit more pronounced alterations in acute coagulation profiles, including prolonged prothrombin time–international normalized ratio, activated partial thromboplastin time and lower fibrinogen concentrations compared with adults [45]. Furthermore, elevated D-dimer levels, reflecting increased fibrinolytic activity, have been associated with poor neurological outcomes in children [46]. These findings suggest that fibrinolysis-mediated secondary injury may represent a particularly relevant therapeutic target in pediatric TBI. Also, greater neuroplasticity and recovery potential of the developing brain may allow the prevention of secondary injury, such as hematoma expansion, to translate more effectively into long-term functional improvement [47]. In contrast, adult patients may remain limited by the extent of irreversible primary brain injury.

However, whether these functional gains, observed in the present study can be attributed to reduced hematoma expansion remains uncertain. Hematoma expansion has been independently associated with worse functional outcome in adult TBI (each 1-mL increase was linked to a 6% higher risk of a 1-point GOS deterioration) [31, 48], which supports a plausible contribution. Nevertheless, TXA may also act through mechanisms unrelated to hematoma size, such as attenuating fibrinolysis-related secondary injury [49, 50]. Because no mechanistic analysis was performed and the sample size was small, reduced hematoma expansion should be considered a plausible contributor, and the functional findings should be regarded as hypothesis-generating.

To evaluate healthcare resource utilization without conflating shorter lengths of stay due to early mortality, the analysis of ICU and hospital stay durations was restricted to patients who survived until hospital discharge. In the present trial, TXA administration was associated with shorter ICU and hospital lengths of stay compared with placebo, with a median reduction of approximately one ICU Day. A potential mechanistic explanation is that TXA attenuates intracranial hemorrhage and hematoma expansion, thereby limiting secondary brain injury and the occurrence of intracranial pressure–related complications, which may subsequently reduce the duration of intensive care support [51]. From a health-system perspective, even a modest reduction in ICU length of stay may be clinically relevant in low- and middle-income settings, where critical care capacity is frequently constrained [52].

Regarding safety outcomes, the results of the current study indicated the absence of thrombotic events across all three study groups which was consistent with the extensive evidence supporting the safety of TXA. Taeuber et al. [53], in a comprehensive meta-analysis, found no association between intravenous TXA administration and the risk of thromboembolic events. Similarly, in the pediatric setting, Hovgesen et al. [54] reported no significant

differences in the incidence or type of adverse events between antifibrinolytic and placebo groups across 50 randomized controlled trials of pediatric surgical patients. These findings further support the favorable safety profile of TXA in children.

This is the first study to investigate the potential effect of TXA in pediatric patients with isolated TBI; however, its findings should be interpreted in light of several limitations. First, the relatively small sample size included in the present study may have limited statistical power, particularly for secondary and safety outcomes; larger trials are needed to confirm these findings. Second, randomization was simple and not stratified by covariates that might influence ICH outcomes, and formal allocation concealment was not implemented; future trials should consider stratified or covariate-adaptive randomization together with robust allocation concealment procedures to reduce selection bias. Third, baseline comparisons did not include markers of hyperfibrinolysis, which may be a potential source of confounding, no coagulation or fibrinolytic biomarkers were measured at baseline or during follow-up. Consequently, baseline hyperfibrinolysis could not be compared between groups and remains a potential source of confounding. In addition, attributing the reduced hematoma expansion to inhibition of fibrinolysis is inferred from the established pharmacology of TXA and prior adult data, not directly demonstrated in this cohort; future trials should incorporate baseline and serial coagulation/fibrinolysis biomarkers (e.g., D-dimer, fibrinogen, plasmin–antiplasmin complex, or viscoelastic testing) to confirm this mechanism and identify children most likely to benefit. Fourth, although hematoma expansion is an objective measure of the hemostatic effect of TXA, its correlation with long-term functional outcomes in pediatric TBI remains incompletely established, and the lack of validated pediatric-specific thresholds for clinically meaningful expansion limits interpretation and generalizability of this radiological endpoint; future studies should pair radiological endpoints with standardized long-term functional outcome measures (e.g., Glasgow Outcome Scale-Extended Pediatrics) and work toward establishing pediatric-specific thresholds for clinically meaningful hematoma expansion. Fifth, hematoma volumes were derived using the ABC/2 method, which may overestimate irregularly shaped hematomas. Each scan was assessed by a single observer masked to treatment allocation; because a second independent reader was not used, formal interrater and intrarater reliability of the volumetric measurements could not be assessed. In addition, while allocation masking was maintained throughout, masking to the chronological order of paired scans (baseline vs. 48 h) was not fully feasible, as the sequential nature of serial imaging made timepoint potentially inferable to the reader despite the fixed measurement protocol. To maximize measurement precision and reproducibility, future studies should adopt computer-assisted or planimetric 3D volumetry as the reference standard, incorporate multiple readers with a predefined mechanism for resolving discrepancies (e.g., a blinded third-reader or averaging of measurements), and implement formal temporal masking of serial scans. Sixth, although this trial included both a low-dose and a high-dose TXA arm, it was not designed for trend dose-response analysis between the two active regimens; future dose-ranging pediatric TXA trials should incorporate formal dose-response modeling to better establish the biological plausibility and optimal dosing of TXA in this population. Seventh, this study did not assess resource-utilization outcomes such as coagulation/blood product use, which, alongside length of stay, carry direct economic relevance to TXA's cost-effectiveness; future trials should prospectively capture blood product and coagulation factor utilization as secondary outcomes.

