INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

EFFECTS OF MEDULLARY CAVITY APPLICATION OF TRANEXAMIC ACID TO REDUCE HEMOSTASIS AND INFLAMMATION MEDIATORS IN CLOSED SHAFT OF TIBIA FRACTURE FIXATION WITH INTRAMEDULLARY INTERLOCKING NAIL

Orthopaedics

Dr. Sudharsanan K	Junior Resident, Department of Orthopaedics, Chettinad Hospital and Research Institute
Dr. Arun Kumar K V*	Professor, Department of Orthopaedics, Chettinad Hospital and Research Institute. *Corresponding Author
Dr. Pradeep E	Professor, Department of Orthopaedics, Chettinad Hospital and Research Institute.
Dr. Chockalingham K	Junior Resident, Department of Orthopaedics, Chettinad Hospital and Research Institute.
Dr. Shivaani Venkatramanan	Junior Resident, Department of Orthopaedics, Chettinad Hospital and Research Institute.

ABSTRACT

Background: Tranexamic Acid (TXA) has been extensively used to reduce perioperative blood loss in orthopaedic procedures. However, the role of medullary-cavity TXA application in reducing both hemostatic loss and inflammatory markers during intramedullary interlocking (IMIL) nailing for tibial fractures remains underexplored. **Objective:** To evaluate the efficacy of medullary cavity TXA application in reducing blood loss, inflammatory markers, and transfusion needs in closed tibial shaft fracture fixation using IMIL nails. **Methods:** A randomized controlled trial was conducted at the Department of Orthopaedics, Chettinad Hospital and Research Institute. Thirty adult patients with closed tibial shaft fractures were randomized into two groups: TXA group (2 g TXA administered into the medullary canal prior to reaming) and control group (normal saline). Hemoglobin, hematocrit, total and hidden blood loss, and serum inflammatory markers (IL-6, CRP, D-dimer) were assessed preoperatively and on postoperative days 1, 3, and 5. Transfusion requirements and complications were also recorded. **Results:** The TXA group showed significantly lower total blood loss (485.6 ± 152.3 mL vs. 882.4 ± 231.7 mL, $p < 0.001$) and hidden blood loss (342.8 ± 128.5 mL vs. 715.2 ± 210.9 mL, $p < 0.001$). IL-6 and CRP levels were significantly lower in the TXA group from Day 3 onward. D-dimer levels were consistently lower postoperatively in the TXA group. No increase in thromboembolic events was observed. **Conclusion:** Medullary-cavity TXA administration significantly reduces hidden blood loss and inflammatory response following IMIL nailing in closed tibial fractures, without increasing thromboembolic risk.

KEYWORDS

INTRODUCTION

Fractures of the tibial shaft remain among the most common long-bone injuries treated by orthopaedic trauma surgeons. The use of an intramedullary interlocking nail provides stable internal fixation while allowing early weight-bearing and fewer soft-tissue complications compared with plating in appropriate cases. However, despite improvements in surgical technique and fixation devices, patients undergoing intramedullary nailing frequently experience significant perioperative bleeding, visible and hidden blood loss, and an associated inflammatory response that may contribute to postoperative morbidity.]

Hidden blood loss is defined as the difference between total blood loss (as estimated by hematologic parameters) and observed intraoperative/ drain output has been shown to be substantial in patients undergoing intramedullary nailing for tibial fractures. For example, one study reported substantial hidden blood loss in tibial extra-articular fracture fixation by intramedullary devices. [1] Addressing this bleeding is important not only to reduce transfusion requirement but also to potentially moderate the subsequent inflammatory cascade triggered by hematoma formation, fibrinolysis and soft-tissue microvascular bleeding.

