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Perioperative Intravenous Tranexamic Acid in Lower Limb Orthopaedic Trauma Surgery: Blood Loss, Transfusion Requirement, and Early Functional Recovery - A Prospective, Randomised, Assessor-Blinded Controlled Trial

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ABSTRACT

Background: Operative fixation of lower limb fractures carries substantial perioperative blood loss and frequent allogeneic transfusion, with immunological, infective, and economic costs. Tranexamic acid (TXA), a lysine analogue that competitively inhibits plasminogen activation, is established in elective arthroplasty, but randomised data in acute lower limb trauma surgery remain limited, particularly in South Asian populations.
Objective: To compare a two-dose weight-based intravenous TXA regimen with normal saline for perioperative blood loss, transfusion requirement, and early functional recovery after operative fixation of lower limb fractures.
Methods: A prospective, randomised, parallel-group, assessor-blinded controlled trial was conducted at a tertiary care teaching hospital in Lucknow, India, between January 2022 and December 2023. One hundred and twenty adults undergoing fixation of intertrochanteric, femoral shaft, or tibial shaft fractures were randomised 1:1 by computer-generated block sequence with sealed opaque envelope concealment. The TXA group received 15 mg/kg intravenously 10 minutes pre-incision and an identical dose at wound closure; controls received matched volumes of normal saline. Primary outcomes were intraoperative blood loss, 48-hour drain output, fall in haemoglobin, and transfusion rate.
Results: Baseline characteristics were comparable. Intraoperative blood loss was 312.4 ± 78.2 mL with TXA versus 487.6 ± 93.8 mL with saline (mean difference 175.2 mL; 95% CI 139.6–211.8; $p < 0.001$). The 48-hour fall in haemoglobin was 1.82 ± 0.61 versus 3.14 ± 0.83 g/dL ($p < 0.001$). Transfusion was required by 15.0% versus 38.3% ($p = 0.006$; OR 0.29; 95% CI 0.12–0.72). Harris Hip Score at 24 weeks was 89.4 ± 6.1 versus 83.7 ± 7.2 ($p < 0.001$), a difference below conventional thresholds for

clinical importance. Symptomatic deep vein thrombosis occurred in 1.7% versus 3.3% (p = 0.56); surveillance was clinically triggered rather than systematic.

Conclusion: A two-dose intravenous TXA regimen reduced blood loss and approximately halved allogeneic transfusion requirement in lower limb trauma surgery, without a detected excess of symptomatic thromboembolic events. Functional scores favoured TXA, but the magnitude of that difference was small and its relationship to blood conservation remains associative. Adequately powered multicentre trials with systematic thromboembolic screening are required before routine protocol adoption.

Keywords: Tranexamic acid, perioperative blood loss, orthopaedic trauma, blood transfusion, intertrochanteric fracture, functional outcome

INTRODUCTION

Lower limb fractures - including intertrochanteric femoral fractures, femoral shaft fractures, and tibial shaft fractures - represent a substantial and growing component of the global musculoskeletal trauma burden. Road traffic injuries and low-energy falls in the elderly collectively contribute to millions of fracture-related hospitalisations annually, with operative management being the standard of care for the majority of these injuries [1]. A near-universal consequence of this surgery is perioperative blood loss, which may range from moderate to clinically significant, depending on fracture type, operative approach, duration of surgery, and patient comorbidity. Resultant anaemia frequently necessitates allogeneic blood transfusion, which carries well-documented risks including febrile non-haemolytic transfusion reactions, alloimmunisation, transfusion-related acute lung injury, and infectious disease transmission, in addition to imposing a considerable economic burden on healthcare systems [2,3].

Tranexamic acid (TXA) is a synthetic analogue of the amino acid lysine, first described by Okamoto and Okamoto in 1962 [4]. Its primary mechanism of action is competitive reversible inhibition of the lysine-binding sites on plasminogen and plasmin, thereby preventing plasminogen activation and fibrin clot degradation [4,5,6]. This antifibrinolytic mechanism is particularly relevant in orthopaedic trauma, where surgical dissection, fracture haematoma, and tourniquet-mediated reperfusion collectively activate the fibrinolytic cascade, accelerating clot dissolution and perpetuating haemorrhage. TXA is approximately eight times more potent than epsilon-aminocaproic acid on a molar basis, with a plasma half-life of approximately two hours, permitting effective perioperative dosing strategies [5,6]. The haemostatic efficacy of TXA has been extensively characterised in the elective arthroplasty literature. Systematic reviews and meta-analyses by Sukeik et al. (hip arthroplasty), Alshryda et al. (knee arthroplasty), and Ker et al. (all surgical bleeding) have consistently demonstrated significant reductions in operative blood loss and transfusion rates [3,7,8]. Large randomised controlled trials, including those by Soni et al. and Whiting et al., confirmed the reproducibility of these benefits across diverse patient populations, including those with significant comorbidities [9,10]. The landmark CRASH-2 trial further established TXA's safety and efficacy in reducing all-cause mortality from haemorrhage in 20,211 trauma patients [11]. Contemporary evidence from combined intravenous and topical protocols has demonstrated additive benefit with an acceptable safety profile [12,13,14].