Finally, this single-center trial enrolled only children with isolated moderate and severe TBI, which limits the generalizability of our findings to other patient populations. Polytrauma introduces additional factors, including hemorrhagic shock, massive transfusion, and trauma-induced coagulopathy, that can alter fibrinolytic activity and shift the balance between the hemostatic benefits of TXA and its thrombotic risks. Our results should therefore be considered applicable only to children with isolated TBI and should not be extrapolated to those with polytrauma, who account for a large proportion of pediatric trauma patients receiving TXA in clinical practice. Multicenter trials across diverse injury patterns are needed to confirm and extend these findings.

In conclusion, the early administration of TXA at a low-dose regimen (15 mg/kg loading dose followed by a maintenance infusion of 2 mg/kg/hour) in pediatric patients with isolated TBI significantly reduced hematoma expansion compared with placebo. Administration of a higher-dose regimen (30 mg/kg loading dose followed by a maintenance infusion of 4 mg/kg/hour) did not provide additional benefit. However, further larger trials are warranted to validate these findings.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by the institutional review board at the Faculty of Pharmacy, Mansoura University (code 2023–192). The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin.

Author contributions

NE: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Resources, Validation, Visualization, Writing – original draft, Writing review and editing. NM: Conceptualization, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing –

review and editing. MSo: Conceptualization, Formal Analysis, Methodology, Supervision, Validation, Visualization, Writing – original draft, Writing – review and editing. AD: Conceptualization, Data curation, Investigation, Methodology, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review and editing. MSh: Conceptualization, Investigation, Methodology, Project administration, Supervision, Validation, Visualization, Writing – review and editing. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The author(s) declared that this work was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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The author(s) declared that generative AI was not used in the creation of this manuscript.

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References

1. Theodorou CM, Galganski LA, Jurkovich GJ, Farmer DL, Hirose S, Stephenson JT, et al. Causes of early mortality in pediatric trauma patients. *J Trauma Acute Care Surg* (2021) 90(3):574–81. doi: 10.1097/TA.0000000000003045

2. Roberts I, Shakur-Still H, Aeron-Thomas A, Belli A, Brenner A, Chaudary MA, et al. Effects of tranexamic acid on death, disability, vascular occlusive events and other morbidities in patients with acute traumatic brain injury (CRASH-3): a randomised, placebo-controlled trial. *The Lancet* (2019) 394(10210):1713–23. doi: 10.1016/S0140-6736(19)32233-0

3. Lin YC, Wang TH, Kang YN, Chiu HH. Effect of tranexamic acid on children with traumatic bleeding: a systematic review and meta-analysis. *Am J Emerg Med* (2025) 97: 65–71. doi: 10.1016/J.AJEM.2025.07.008