Tranexamic acid (TXA) is a synthetic lysine analog antifibrinolytic agent which blocks plasminogen activation and thereby stabilises fibrin clots and reduces fibrinolysis. Its use in orthopaedic surgery particularly joint arthroplasty has been well documented to reduce blood loss and transfusion rates without clear increase in thromboembolic complications. [2] In the context of fracture surgery, intravenous TXA has been reported to reduce bleeding in tibial diaphyseal fractures treated with intramedullary nailing, and was found safe in a small randomized study. [3] Although systemic and topical TXA applications have been explored, the direct injection of TXA into the medullary cavity (prior to nail insertion) of the fractured tibia represents a novel strategy to target local bleeding and fibrinolysis at the fracture site and intramedullary canal. A recent randomized controlled trial in tibial intramedullary nailing demonstrated that injection of 2 g TXA into the medullary cavity significantly reduced

total blood loss and hidden blood loss compared with saline, with no increase in deep vein thrombosis. [4] However, while the hemostatic benefit has been documented, there remains limited data on the effect of this strategy on local and systemic inflammatory mediators (such as C-reactive protein, interleukin-6) and on hemostasis-inflammation interplay in the fracture healing environment.

The rationale for the current study is therefore threefold. First, reducing bleeding within the medullary canal and fracture site may limit hematoma expansion, reduce the subsequent fibrinolytic and inflammatory cascade, and thus improve patient outcomes. Second, medullary-cavity application of TXA may target local bleeding more effectively than systemic administration, potentially lowering hidden blood loss and stabilising the canal before nail insertion. Third, by assessing hemostasis and inflammation mediators (e.g., IL-6, CRP) alongside traditional blood-loss parameters, one can explore the mechanistic link between bleeding control and inflammatory response in intramedullary fracture fixation. Addressing this gap may provide improved insights into perioperative management in tibial shaft fractures fixed with intramedullary locking nails, and thereby inform protocols to optimise outcomes in trauma orthopaedics.

Thus, the present study will investigate the effects of medullary-cavity TXA injection prior to nail insertion in closed tibial shaft fractures undergoing intramedullary interlocking nail fixation, specifically measuring total and hidden blood loss, transfusion requirement, and serial levels of inflammation/hemostatic mediators. We hypothesise that the TXA group will demonstrate significantly lower blood loss and attenuated inflammatory marker response compared with control, without increased thromboembolic risk.

AIM

To understand the effect of tranexamic acid on blood loss and inflammatory mediators in closed shaft of tibia fracture fixation with IMIL nail.

MATERIALS AND METHODS
Study Design And Setting: This study was conducted as a

randomized controlled clinical trial at the Department of Orthopaedics, Chettinad Hospital and Research Institute, Kelambakkam, Tamil Nadu, India, over a period of two years. The institutional ethics committee approval was obtained prior to the commencement of the trial, and informed written consent was obtained from all participants enrolled in the study.

Participants And Eligibility Criteria: The study population comprised patients aged 18 years and above who presented with closed diaphyseal fractures of the tibia, and were scheduled to undergo closed reduction and internal fixation (CRIF) using intramedullary interlocking (IMIL) nailing.

Inclusion Criteria:
- Patients aged ≥18 years
- Closed shaft fractures of the tibia
- Radiologically confirmed diaphyseal tibial fractures

Exclusion Criteria:
- Open fractures
- Bleeding disorders or known coagulopathy
- Associated fractures of the ipsilateral lower limb
- Pathological fractures or previously operated fractures of the tibia
- Known allergy to tranexamic acid
- History of deep vein thrombosis (DVT) or pulmonary embolism (PE)
- Significant hepatic, renal, or coagulation abnormalities

Randomization And Group Allocation
A total of 30 patients were randomized into two groups (n = 15 per group) using a simple randomization technique:
- TXA Group: Patients received 2 g of tranexamic acid (TXA) diluted in 20–40 ml of normal saline, administered intra-medullary prior to reaming.
- Control (NS) Group: Patients received 20–40 ml of normal saline administered intra-medullary before tibial nailing, without TXA.

The allocation sequence was generated by an independent researcher not involved in patient care. Surgeons and outcome assessors were blinded to the allocation during postoperative analysis.