Despite this robust arthroplasty evidence base, the application of TXA to acute lower limb orthopaedic trauma surgery - wherein operative urgency, variable injury severity, and a physiologically more vulnerable population create a clinically distinct milieu - has not been as thoroughly prospectively characterised. Published data from South

Asian centres, where baseline nutritional anaemia is prevalent and allogeneic blood resources are frequently limited, are particularly sparse. Furthermore, the functional consequences of superior perioperative haemostasis - specifically, whether reduced blood loss and avoided transfusion translates into measurably improved early rehabilitation outcomes - have rarely been assessed in this population using validated functional scoring instruments.

The present trial was designed to compare the efficacy of a two-dose intravenous TXA protocol against normal saline in reducing perioperative blood loss, transfusion requirements, and improving early functional recovery in adult patients undergoing operative fixation for lower limb fractures at a tertiary care government teaching hospital in Lucknow, India.

MATERIALS & METHODS

Study Design and Setting

This was a prospective, randomised, parallel-group, assessor-blinded controlled trial conducted in the Department of Orthopaedic Surgery, Balrampur Hospital, Golaganj, Lucknow, Uttar Pradesh - a government tertiary care and teaching hospital. Recruitment ran over 24 consecutive months, from January 2022 to December 2023. Approval was obtained from the Institutional Ethics Committee of Balrampur Hospital. Written informed consent was obtained from every participant before enrolment, and the trial was conducted in accordance with the Declaration of Helsinki (2013 revision). The manuscript is reported in accordance with the CONSORT 2010 statement.

Eligibility Criteria

Inclusion Criteria

- Adults aged 18–75 years presenting with a closed fracture of the intertrochanteric region, femoral shaft, or tibial shaft
- Planned operative fixation by intramedullary nailing or dynamic hip screw fixation
- American Society of Anesthesiologists (ASA) physical status classification grade I, II, or III
- Preoperative haemoglobin ≥ 9.0 g/dL
- Willingness to provide written informed consent and comply with follow-up schedule

Exclusion Criteria

- Known hypersensitivity or previous adverse reaction to tranexamic acid
- Documented prior thromboembolic event (deep vein thrombosis, pulmonary embolism, ischaemic stroke, or myocardial infarction)
- Active coronary artery disease or intravascular stent placement within the preceding six months
- Pre-existing coagulopathy, bleeding diathesis, or therapeutic anticoagulant use (excluding prophylactic low molecular weight heparin)
- Renal impairment (serum creatinine > 1.5 mg/dL) or significant hepatic dysfunction
- Pregnancy or lactation
- Open fractures (Gustilo-Anderson classification Type I–III), periprosthetic fractures, or polytrauma patients requiring damage control orthopaedics (DCO)
- Preoperative haemoglobin < 9.0 g/dL or requirement for blood transfusion prior to surgery
- Refusal to consent or inability to comply with follow-up

Sample Size Calculation

Sample size was estimated using the formula for the comparison of two independent means:

$$n = 2(Z_{\alpha/2} + Z_{\beta})^2 \times \sigma^2 / d^2$$

The calculation was anchored on intraoperative blood loss, the principal haemostatic endpoint. Control-group intraoperative blood loss was assumed to be 480 mL with a standard deviation of 100 mL, and a between-group difference of 65 mL was pre-specified as the smallest reduction

considered clinically worthwhile. With a two-sided α of 0.05 ($Z_{\alpha/2}$ = 1.96) and 90% power (Z_{β} = 1.282):

$$n = 2(1.96 + 1.282)^2 \times (100)^2 / (65)^2 = 2 \times 10.509 \times 10000 / 4225 \approx 50 \text{ per group}$$

This yielded 50 participants per group. Allowing for approximately 15% attrition, enrolment was inflated to 60 per group, giving a total of 120 participants. The trial was powered for the primary haemostatic endpoint only; secondary functional and safety endpoints were not independently powered.

Randomisation and Allocation Concealment

Participants were allocated 1:1 using a computer-generated block randomisation sequence with a fixed block size of four, prepared by a biostatistician with no clinical involvement in the trial. Allocation was concealed in sequentially numbered, sealed, opaque envelopes held by the theatre pharmacy and opened only at the point of intraoperative drug preparation. Eligible participants were enrolled by the admitting orthopaedic registrar, who took no part in sequence generation or envelope preparation. Participants, operating surgeons, ward staff, physiotherapists, and the independent assessors who recorded functional scores were all blinded to allocation. The anaesthesiologist who prepared and administered the study solution was necessarily unblinded; no other member of the clinical or assessment team had access to allocation status until the database was locked.