4. Alsuwais S, Kennedy C, Bressan S, Lyttle M, Body R, Gregorio Milani C, et al. An update on paediatric traumatic brain injury in the emergency department: a narrative review keywords paediatric traumatic brain injury · emergency department · clinical decision rules. *Eur J Pediatr*. 184: 523. doi: 10.1007/s00431-025-06345-9

5. Savioli G, Ceresa IF, Caneva L, Gerosa S, Ricevuti G. Trauma-induced coagulopathy: overview of an emerging medical problem from pathophysiology to outcomes. *Medicines* (2021) 8(4):16. doi: 10.3390/MEDICINES8040016

6. Epstein DS, Mitra B, Cameron PA, Fitzgerald M, Rosenfeld JV. Acute traumatic coagulopathy in the setting of isolated traumatic brain injury: definition, incidence and outcomes. *Br J Neurosurg* (2015) 29(1):118–22. doi: 10.3109/02688697.2014.950632

7. Prudovsky I, Kacer D, Zucco VV, Palmeri M, Falank C, Kramer R, et al. Tranexamic acid: beyond antifibrinolysis. *Transfusion (Paris).* (2022) 62(S1):S301–12. doi: 10.1111/TRF.16976

8. Roberts I, Prieto-Merino D, Manno D. Mechanism of action of tranexamic acid in bleeding trauma patients: an exploratory analysis of data from the CRASH-2 trial. *Crit Care* (2014) 18(6):685. doi: 10.1186/S13054-014-0685-8

9. Guerriero C, Cairns J, Perel P, Shakur H, Roberts I. Cost-effectiveness analysis of administering tranexamic acid to bleeding trauma patients using evidence from the CRASH-2 trial. *PLoS One* (2011) 6(5):e18987. doi: 10.1371/JOURNAL.PONE.0018987

10. Perel P, Salman RAS, Constain A, Dewan Y, Herrera J, Kawahara T, et al. Effect of tranexamic acid in traumatic brain injury: a nested randomised, placebo controlled trial (CRASH-2 intracranial bleeding study). *BMJ* (2011) 343(7816): d3795. doi: 10.1136/bmj.d3795

11. Jokar A, Ahmadi K, Salehi T, Sharif-Alhoseini M, Rahimi-Movaghar V. The effect of tranexamic acid in traumatic brain injury: a randomized controlled trial. *Chin J Traumatol* (2017) 20(1):49–51. doi: 10.1016/J.CJTEE.2016.02.005

12. Nakae R, Murai Y, Wada T, Fujiki Y, Kanaya T, Takayama Y, et al. Hyperfibrinolysis and fibrinolysis shutdown in patients with traumatic brain injury. *Scientific Rep* (2022) 12(1):19107. doi: 10.1038/s41598-022-23912-4

13. Shimizu K, Toda Y, Iwasaki T, Takeuchi M, Morimatsu H, Egi M, et al. Effect of tranexamic acid on blood loss in pediatric cardiac surgery: a randomized trial. *J Anesth* (2011) 25(6):823–30. doi: 10.1007/s00540-011-1235-z

14. Reyes D, González J, Matta C, Arrieta A, Figueroa G, Tejada A, et al. Current guidelines and considerations on the use of tranexamic acid (TXA) in pediatric and obstetric trauma: a review. *Med Res Arch* (2025) 13(7). doi: 10.18103/MRA.V13I7.6636

15. Nishijima DK, VanBuren JM, Linakis SW, Hewes HA, Myers SR, Tran NK, et al. Traumatic injury clinical trial evaluating tranexamic acid in children (TIC-TOC): a pilot randomized trial. *Acad Emerg Med* (2022) 29(7):862–73. doi: 10.1111/ACEM.14481

16. Utsumi S, Ohki S, Amagasa S, Ohshimo S, Shime N. Tranexamic acid in pediatric traumatic brain injury: a multicenter retrospective observational study. *Ann Emerg Med* (2024) 85:101–8. doi: 10.1016/J.ANNEMERGMED.2024.07.014

17. Royal College of Paediatrics and Child Health. *Major Trauma and the Use of Tranexamic Acid in Children: Evidence Statement*. London (2012). Available online at: https://tccc.org.ua/files/uploads/tccc-cpg19/txa-evidence-statement-final-v-2.pdf (Accessed May 7, 2026).