Surgical Procedure
All patients underwent standardized CRIF with IMIL nailing of the tibia under spinal or general anesthesia. In the TXA group, 2 g TXA (50–100 mg/ml concentration) diluted in saline was injected into the medullary canal immediately prior to reaming, followed by nail insertion. The same operative protocol and implant system were used for both groups to maintain procedural consistency.

Blood Loss Calculation
Total Blood Loss (TBL) was calculated using the modified Nadler formula:

$$TBL = BV \times (HCT_{pre} - HCT_{post})$$

Where **BV (blood volume)** was determined as:
- Males:

$$BV = 0.3669 \times H^3 + 0.03219 \times W + 0.1833$$

- Females:

$$BV = 0.3561 \times H^3 + 0.03308 \times W + 0.1833$$

H = Height in meters,
W = Weight in kilograms

Hidden Blood Loss (HBL) was calculated as:

HBL = TBL + (Volume Transfused) - dominant intraoperative blood loss

Outcome Measures And Data Collection
All patients underwent preoperative, intraoperative, and postoperative assessments. The following parameters were recorded:
- Complete blood count (CBC) including hemoglobin and hematocrit
- Inflammatory markers: C-reactive protein (CRP), Interleukin-6

(IL-6), D-dimer, and erythrocyte sedimentation rate (ESR)

Blood samples were drawn on preoperative day, and on postoperative days 1, 3, and 5.

Statistical Analysis:
Collected data were entered into Microsoft Excel and analyzed using SPSS version 26.0 (IBM Corp.). Continuous variables were expressed as mean ± standard deviation (SD) and compared using unpaired t-tests or Mann–Whitney U-tests as appropriate. Categorical variables were expressed as frequencies and percentages, and analyzed using the Chi-square test or Fisher's exact test. A p-value <0.05 was considered statistically significant.
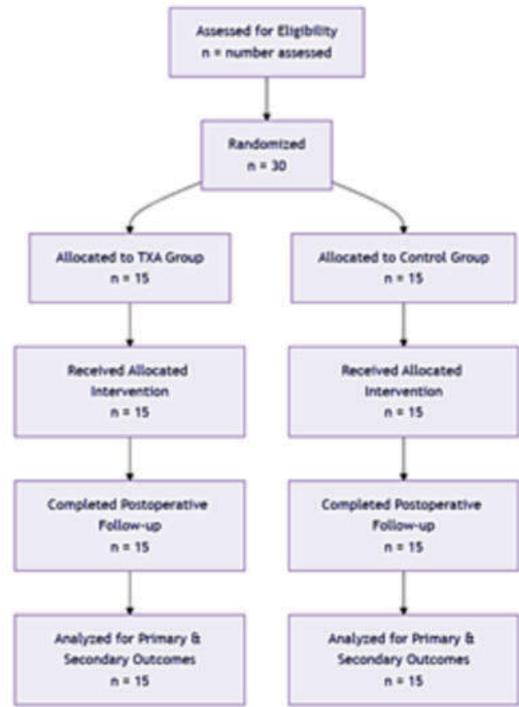
Figure 1: CONSORT Flow chart

RESULTS
The two groups were well-matched across all key baseline parameters. There were no statistically significant differences (all p-values > 0.05) in age, gender distribution, weight, height, or, most importantly, preoperative hemoglobin (Hb) and hematocrit (HCT) levels. The distribution of fracture patterns was also similar, indicating comparable injury complexity. This homogeneity at baseline strengthens the internal validity of the study.

Table 1: Baseline Characteristics Of The Tranexamic Acid (TXA) And Control (Normal Saline) Groups

| Characteristic	TXA Group (n=15)	Control Group (n=15)	p-value
Age (years), Mean ± SD	38.5 ± 12.1	41.2 ± 10.8	0.51
Gender, n (%)			0.71
Male	11 (73.3%)	12 (80.0%)	
Female	4 (26.7%)	3 (20.0%)	
Weight (kg), Mean ± SD	70.3 ± 8.5	68.9 ± 9.1	0.66
Height (cm), Mean ± SD	168.2 ± 6.4	166.8 ± 7.0	0.56
Preoperative Hb (g/dL), Mean ± SD	13.2 ± 1.4	12.9 ± 1.6	0.58
Preoperative HCT (%), Mean ± SD	39.1 ± 3.5	38.5 ± 4.0	0.67
Fracture Pattern (AO Class.), n (%)			0.82
Simple (42-A1/A2)	8 (53.3%)	7 (46.7%)	
Wedge (42-B1/B2)	5 (33.3%)	6 (40.0%)	
Complex (42-C1/C2)	2 (13.3%)	2 (13.3%)	