Intervention: TXA Dosage Protocol

Patients in the TXA group received intravenous tranexamic acid at a dose of 15 mg/kg (maximum single dose: 1 g) dissolved in 100 mL of 0.9% normal saline, administered as a slow intravenous infusion over 15 minutes, commencing 10 minutes prior to surgical skin incision. A second identical dose was administered intravenously at the time of wound closure. Patients in the control group received identical volumes of 0.9% normal saline at corresponding time points. Both formulations were prepared by the anaesthesiologist in identical syringes to maintain blinding of the outcome assessors.

All patients received standard pharmacological thromboprophylaxis: subcutaneous low molecular weight heparin (Enoxaparin 40 mg once daily) was initiated 12 hours postoperatively and continued until hospital discharge or clinical decision to terminate, in accordance with the institutional thromboprophylaxis protocol. Mechanical prophylaxis (graduated compression stockings) was applied to all patients from the time of admission.

Surgical Procedures

The following operative procedures were performed: closed or open reduction with cephalomedullary intramedullary nailing (Proximal Femoral Nail Anti-rotation, PFNA) for intertrochanteric fractures; antegrade intramedullary nailing for femoral shaft fractures; and closed intramedullary interlocking nailing for tibial shaft fractures. All surgeries were performed under fluoroscopic guidance by consultant orthopaedic surgeons with a minimum of five years of post-fellowship experience. Spinal anaesthesia was employed as the primary anaesthetic modality in all cases. Intraoperative cell salvage was not utilised in any participant.

Outcome Measures

Primary Outcomes

- Intraoperative blood loss: estimated by gravimetric swab weighing and calibrated suction canister measurement

- Postoperative drain output: cumulative volume recorded at 48 hours following surgery
- Fall in haemoglobin: difference between preoperative and 48-hour postoperative haemoglobin (g/dL)
- Allogeneic blood transfusion rate: proportion of patients receiving packed red blood cell transfusion (trigger threshold: Hb < 8.0 g/dL or symptomatic anaemia despite Hb > 8.0 g/dL)

Secondary Outcomes

- Harris Hip Score (HHS) for intertrochanteric and femoral shaft fracture patients at 6, 12, and 24 weeks postoperatively
- Lysholm Knee Score for tibial shaft fracture patients at 6, 12, and 24 weeks postoperatively
- Time to achievement of full weight bearing (days)
- Return to pre-injury functional activity level at 24 weeks
- Length of hospital stay (days)
- Postoperative complications: deep vein thrombosis, wound infection, acute kidney injury, and pulmonary embolism. Thromboembolic surveillance was clinically triggered rather than systematic — colour Doppler ultrasonography of the lower limbs was performed only in participants who developed symptoms or signs suggestive of deep vein thrombosis at any point up to the 24-week review. Routine screening ultrasonography was not performed in asymptomatic participants.

The Harris Hip Score was selected for intertrochanteric and femoral shaft fractures and the Lysholm Knee Score for tibial shaft fractures on the basis of the anatomical region whose function is most affected by each injury and by the corresponding rehabilitation demands. Both are validated, widely reported instruments that permit comparison with the existing arthroplasty and trauma literature; their limitations in this population are addressed below.

Statistical Analysis

Analyses were performed in IBM SPSS Statistics version 26.0 (IBM Corp., Armonk, NY, USA) on the full randomised cohort; no participant was lost to follow-up and no data were missing, so complete-case and intention-to-treat analyses were identical and no imputation was required. Distributional assumptions for continuous variables were examined with the Shapiro-Wilk test and by inspection of histograms and Q-Q plots; all continuous variables met the assumption of normality and were summarised as mean ± standard deviation and compared with the independent samples t-test, with the Mann-Whitney U test held in reserve had the assumption failed. Homogeneity of variance was assessed by Levene's test. Categorical variables were summarised as counts and percentages and compared with the Pearson chi-square test, or Fisher's exact test where any expected cell count fell below five. Between-group differences in continuous outcomes are reported as mean differences with 95% confidence intervals, and dichotomous outcomes as odds ratios with 95% confidence intervals. A two-sided p-value below 0.05 was taken as significant. No adjustment was made for multiplicity; all secondary and subgroup analyses are therefore exploratory and their p-values should be interpreted accordingly.

RESULT

Patient Flow and Baseline Characteristics

A total of 148 patients with lower limb fractures were assessed for eligibility during the study period. Of these, 28 were excluded: 14 met pre-defined exclusion criteria (thromboembolic history in 5, renal impairment in 5, open fractures in 4), 9 declined participation, and 5 were excluded due to incomplete preoperative investigation data. The final study cohort comprised 120 patients (60 per group), with complete follow-up achieved in all participants through 24 weeks. No participant withdrew from the study after enrolment. The CONSORT flow diagram describes the

progression of participants through the randomized controlled trial from eligibility assessment to final analysis (Figure 1).