18. Linakis SW, Kuppermann N, Stanley RM, Hewes H, Myers S, VanBuren JM, et al. Enrollment with and without exception from informed consent in a pilot trial of tranexamic acid in children with hemorrhagic injuries. *Acad Emerg Med* (2021) 28(12): 1421–9. doi: 10.1111/ACEM.14343

19. *Recommendations for Research | Head Injury: Assessment and Early Management | Guidance*. London, United Kingdom: National Institute for Health and Care Excellence (NICE) (2026). Available online at: https://www.nice.org.uk/guidance/ng232/chapter/recommendations-for-research#tranexamic-acid-2 (Accessed August 17, 2026).

20. Kothari RU, Brott T, Broderick JP, Barsan WG, Sauerbeck LR, Zuccarello M, et al. The ABCs of measuring intracerebral hemorrhage volumes. *Stroke* (1996) 27(8):1304–5. doi: 10.1161/01.STR.27.8.1304

21. Brott T, Broderick J, Kothari R, Barsan W, Tomsick T, Sauerbeck L, et al. Early hemorrhage growth in patients with intracerebral hemorrhage. *Stroke* (1997) 28(1):1–5. doi: 10.1161/01.STR.28.1.1

22. He GN, Guo HZ, Han X, Wang EF, Zhang YQ. Comparison of CT Black hole sign and other CT features in predicting hematoma expansion in patients with ICH. *J Neurol* (2018) 265(8):1883–90. doi: 10.1007/S00415-018-8932-6

23. Elsawaf Y, Anetsberger S, Luzzi S, Elbabaa SK. Early decompressive craniectomy as management for severe traumatic brain injury in the pediatric population: a comprehensive literature review. *World Neurosurg* (2020) 138:9–18. doi: 10.1016/j.wneu.2020.02.065

24. Form Structure. Pediatric Glasgow outcome scale - Extended (GOS-E peds): FITBIR: federal interagency traumatic brain injury research informatics system (2026). Available online at: https://fitbir.nih.gov/dictionary/publicData/dataStructureAction!view.action?dataStructureName=GOSE_Peds&publicArea=true&style.key=fitbir-style (Accessed August 16, 2026).

25. Evans E, Cook NE, Iverson GL, Townsend EL, Duhaime AC, Adeoye O, et al. Monitoring outcome after hospital-presenting milder spectrum pediatric traumatic brain injury using the Glasgow outcome scale-extended, pediatric revision. *J Neurotrauma* (2020) 37:1627–36. doi: 10.1089/neu.2019.6893

26. Varni JW, Seid M, Knight TS, Uzark K, Szer IS. The PedsQL 4.0 generic core scales: sensitivity, responsiveness, and impact on clinical decision-making. *J Behav Med* (2002) 25(2):175–93. doi: 10.1023/A:1014836921812

27. Varni JW, Seid M, Kurtin PS. PedsQL 4.0: reliability and validity of the pediatric quality of life inventory version 4.0 generic core scales in healthy and patient populations. *Med Care* (2001) 39(8):800–12. doi: 10.1097/00005650-200108000-00006

28. Spinella PC, Bochicchio K, Thomas KA, Staudt A, Shea SM, Pusateri AE, et al. The risk of thromboembolic events with early intravenous 2- and 4-g bolus dosing of tranexamic acid compared to placebo in patients with severe traumatic bleeding: a secondary analysis of a randomized, double-blind, placebo-controlled, single-center trial. *Transfusion (Paris).* (2022) 62 (S1):S139–50. doi: 10.1111/TRF.16962

29. Kleinman JT, Hillis AE, Jordan LC. ABC/2: estimating intracerebral haemorrhage volume and total brain volume, and predicting outcome in children. *Dev Med Child Neurol* (2011) 53(3):281–4. doi: 10.1111/J.1469-8749.2010.03798.X