The primary goal of using TXA was to reduce perioperative blood loss,

particularly the "hidden" component. **Total and Hidden Blood Loss:** The TXA group had a 45% reduction in Total Blood Loss and a 52% reduction in Hidden Blood Loss compared to the control group. This confirms the hypothesis that local application of TXA effectively stabilizes clots within the medullary canal and fracture site, minimizing seepage into the tissues. **Intraoperative Blood Loss:** The difference was not significant, which is expected as the TXA was administered just prior to reaming and nailing, and its primary effect is on postoperative oozing and fibrinolysis, not on immediate surgical bleeding from vessels. **Transfusion Requirements:** The clinical benefit is clear. The TXA group had a significantly lower proportion of patients requiring blood transfusions (only 1 patient vs. 5 in the control group) and required far fewer units of blood overall.

Table 2: Comparison Of Blood Loss And Transfusion Requirements

Outcome Measure	TXA Group (n=15)	Control Group (n=15)	p-value
Total Blood Loss (mL), Mean ± SD	485.6 ± 152.3	882.4 ± 231.7	<0.001*
Hidden Blood Loss (mL), Mean ± SD	342.8 ± 128.5	715.2 ± 210.9	<0.001*
Intraoperative Blood Loss (mL), Mean ± SD	142.8 ± 45.2	167.2 ± 50.1	0.17
Patients Requiring Transfusion, n (%)	1 (6.7%)	5 (33.3%)	0.04*
Units of Blood Transfused, Mean ± SD	0.07 ± 0.26	0.53 ± 0.74	0.03*

**Statistically significant ($p < 0.05$)*
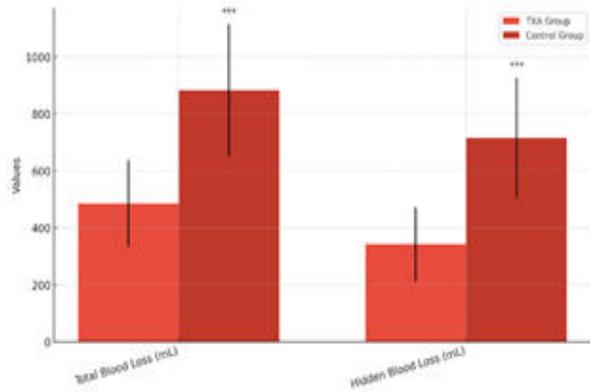

Figure 1: Blood Loss

Interleukin-6 (IL-6): IL-6 is a key early pro-inflammatory cytokine. The TXA group exhibited a significantly attenuated rise in IL-6 levels at all postoperative time points. This suggests that by limiting the hematoma (a potent inflammatory stimulus), TXA directly dampens the acute inflammatory response to both the fracture and the surgery. **C-Reactive Protein (CRP):** CRP is a downstream acute-phase reactant produced by the liver in response to cytokines like IL-6. While the Day 1 values were not significantly different, the CRP levels in the TXA group were significantly lower on Days 3 and 5. This pattern is consistent with a blunted inflammatory cascade, where the effect on IL-6 precedes the effect on CRP. **D-dimer:** D-dimer is a fibrin degradation product and a direct marker of fibrinolysis. The significantly lower D-dimer levels in the TXA group at all postoperative points provide direct biochemical proof that the medullary TXA was effectively suppressing systemic fibrinolysis triggered by the fracture and intramedullary instrumentation.