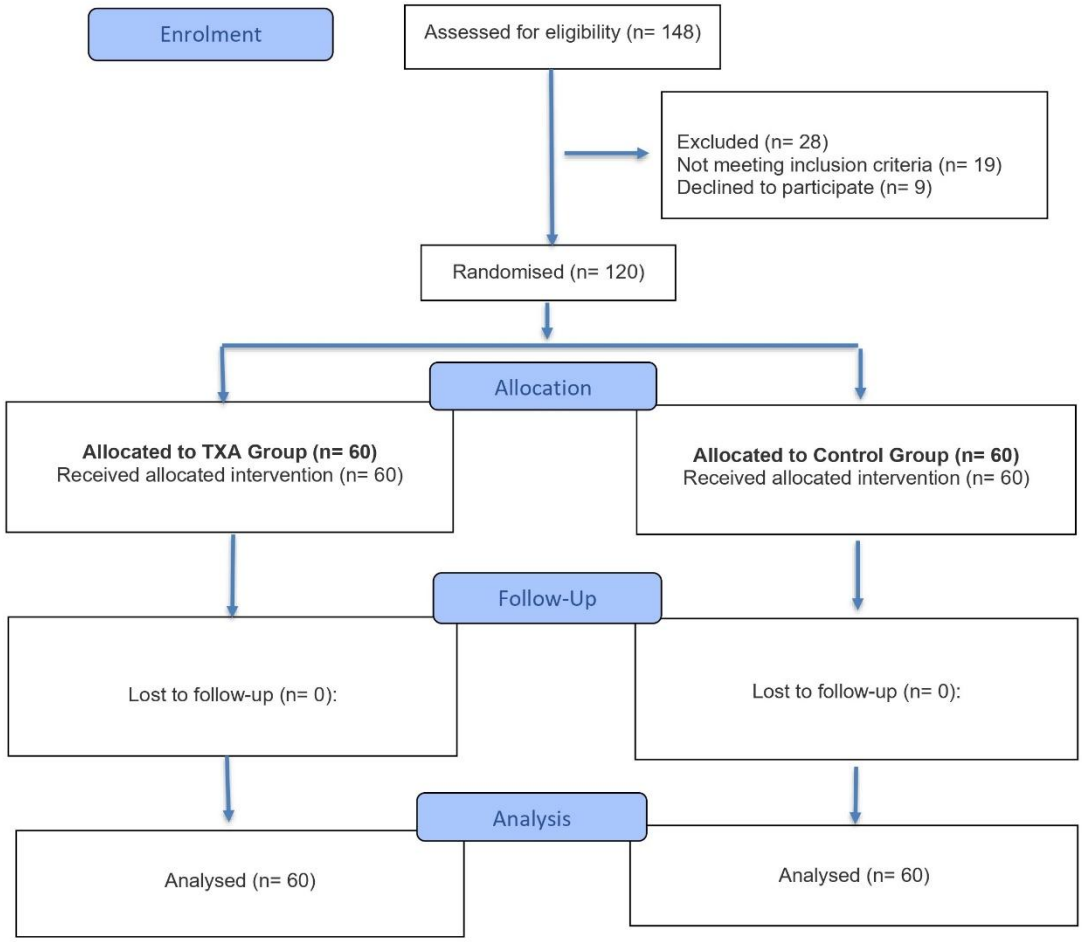

Figure 1: CONSORT flow diagram.

Baseline demographic and clinical parameters were comparable between the two groups, with no statistically significant differences across any variable examined (Table 1). The mean age of the overall cohort was 52.8 ± 12.1 years, with a male predominance (74 of 120; 61.7%). Intertrochanteric fractures were the most frequent fracture pattern (40%), followed by femoral shaft (35%) and tibial shaft (25%) fractures. Preoperative haemoglobin, platelet count, and coagulation parameters were within normal limits and comparable between groups. The mean time from injury to operative intervention was 18.4 ± 6.2 hours in the TXA group and 19.1 ± 5.8 hours in the control group (p = 0.54).