30. Zhang M, Liu T. Efficacy and safety of tranexamic acid in acute traumatic brain injury: a meta-analysis of randomized controlled trials. *Am J Emerg Med* (2024) 80: 35–43. doi: 10.1016/J.AJEM.2024.03.005

31. Fletcher-Sandersjöö A, Tatter C, Tjerkaski J, Bartek J, Maegele M, Nelson DW, et al. Time course and clinical significance of hematoma expansion in moderate-to-severe traumatic brain injury: an observational cohort study. *Neurocrit Care* (2023) 38(1): 60–70. doi: 10.1007/S12028-022-01609-W

32. Picetti R, Shakur-Still H, Medcalf RL, Standing JF, Roberts I. What concentration of tranexamic acid is needed to inhibit fibrinolysis? A systematic review of pharmacodynamics studies. *Blood Coagul Fibrinolysis* (2019) 30(1):1–10. doi: 10.1097/MBC.0000000000000789

33. Ducloy-Bouthors AS, Gilliot S, Kyheng M, Faraoni D, Turbelin A, Keita-Meyer H, et al. Tranexamic acid dose–response relationship for antifibrinolysis in postpartum haemorrhage during caesarean delivery: TRACES, a double-blind, placebo-controlled, multicentre, dose-ranging biomarker study. *Br J Anaesth* (2022) 129(6):937–45. doi: 10.1016/j.bja.2022.08.033

34. Li Z, You M, Long C, Bi R, Xu H, He Q, et al. Hematoma expansion in intracerebral hemorrhage: an update on prediction and treatment. *Front Neurol* (2020) 11:702. doi: 10.3389/FNEUR.2020.00702

35. Mayer SA, Frontera JA, Jankowitz B, Kellner CP, Kuppermann N, Naik BI, et al. Recommended primary outcomes for clinical trials evaluating hemostatic agents in patients with intracranial hemorrhage: a consensus statement. *JAMA Netw Open* (2021) 4(9):e2123629. doi: 10.1001/JAMANETWORKOPEN.2021.23629

36. Morotti A, Boulouis G, Dowlatshahi D, Li Q, Shamy M, Salman RAS, et al. Intracerebral haemorrhage expansion: definitions, predictors, and prevention. *Lancet Neurol* (2023) 22(2):159–71. doi: 10.1016/S1474-4422(22)00338-6

37. Boulouis G, Hak JF, Kerleroux B, Benichi S, Stricker S, Gariel F, et al. Hemorrhage expansion after pediatric intracerebral hemorrhage. *Stroke* (2021) 52(2):588–94. doi: 10.1161/STROKEAHA.120.030592

38. Bögli SY, Olakorede I, Smith CA, Czosnyka M, Hutchinson P, Agrawal S, et al. The value of dynamic cerebral compliance monitoring after pediatric traumatic brain injury: a STARSHIP study sub-analysis. *Crit Care* (2025) 29(1):219. doi: 10.1186/S13054-025-05403-W

39. Kornelsen E, Kuppermann N, Nishijima DK, Ren LY, Rumantir M, Gill PJ, et al. Effectiveness and safety of tranexamic acid in pediatric trauma: a systematic review and meta-analysis. *Am J Emerg Med* (2022) 55:103–10. doi: 10.1016/j.ajem.2022.01.069

40. Weng S, Wang W, Wei Q, Lan H, Su J, Xu Y. Effect of tranexamic acid in patients with traumatic brain injury: a systematic review and meta-analysis. *World Neurosurg* (2019) 123:128–35. doi: 10.1016/j.wneu.2018.11.214

41. Hollingworth M, Woodhouse LJ, Law ZK, Ali A, Krishnan K, Dineen RA, et al. The effect of tranexamic acid on neurosurgical intervention in spontaneous intracerebral hematoma: data from 121 surgically treated participants from the tranexamic acid in IntraCerebral Hemorrhage-2 randomized controlled trial. *Neurosurgery* (2024) 95(3): 605–16. doi: 10.1227/NEU.0000000000002961

42. Rowell SE, Rowell SE, Meier EN, McKnight B, Kannas D, May S, et al. Effect of out-of-hospital tranexamic acid vs placebo on 6-month functi onal neurologic outcomes in patients with moderate or severe traumatic brain injury. *JAMA* (2020) 324:961–74. doi: 10.1001/JAMA.2020.8958