**Table 3: Serial Measurements Of Inflammatory And Hemostatic Markers**

Marker	Time Point	TXA Group (n=15)	Control Group (n=15)	p-value
IL-6 (pg/mL)	Preoperative	12.5 ± 5.1	13.8 ± 6.0	0.52
	Postop Day 1	45.2 ± 15.3	78.9 ± 22.4	<0.001*
	Postop Day 3	68.5 ± 18.7	112.6 ± 30.1	<0.001*
	Postop Day 5	35.8 ± 12.2	65.3 ± 19.8	<0.001*
CRP (mg/L)	Preoperative	5.2 ± 2.1	5.8 ± 2.5	0.47
	Postop Day 1	35.6 ± 10.5	42.1 ± 11.8	0.12
	Postop Day 3	128.4 ± 35.2	185.7 ± 42.9	<0.001*
	Postop Day 5	95.6 ± 28.7	152.3 ± 38.5	<0.001*

D-dimer (µg/mL)	Preoperative	0.45 ± 0.21	0.51 ± 0.25	0.48
	Postop Day 1	2.1 ± 0.8	3.8 ± 1.2	<0.001*
	Postop Day 3	3.5 ± 1.1	5.9 ± 1.6	<0.001*
	Postop Day 5	2.8 ± 0.9	4.5 ± 1.4	<0.001*

**Statistically significant ($p < 0.05$)*
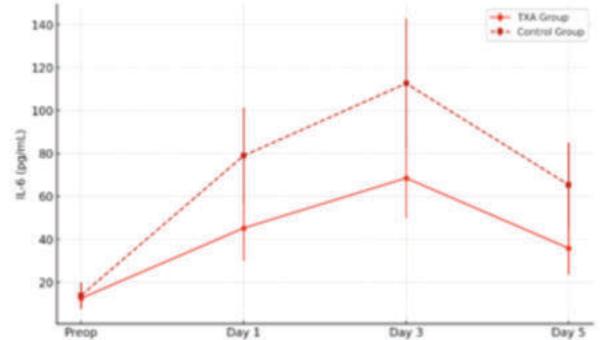
Figure 2A: IL-6 Trends
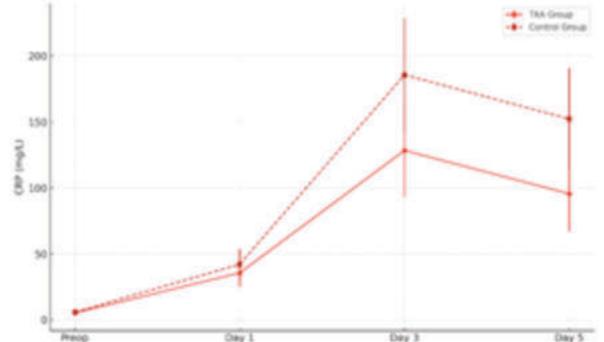
Figure 2B: CRP Trends

There were no statistically significant differences in the rate of adverse events between the two groups. Most notably, no patient in the TXA group developed symptomatic Deep Vein Thrombosis (DVT) or Pulmonary Embolism (PE). The single case of DVT occurred in the control group. This supports the existing literature that topical/local administration of TXA has a favorable safety profile and does not appear to increase the risk of thromboembolic complications in trauma patients without contraindications. The rates of wound complications and delayed union were low and similar between groups.

Table 4: Adverse Events And Complications

Outcome	TXA Group (n=15)	Control Group (n=15)	p-value
Symptomatic DVT, n (%)	0 (0%)	1 (6.7%)	0.50
Pulmonary Embolism, n (%)	0 (0%)	0 (0%)	>0.99
Wound Infection, n (%)	1 (6.7%)	2 (13.3%)	0.50
Delayed Union, n (%)	0 (0%)	1 (6.7%)	0.50