Table 1. Baseline Demographic and Clinical Characteristics (n = 120)

Variable	TXA Group (n = 60)	Control Group (n = 60)	p-value	Significance
Age (years), mean ± SD	52.4 ± 12.3	53.1 ± 11.8	0.76	NS
Sex (Male: Female)	38: 22	36: 24	0.71	NS

Variable	TXA Group (n = 60)	Control Group (n = 60)	p-value	Significance
Body Mass Index (kg/m²), mean ± SD	24.6 ± 3.1	24.9 ± 2.8	0.58	NS
Fracture Type			—	—
Intertrochanteric fracture	24 (40.0%)	24 (40.0%)	—	—
Femoral shaft fracture	21 (35.0%)	21 (35.0%)	—	—
Tibial shaft fracture	15 (25.0%)	15 (25.0%)	—	—
ASA Physical Status Grade I/II	52 (86.7%)	50 (83.3%)	0.62	NS
ASA Physical Status Grade III	8 (13.3%)	10 (16.7%)	0.62	NS
Preoperative Haemoglobin (g/dL)	12.6 ± 1.4	12.8 ± 1.3	0.43	NS
Preoperative Platelets (×10³/µL)	214 ± 38	219 ± 41	0.51	NS
Preoperative PT/INR	1.04 ± 0.08	1.05 ± 0.07	0.48	NS
Time from injury to surgery (hours)	18.4 ± 6.2	19.1 ± 5.8	0.54	NS
Anaesthetic technique (Spinal)	60 (100%)	60 (100%)	—	—
Thromboprophylaxis (LMWH)	60 (100%)	60 (100%)	—	—

ASA = American Society of Anesthesiologists; Hb = Haemoglobin; INR = International Normalised Ratio; LMWH = Low Molecular Weight Heparin; NS = Not Significant; SD = Standard Deviation. p-values derived from independent samples t-test (continuous variables) and Pearson chi-square test (categorical variables). Statistical significance: $p < 0.05$.

Primary Outcomes: Perioperative Blood Loss and Transfusion

Perioperative haemostatic outcomes were significantly superior in the TXA group across all primary endpoints (Table 2). Mean intraoperative blood loss was 312.4 ± 78.2 mL in the TXA group compared to 487.6 ± 93.8 mL in controls — a reduction of 175.2 mL (35.9%; $p < 0.001$; 95% CI: 139.6–211.8 mL). Postoperative drain output at 48 hours was similarly reduced: 147.8 ± 41.6 mL versus 264.3 ± 60.9 mL ($p < 0.001$). Consequently, total perioperative blood loss was 460.2 ± 96.4 mL in the TXA group versus 751.9 ± 112.3 mL in controls ($p < 0.001$).

The fall in haemoglobin from preoperative baseline to 48 hours postoperatively was significantly attenuated in the TXA group (1.82 ± 0.61 g/dL vs 3.14 ± 0.83 g/dL; $p < 0.001$), with a correspondingly higher mean postoperative haemoglobin (10.78 ± 1.22 vs 9.66 ± 1.34 g/dL; $p < 0.001$). Nine patients in the TXA group (15.0%) required allogeneic transfusion compared to 23 patients in the control group (38.3%), yielding a statistically and clinically significant reduction in transfusion rate ($p = 0.006$; OR: 0.29; 95% CI: 0.12–0.72). Mean units of packed red blood cells transfused per patient was 0.21 ± 0.48 in the TXA group versus 0.74 ± 0.93 in controls ($p < 0.001$).

Operative time was similar in the two groups (96.2 ± 18.4 versus 98.7 ± 19.1 minutes; $p = 0.47$). Symptomatic deep vein thrombosis was confirmed on Doppler ultrasonography in one participant (1.7%) in the TXA group and two (3.3%) in the control group ($p = 0.56$; OR 0.49; 95% CI 0.04–5.59); no pulmonary embolism occurred in either group. Wound infection occurred in two TXA and three control participants ($p = 0.65$). No participant developed acute kidney injury. Length of hospital stay was shorter in the TXA group (6.8 ± 1.9 versus 8.4 ± 2.3 days; $p < 0.001$).

Table 2. Perioperative Blood Loss, Transfusion Requirements, and Safety Outcomes

Outcome Measure	TXA Group (n = 60)	Control Group (n = 60)	p-value	95% CI / OR
Intraoperative blood loss (mL)	312.4 ± 78.2	487.6 ± 93.8	< 0.001	139.6 – 211.8
Postoperative drain output at 48 h (mL)	147.8 ± 41.6	264.3 ± 60.9	< 0.001	98.2 – 134.8
Total perioperative blood loss (mL)	460.2 ± 96.4	751.9 ± 112.3	< 0.001	250.3 – 333.1
Fall in Hb at 48 hours (g/dL)	1.82 ± 0.61	3.14 ± 0.83	< 0.001	1.06 – 1.58
Postoperative Hb at 48 hours (g/dL)	10.78 ± 1.22	9.66 ± 1.34	< 0.001	0.68 – 1.56
Blood transfusion rate, n (%)	9 (15.0%)	23 (38.3%)	0.006	OR: 0.29 (0.12–0.72)
Mean units transfused per patient	0.21 ± 0.48	0.74 ± 0.93	< 0.001	0.29 – 0.77
Operative time (minutes)	96.2 ± 18.4	98.7 ± 19.1	0.47	−2.8 – 7.8
DVT events, n (%)	1 (1.7%)	2 (3.3%)	0.56	OR: 0.49 (0.04–5.59)
Wound infection, n (%)	2 (3.3%)	3 (5.0%)	0.65	—
Acute kidney injury, n (%)	0 (0%)	0 (0%)	—	—
Length of hospital stay (days)	6.8 ± 1.9	8.4 ± 2.3	< 0.001	0.86 – 2.34

DVT = Deep Vein Thrombosis; Hb = Haemoglobin; OR = Odds Ratio; CI = Confidence Interval; SD = Standard Deviation. Independent samples t-test used for continuous variables; chi-square or Fisher's exact test used for categorical variables. p < 0.05 considered statistically significant.