43. Olsen M, Vik A, Lien E, Schirmer-Mikalsen K, Fredriksli O, Follestad T, et al. A population-based study of global outcome after moderate to severe traumatic brain injury in children and adolescents. *J Neurosurg Pediatr* (2022) 29(4):397–406. doi: 10.3171/2021.11.PEDS21285

44. Lawati KA, Sharif S, Maqbali SA, Al RH, Petrosoniak A, Belley-Cote EP, et al. Efficacy and safety of tranexamic acid in acute traumatic brain injury: a systematic review and meta-analysis of randomized-controlled trials. *Intensive Care Med* (2021) 47(1):14–27. doi: 10.1007/S00134-020-06279-W

45. Nakae R, Fujiki Y, Takayama Y, Kanaya T, Igarashi Y, Suzuki G, et al. Time course of coagulation and fibrinolytic parameters in pediatric traumatic brain injury. *J Neurosurg Pediatr* (2021) 28(5):526–32. doi: 10.3171/2021.5.PEDS21125

46. Goldenberg NA, Jenkins S, Jack J, Armstrong-Wells J, Fenton LZ, Stence NV, et al. Arteriopathy, D-Dimer, and risk of poor neurologic outcome in childhood-onset arterial ischemic stroke. *J Pediatr* (2013) 162(5):1041–6.e1. doi: 10.1016/j.jpeds.2012.11.035

47. Johnston MV, Ishida A, Ishida WN, Matsushita HB, Nishimura A, Tsuji M. Plasticity and injury in the developing brain. *Brain Dev* (2008) 31(1):1–10. doi: 10.1016/J.BRAINDEV.2008.03.014

48. Diaz-Arrastia R, Czeiter E, Hinson HE, Janez Brett Clarke G, Xie K, Liang J. Early hematoma expansion provides incremental prognostic information beyond admission characteristics for 6-month functional outcome after adult traumatic brain injury. *Front Neurol* (2026) 17:1942791. doi: 10.3389/FNEUR.2026.1942791

49. Sigmon J, Crowley KL, Groth CM. Therapeutic review: the role of tranexamic acid in management of traumatic brain injury, nontraumatic intracranial hemorrhage, and aneurysmal subarachnoid hemorrhage. *Am J Health-System Pharm* (2023) 80(18): 1213–22. doi: 10.1093/AJHP/ZXAD134

50. Culkin MC, Bele P, Georges AP, Lopez AJ, Niziolek G, Jacovides CL, et al. Early posttraumatic brain injury tranexamic acid prevents blood-brain barrier hyperpermeability and improves surrogates of neuroclinical recovery. *J Trauma Acute Care Surg* (2023) 95(1):47–54. doi: 10.1097/TA.0000000000003971

51. Barton CA, Oetken HJ, Hall NL, Webb AJ, Hoops HE, Schreiber M. Incidence of traumatic intracranial hemorrhage expansion after stable repeat head imaging: a retrospective cohort study. *Am J Surg* (2022) 224(2):775–9. doi: 10.1016/j.amjsurg.2022.01.028

52. I F Salluh J, Amado F, Pisani L, Quintairos A, Nassar AP, Besen B, et al. Critical care research in low- and middle-income countries: a narrative review. *Thorax* (2025) 81: 1022–32. doi: 10.1136/THORAX-2024-221988

53. Taeuber I, Weibel S, Herrmann E, Neef V, Schlesinger T, Kranke P, et al. Association of intravenous tranexamic acid with thromboembolic events and mortality: a systematic review, meta-analysis, and meta-regression. *JAMA Surg* (2021) 156(6):e210884. doi: 10.1001/JAMASURG.2021.0884

54. Hovgesen NT, Larsen JB, Fenger-Eriksen C, Hansen AK, Hvas AM. Efficacy and safety of antifibrinolytic drugs in pediatric surgery: a systematic review. *Semin Thromb Hemost* (2021) 47(5):538–68. doi: 10.1055/S-0040-1721736