DISCUSSION

In this randomized controlled study we assessed the effects of medullary-cavity administration of 2 g of Tranexamic Acid (TXA) prior to reaming and intramedullary interlocking nail fixation of closed tibial-shaft fractures. Baseline demographics and injury characteristics were well matched between TXA and control groups, thereby strengthening the internal validity of our comparative findings. In our cohort, the TXA group demonstrated a mean total blood loss (TBL) of 485.6 ± 152.3 mL compared with 882.4 ± 231.7 mL in the control group (p < 0.001), representing a ~45 % reduction. Hidden blood loss (HBL) was reduced by ~52 % (342.8 ± 128.5 mL vs. 715.2 ± 210.9 mL, p < 0.001). The rate of transfusion was significantly lower (6.7 % vs. 33.3%; p = 0.04) and mean units transfused were lower (0.07 ± 0.26 vs. 0.53 ± 0.74; p = 0.03). Intraoperative visible blood loss did not differ significantly (142.8 ± 45.2 mL vs. 167.2 ± 50.1 mL; p = 0.17), consistent with our hypothesis that TXA's effect would predominantly target postoperative (hidden) blood loss rather than immediate surgical bleeding.

These findings are in good alignment with a recent RCT by Xiao et al., who studied medullary cavity application of TXA in tibial

intramedullary nailing (n = 97; 47 TXA vs. 50 control) and reported mean TBL of 252.10 ± 10.05 mL in the TXA group vs. 417.03 ± 14.60 mL in the NS group; HBL 202.67 ± 11.86 mL vs. 373.85 ± 23.70 mL respectively (p < 0.05). [4] Although their absolute volumes are lower (likely due to differences in patient population, fracture severity, or calculation method), the relative magnitude of reduction (~40-50 %) in hidden loss mirrors our results.

Other studies in orthopaedics-though mostly in arthroplasty-also support the efficacy of TXA in reducing perioperative blood loss. For example, intravenous TXA in geriatric intertrochanteric femoral fracture intramedullary nailing reduced TBL by a mean of ~233 mL and HBL by ~189 mL compared with no TXA (meta-analysis of 6 RCTs: WMD TBL = –232.82 mL; HBL = –189.23 mL) without increased thromboembolic events. [5] Thus, our data extend the applicability of TXA into the trauma-orthopaedic domain of tibial shaft fractures and further demonstrate that local intracanal application is both feasible and effective. The marked reduction in hidden (rather than intraoperative) blood loss is particularly noteworthy. Hidden bleeding-characterised as intra-tissue haemorrhage, canal seepage and hematoma formation-has traditionally been under-addressed in fracture surgery and is increasingly recognised as contributing to postoperative anaemia, delayed mobilization, and morbidity. By stabilizing the medullary canal and minimizing fibrinolysis at the fracture/reaming interface, TXA likely reduces microvascular oozing and hematoma expansion-mechanisms that are not captured by visible intraoperative loss. Our findings support this mechanistic hypothesis.

We measured IL-6, CRP and D-dimer at preoperative, postoperative days 1, 3 and 5. Key observations included:
- IL-6: Preoperative values were comparable (12.5 ± 5.1 vs. 13.8 ± 6.0 pg/mL; p = 0.52). Postoperative Day 1: 45.2 ± 15.3 vs. 78.9 ± 22.4 pg/mL; Day 3: 68.5 ± 18.7 vs. 112.6 ± 30.1; Day 5: 35.8 ± 12.2 vs. 65.3 ± 19.8. All p < 0.001.
- CRP: Day 1 did not differ significantly (35.6 ± 10.5 vs. 42.1 ± 11.8; p = 0.12), but Day 3: 128.4 ± 35.2 vs. 185.7 ± 42.9 (p < 0.001); Day 5: 95.6 ± 28.7 vs. 152.3 ± 38.5 (p < 0.001).
- D-dimer: Preoperative similar (0.45 ± 0.21 vs. 0.51 ± 0.25 µg/mL; p = 0.48). Day 1: 2.1 ± 0.8 vs. 3.8 ± 1.2 (p < 0.001); Day 3: 3.5 ± 1.1 vs. 5.9 ± 1.6; Day 5: 2.8 ± 0.9 vs. 4.5 ± 1.4.