Secondary Outcomes: Functional Recovery

Functional scores were higher in the TXA group at every assessment point for both instruments (Table 3). Among participants with intertrochanteric and femoral shaft fractures (n = 45 per group), the Harris Hip Score at 6 weeks was 72.4 ± 8.2 versus 65.8 ± 9.1 (p < 0.001; 95% CI 3.96–9.24), at 12 weeks 83.6 ± 7.4 versus 76.2 ± 8.6 (p < 0.001), and at 24 weeks 89.4 ± 6.1 versus 83.7 ± 7.2 (p < 0.001). An excellent or good Harris Hip Score at 24 weeks was recorded in 38 of 45 TXA participants (84.4%) versus 29 of 45 controls (64.4%; p = 0.03; OR 2.96; 95% CI 1.09–8.02).

Among participants with tibial shaft fractures (n = 15 per group), the Lysholm Knee Score was 68.3 ± 7.1 versus 61.2 ± 8.4 at 6 weeks (p = 0.002), 79.6 ± 6.8 versus 71.4 ± 7.9 at 12 weeks (p = 0.001), and 86.2 ± 5.9 versus 78.8 ± 6.7 at 24 weeks (p = 0.001). A good or excellent Lysholm result at 24 weeks was recorded in 80.0% of the TXA subgroup versus 53.3% of controls; this difference was not statistically significant (p = 0.10) in a subgroup of this size.

Across the whole cohort, mean time to full weight bearing was 82.6 ± 14.2 days with TXA versus 96.4 ± 18.8 days with saline (p < 0.001; 95% CI 7.16–20.44 days). Return to pre-injury activity level at 24 weeks was reported by 42 TXA participants (70.0%) versus 28 controls (46.7%; p = 0.01; OR 2.70; 95% CI 1.26–5.79).

Table 3. Functional Outcome Scores at 6, 12, and 24 Weeks Postoperatively

Functional Outcome Parameter	TXA Group (n = 60)	Control Group (n = 60)	p-value	95% CI / OR
Harris Hip Score (HHS) – Intertrochanteric & Femoral Shaft Fractures (n = 45 per group)				
Week 6, mean ± SD	72.4 ± 8.2	65.8 ± 9.1	< 0.001	3.96 – 9.24
Week 12, mean ± SD	83.6 ± 7.4	76.2 ± 8.6	< 0.001	4.78 – 10.02
Week 24, mean ± SD	89.4 ± 6.1	83.7 ± 7.2	< 0.001	3.32 – 8.08
Excellent/Good result at 24 weeks, n (%)	38 (84.4%)	29 (64.4%)	0.03	OR: 2.96 (1.09–8.02)
Lysholm Knee Score – Tibial Shaft Fractures (n = 15 per group)				
Week 6, mean ± SD	68.3 ± 7.1	61.2 ± 8.4	0.002	3.02 – 11.18
Week 12, mean ± SD	79.6 ± 6.8	71.4 ± 7.9	0.001	3.88 – 12.52
Week 24, mean ± SD	86.2 ± 5.9	78.8 ± 6.7	0.001	3.52 – 11.28
Good/Excellent result at 24 weeks, n (%)	12 (80.0%)	8 (53.3%)	0.10	—
Overall Functional Recovery – All Patients (n = 60 per group)				
Time to full weight bearing (days)	82.6 ± 14.2	96.4 ± 18.8	< 0.001	7.16 – 20.44
Return to pre-injury activity at 24 weeks	42 (70.0%)	28 (46.7%)	0.01	OR: 2.70 (1.26–5.79)

HHS = Harris Hip Score; CI = Confidence Interval; OR = Odds Ratio; SD = Standard Deviation. Harris Hip Score applied to intertrochanteric and femoral shaft fracture patients (n = 45 per group). Lysholm Knee Score applied to tibial shaft fracture patients (n = 15 per group). $p < 0.05$ considered statistically significant.

DISCUSSION

In this randomised, assessor-blinded trial, a two-dose perioperative intravenous TXA regimen reduced intraoperative blood loss, drain output, and the postoperative fall in haemoglobin, and approximately halved the proportion of patients requiring allogeneic transfusion after operative fixation of lower limb fractures. Functional scores and time to full weight bearing also favoured TXA. No excess of symptomatic thromboembolic events was detected, although the trial was neither designed nor powered to address that question. The haemostatic findings are consistent with the established arthroplasty literature and extend it to an acute trauma population.

The mechanism is well characterised. Operative trauma to bone and soft tissue provokes local fibrinolysis, driven principally by tissue plasminogen activator released from injured endothelium and bone marrow. TXA competitively and reversibly occupies the lysine-binding sites of plasminogen and plasmin, preventing their engagement with fibrin and preserving clot integrity at the surgical site [4,6]. The two-dose schedule used here - loading before incision and a repeat dose at closure - was intended to maintain plasma concentrations across the period of peak fibrinolytic activation, which begins intraoperatively and persists into the first postoperative hours [6]. Weight-based dosing was chosen in preference to a fixed dose given the wide range of body mass in this population.

The reduction in intraoperative blood loss is consistent in direction with the meta-analysis by Gausden and colleagues, which pooled 12 studies (1,333 patients) of TXA in orthopaedic trauma surgery and found a significantly lower risk of transfusion in TXA recipients (odds ratio 0.41; 95% CI 0.28–0.59) [15]. Tengberg and colleagues, in a

randomised controlled trial in extracapsular hip fractures, reported comparable proportional reductions in blood loss and transfusion rate [2]. Yuan and colleagues found that combining intravenous with topical administration conferred additive haemostatic benefit in arthroplasty, which may account for the larger effect sizes reported in trials using combined protocols [13].

The fall in allogeneic transfusion, from 38.3% to 15.0%, is the finding of greatest practical consequence. The absolute risk reduction of 23.3% corresponds to a number needed to treat of approximately four patients to avoid one transfusion. In the arthroplasty literature, Sukeik and colleagues and Alshryda and colleagues both reported significant reductions in transfusion requirement [7,8], and the present data indicate that a comparable effect is obtainable in acute trauma surgery, where baseline anaemia is more common and blood supply is often less secure.

Several mechanisms may link blood conservation to the functional differences observed, though none is established by these data. Postoperative anaemia is independently associated with reduced exercise capacity, impaired wound healing, and slower progression through rehabilitation, and avoiding allogeneic transfusion also avoids its immunomodulatory consequences [10]. Earlier full weight bearing in the TXA group may reflect some combination of better haematological status, less wound haematoma, and shorter admission. Xie and colleagues reported higher Harris Hip Scores at three months after combined TXA protocols in total hip arthroplasty [12], and Vijay and colleagues found reduced blood loss and transfusion requirement in hip and femoral surgery [16]. These associations are consistent with the present findings but do not establish that the functional difference is attributable to blood conservation; residual confounding and the unblinded administering clinician cannot be excluded as contributors.

The size of the functional difference deserves comment. The 5.7-point separation in Harris Hip Score and the 7.4-point separation in Lysholm score at 24 weeks were statistically significant, but both fall below the thresholds commonly cited as the minimal clinically important difference for these instruments. Statistical significance here reflects tight variance and complete follow-up rather than a large effect. The functional findings are best read as supportive and hypothesis-generating; the primary justification for tranexamic acid in this setting remains blood conservation and transfusion avoidance, for which the effect size was large and unambiguous.

No excess of symptomatic thromboembolism was observed. This is consistent with the wider evidence base: the meta-analysis by Alshryda and colleagues of randomised trials in total knee replacement found no significant increase in deep vein thrombosis, pulmonary embolism, or other vascular occlusive events [8], Ker and colleagues reached the same conclusion across 129 trials [3], and CRASH-2 showed reduced mortality from haemorrhage without an excess of thrombotic complications [11]. Whiting and colleagues extended that reassurance to arthroplasty patients with severe comorbidity [10]. The present data should nonetheless be read with caution: surveillance was clinically triggered, asymptomatic events were not sought, and three events across 120 participants cannot support any inference about thromboembolic safety.

The Asian population-specific context of this study carries particular relevance. Studies from South and Southeast Asian centres consistently document a higher baseline prevalence of nutritional and iron-deficiency anaemia in orthopaedic trauma patients, lower average body habitus influencing weight-based TXA pharmacokinetics, and a greater proportion presenting with delayed operative intervention due to logistical, systemic, and healthcare access constraints. These factors collectively narrow the margin

between preoperative haemoglobin and the transfusion trigger, amplifying the clinical imperative for pharmacological blood conservation. Sun et al. demonstrated that the haemostatic benefits of TXA were preserved across BMI strata and baseline haemoglobin levels in an Asian arthroplasty cohort, supporting generalisability to the lower-BMI Indian trauma population [14].