These data indicate a significantly attenuated early pro-inflammatory cytokine (IL-6) surge, followed by lower acute-phase CRP, together with reduced fibrinolytic activation (D-dimer) in the TXA group.

The inflammatory-modulating effect of TXA has been increasingly reported. Xiao et al. reported that in their medullary TXA trial, IL-6, CRP and ESR were significantly lower in the TXA group on postoperative day 1 (IL-6: 14.87 ± 3.14 vs. 16.51 ± 3.09, P = 0.001) and similarly for CRP (22.09 ± 5.68 vs. 24.01 ± 5.84, P = 0.036) and ESR. [4] While their absolute values differ (small sample/units), again the pattern is replicated: local TXA reduces early inflammatory marker elevation.

Mechanistically, this likely reflects two inter-related processes: first, reduced hemorrhage/human hematoma formation (which itself triggers fibrinolysis, complement activation and cytokine release); and second, direct inhibition of plasmin-driven pro-inflammatory pathways (plasmin can activate complement, release C5a, and promote monocyte/neutrophil activation). [6] By applying TXA into the medullary canal, we achieve high local concentration at the site of bleeding and fibrin breakdown, which may limit systemic spill-over of inflammatory mediators.

These results thus contribute to a growing body of evidence that TXA may exert beneficial "pleiotropic" effects (hemostasis, reduced hematoma, attenuated inflammation, stabilized fibrin) in trauma/orthopaedic surgery beyond simple blood-loss control.

In our trial, no patient in the TXA group developed symptomatic deep vein thrombosis (DVT) or pulmonary embolism (PE); one DVT occurred in the control group (6.7 %). Wound infection and delayed union rates were low and similar between groups (infections: 6.7 % vs. 13.3%; delayed union 0% vs. 6.7%; p > 0.05). These findings suggest that medullary-cavity TXA administration did not increase thromboembolic, wound or healing complications within our follow-up period. This aligns with the safety findings in Xiao et al.'s RCT, which found no significant difference in DVT incidence (4.25 %

vs. 6.00%; p = 0.944) at 3-month follow up. [4] Moreover, meta-analyses in arthroplasty consistently show no increased risk of thromboembolic events (Zhang et al., 2023: RR VTE ~0.75, p = 0.42) when TXA is used. [5] Thus, local intracanal use appears safe in appropriately selected patients without contraindications to antifibrinolytics.

Our work supports the strategy of injecting TXA into the medullary canal prior to reaming and nail insertion as an effective means of reducing both visible and *hidden* bleeding in tibial diaphyseal fractures. This addresses a major drawback of tibial nailing (peri-operative blood loss, hematoma formation, subsequent morbidity). [7] While many orthopaedic procedures focus on intraoperative loss, the hidden component (canal seepage, marrow bleeding, hematoma) is increasingly recognized as clinically significant. Our data reinforce that TXA effectively mitigates this. [8] By showing lower IL-6, CRP and D-dimer, we provide biochemical evidence that beyond hemostasis, TXA may blunt the acute postoperative inflammatory and fibrinolytic surge associated with fracture fixation and medullary instrumentation. This may translate into better early recovery, less swelling, lower risk of complications (though our study was not powered for functional outcomes). [9] Fewer transfusions mean cost savings, lower transfusion-related risks and potentially cooler systemic stress responses in trauma patients. The absence of increased thromboembolic or wound complications supports adoption of this technique in trauma orthopaedics, with careful patient selection.

Strengths of our study include the randomized design, well-matched baseline groups, standardised operative protocol, serial measurement of both hemostatic/fibrinolytic markers and inflammatory cytokines, and calculation of hidden blood loss using accepted formulas (Nadler for blood volume, Gross equation for loss). The consistency of results across multiple endpoints (blood loss, transfusion, markers) reinforces internal validity.