An indicative cost comparison is worth setting out, although no formal economic evaluation was undertaken. At an institutional procurement cost of roughly ₹150–200 per 500 mg ampoule, the two-dose regimen for a 60 kg patient (approximately 1.8 g, four ampoules) costs under ₹800. A single unit of cross-matched packed red cells in the Indian public sector costs ₹1,500–₹3,000 before cross-matching, administration, nursing time, and management of transfusion reactions are counted. Johansson and colleagues, in a randomised double-blind trial in hip arthroplasty, reported a saving of approximately 1.3 units per patient and concluded that TXA saves both blood and money [17]. The comparable blood-sparing effect seen here suggests a similar direction of economic benefit, but an incremental cost-effectiveness analysis would be needed to quantify it.

Limitations

Thromboembolic surveillance was clinically triggered. Doppler ultrasonography was performed only where symptoms or signs prompted it, so asymptomatic events were not detected and the observed rates of 1.7% and 3.3% underestimate true incidence. With three events in 120 participants the trial had no power for thromboembolic endpoints, and these data are hypothesis-generating only.

The functional instruments were chosen pragmatically. The Harris Hip Score is validated for hip pathology and the Lysholm Knee Score for knee ligament and meniscal injury; applying them to femoral shaft and tibial shaft fractures respectively extends both beyond their validation populations, and no fracture-specific patient-reported measure was used alongside them.

Secondary and subgroup analyses were not adjusted for multiplicity and are exploratory. The tibial shaft subgroup contained 15 participants per arm and was underpowered for the dichotomised Lysholm endpoint. Recruitment was from a single government tertiary hospital serving a population with a relatively homogeneous socioeconomic and nutritional profile, and external validity to private-sector, district, or high-income settings is untested. The absence of a topical or combined intravenous-plus-topical arm precludes comparison between routes of administration [13,14]. Radiological union, patient-reported outcome measures, and function beyond 24 weeks were not assessed.

Several limitations qualify these findings. Allocation was concealed and assessors were blinded, but the anaesthesiologist preparing and administering the study solution was necessarily aware of allocation, and performance bias cannot be excluded. Blood loss was estimated gravimetrically and from suction canister volume; neither method captures occult haematoma, which is substantial after intertrochanteric and femoral shaft fixation, so total blood loss was probably underestimated in both arms. Haematocrit-based estimation using the Nadler equation [18] was not performed in parallel, and the absolute volumes reported should be read as internally comparable rather than absolute.

CONCLUSION

In this randomised, assessor-blinded trial, a weight-based two-dose intravenous tranexamic acid regimen reduced intraoperative blood loss, postoperative drain output, and the fall in haemoglobin after operative fixation of lower limb fractures, and approximately halved the proportion of patients receiving allogeneic transfusion. Participants receiving tranexamic acid also achieved higher functional scores and earlier full weight bearing, although the magnitude of the functional difference fell below

conventional thresholds for clinical importance and its relationship to blood conservation remains associative. No excess of symptomatic thromboembolic events was detected, but surveillance was clinically triggered and the trial was not powered for safety endpoints. Within these constraints, the findings support intravenous tranexamic acid as an inexpensive and practical adjunct for blood conservation in lower limb trauma surgery, particularly where allogeneic blood supply is constrained. Adequately powered multicentre trials with systematic thromboembolic screening and longer follow-up are needed before routine protocol adoption can be recommended.

Clinical Message

- Two-dose intravenous tranexamic acid (15 mg/kg pre-incision, repeated at wound closure) reduced perioperative blood loss and allogeneic transfusion requirement in lower limb trauma surgery, with approximately four patients treated to prevent one transfusion.
- Functional scores and time to full weight bearing favoured tranexamic acid, but the differences were small and should not on their own justify the intervention.
- No excess of symptomatic thromboembolism was observed; surveillance was clinically triggered, so this does not constitute evidence of thromboembolic safety. Routine low molecular weight heparin prophylaxis should continue alongside tranexamic acid.
- Tranexamic acid is inexpensive and simple to administer, making it a practical adjunct where allogeneic blood supply is limited.

Declaration by Authors

Ethical Approval: Approval for this study was granted by the Institutional Ethics Committee of Balrampur Hospital, Golaganj, Lucknow, Uttar Pradesh, India. All procedures involving human participants conformed to the ethical standards of the institutional research committee and to the Declaration of Helsinki (2013 revision). Written informed consent was obtained from every participant before enrolment; where decision-making capacity was temporarily impaired, consent was obtained from a legally authorised representative in accordance with national guidelines.

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Conflict of Interest: The authors declare that they have no conflict of interest. No pharmaceutical company, medical device manufacturer, or any commercial entity had any role in the study design, data collection, analysis, interpretation of results, or decision to submit for publication.

Authors' Contributions

AY: Study conceptualisation and design, patient enrolment, data collection, statistical analysis, and manuscript preparation. P: Perioperative protocol administration, anaesthetic management, and critical intellectual revision of the manuscript. SK: Patient enrolment, data collection, postoperative follow-up, and functional outcome assessment. All authors have read and approved the final submitted version of the manuscript.

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