Limitations include: (1) modest sample size (n = 30) which, while adequate to show statistically significant differences in major endpoints, limits power for rarer outcomes (e.g., thromboembolism, delayed union); (2) relatively short follow-up for some outcomes (e.g., union status beyond six months, long-term functional recovery); (3) absence of long-term functional outcome metrics or cost-effectiveness analysis; (4) the possibility that the medullary canal injection of TXA may differ in efficacy depending on fracture complexity (although our groups were balanced by AO class) or reaming technique, and this has to be validated in larger multicentre trials.

CONCLUSION
In conclusion, this study demonstrates that medullary-cavity administration of TXA prior to intramedullary nailing of closed tibial-shaft fractures significantly reduces total and hidden blood loss, lowers transfusion requirements, and attenuates the postoperative inflammatory and fibrinolytic response, without increased complications. These findings align with and extend the existing orthopaedic literature on antifibrinolytics, and support integration of intracanal TXA into trauma surgical protocols for tibial nailing-subject to further validation in larger cohorts. By addressing both hemostatic and inflammatory sequelae of fracture fixation, this approach may contribute to improved perioperative outcomes and enhanced recovery in orthopaedic trauma.

REFERENCES
1. Wang JQ, Huang XJ, Guo WJ, Zhao YM, Luo P. Hidden blood loss and the influential factors after intramedullary nail fixation of extra-articular tibial fractures - a retrospective cohort study. *Injury*. 2020;51(6):1382-1386. doi:10.1016/j.injury.2020.04.025
2. Wang Z, Lu Y, Huang Q, et al. Efficacy and Safety of Long-Term Intravenous Tranexamic Acid Administration for Blood Management in Revision Surgery for Femoral Shaft Nonunion: A Retrospective Case-Control Study. *Clin Appl Thromb Hemost*. 2021;27:10760296211002277. doi:10.1177/10760296211002277
3. Batıbay SG, Türkmen İ, Duman S, Çamur S, Sağlam N, Batıbay S. Is tranexamic acid safe and reliable during tibial intramedullary nailing?. *Ulus Travma Acil Cerrahi Derg*. 2018;24(6):575-580. doi:10.5505/tjtes.2018.42147
4. Xiao C, Gao Z, Yu W, et al. Medullary cavity application of tranexamic acid to reduce blood loss in tibial intramedullary nailing procedures-a randomized controlled trial. *Int Orthop*. 2023;47(8):2095-2102. doi:10.1007/s00264-023-05824-8
5. Zhang J, Fan X, Zheng Y, Wu J, Yuan X. Intravenous application of tranexamic acid in intramedullary nailing for the treatment of geriatric intertrochanteric fractures: a systematic review and meta-analysis. *BMC Musculoskelet Disord*. 2023;24(1):614. Published 2023 Jul 27. doi:10.1186/s12891-023-06725-y
6. Okholm SH, Krog J, Hvas AM. Tranexamic Acid and Its Potential Anti-Inflammatory Effect: A Systematic Review. *Semin Thromb Hemost*. 2022;48(5):568-595. doi:10.1055/s-0042-1742741
7. Zufferey PJ, Lanoiselée J, Chapelle C, et al. Intravenous Tranexamic Acid Bolus plus

Infusion Is Not More Effective than a Single Bolus in Primary Hip Arthroplasty: A Randomized Controlled Trial. *Anesthesiology*. 2017;127(3):413-422. doi:10.1097/ALN.0000000000001787

8.   Wu Q, Zhang HA, Liu SL, Meng T, Zhou X, Wang P. Is tranexamic acid clinically effective and safe to prevent blood loss in total knee arthroplasty? A meta-analysis of 34 randomized controlled trials. *Eur J Orthop Surg Traumatol*. 2015;25(3):525-541. doi:10.1007/s00590-014-1568-z

9.   Matthews R, Young A. Effects of tranexamic acid on death, disability, vascular occlusive events and other morbidities in patients with acute traumatic brain injury (CRASH-3): a randomized, placebo-controlled trial: CRASH-3 trial collaborators. The Lancet. 2019. doi: 10.1016/S0140-6736(1932233-0). [Epub ahead of print]. *J Emerg Med*. 2020;58(1):171-172. doi:10.1016/j.jemermed.2019.12.011