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Topical use of tranexamic acid for antifibrinolysis in cardiac surgery with cardiopulmonary bypass: A randomized clinical study

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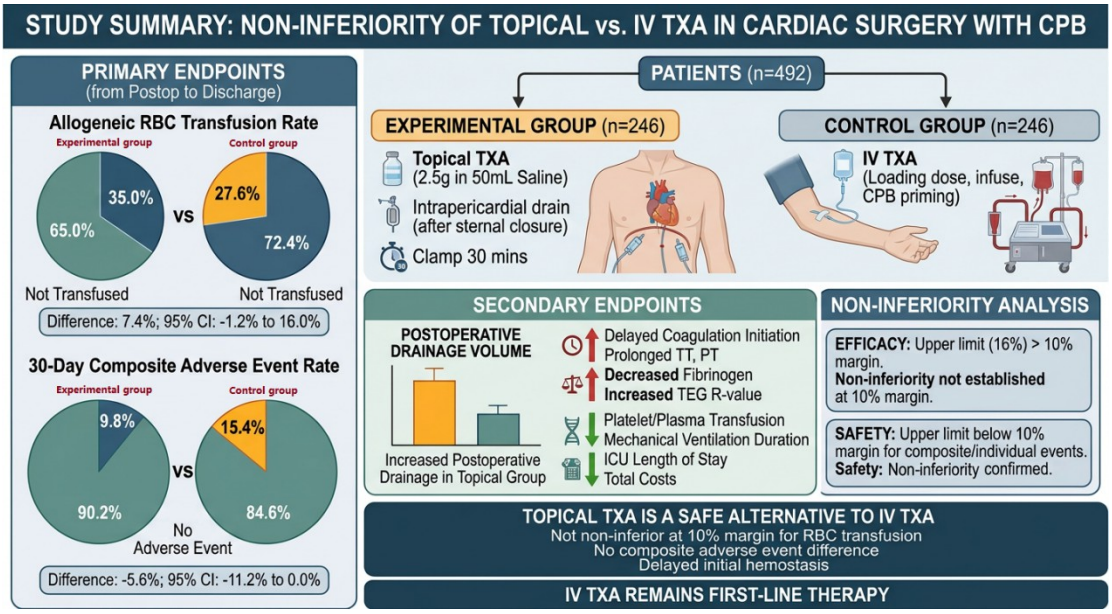
Graphic abstract (if applicable)



Abstract

Objective: To assess the non-inferiority of topical intrapericardial tranexamic acid (TXA) versus intravenous TXA for efficacy and safety in patients undergoing cardiac surgery with cardiopulmonary bypass (CPB).

Methods: In this single-center randomized trial, 492 patients were assigned 1:1 to topical TXA (2.5 g in 50 mL saline via pericardial drain, clamp 30 minutes) or standard intravenous TXA. Primary endpoints: allogeneic red blood cell (RBC) transfusion rate (postoperative to discharge); 30-day composite adverse events (mortality, renal dysfunction, stroke, myocardial infarction, thromboembolism, seizures). Secondary endpoints included drainage volume, coagulation, and thromboelastography (TEG). The non-inferiority threshold was established at 10% for sensitivity.

Results: RBC transfusion rate was 35.0% (topical) vs. 27.6% (intravenous; 95%CI −1.2% to 16.0%, P=0.080). Composite adverse events were 9.8% vs. 15.4% (95%CI −11.2% to 0.0%, P=0.057). Topical TXA showed delayed coagulation initiation, lower fibrinogen, and higher 24-hour drainage (all P<0.05). At 10% margin, efficacy non-inferiority was not confirmed, but safety non-inferiority was verified for all endpoints.

Conclusion: Topical intrapericardial TXA is non-inferior to intravenous TXA in safety but fails strict efficacy non-inferiority. Intravenous TXA remains first-line;

topical TXA is a reasonable alternative for patients intolerant to systemic administration. Dose and timing optimization is needed to improve hemostasis.

Trial registration

http://www.chictr.org.cn, ChiCTR2500113718, Registration date: 2 December 2025. Retrospectively registratered.

***Keywords*:** Tranexamic acid; Cardiovascular surgery; Cardiopulmonary bypass; Topical administration; Antifibrinolysis; Coagulation dynamics

Introduction

In cardiac surgery with cardiopulmonary bypass (CPB), hyperactivation of the fibrinolytic system is a key pathophysiological factor contributing to perioperative hemorrhage. Clinical evidence indicates that more than 20% of patients require allogeneic blood product transfusions due to postoperative bleeding, an approximately 5% undergo reoperation for hemorrhage control [1-2]. Tranexamic acid (TXA), a potent antifibrinolytic agent, exerts its hemostatic effect by competitively inhibiting the lysine-binding sites of plasminogen, thereby preventing plasminogen-fibrin interactions and suppressing fibrin degradation [3]. Its efficacy in reducing perioperative bleeding has been well documented across multiple surgical specialties.

Intravenous TXA remains the standard prophylactic antifibrinolytic regimen for CPB cardiac surgery, with clinical studies confirming its ability to significantly decrease postoperative allogeneic red blood cell (RBC) transfusion requirements and total blood loss [4]. Beyond cardiac surgery, TXA is widely used in major orthopedic procedures [5-6], hepatic resections [7], and plastic surgery [8-9], consistently demonstrating clinical benefits in hemorrhage reduction. However, systemic intravenous TXA administration, particularly high-dose bolus therapy, is associated with an increased risk of postoperative seizures due to elevated peak plasma concentrations [10-11]. It may also cause central nervous system adverse effects

(visual disturbances, cephalalgia, vertigo) [12], and the potential association with thromboembolic complications and renal dysfunction remains a subject of debate [13-14].

Topical intrapericardial TXA (hereafter referred to as topical TXA) administration has emerged as a promising strategy to maintain antifibrinolytic efficacy while minimizing systemic adverse effects, as it achieves high local tissue concentrations with low systemic exposure [6,15-16]. However, considerable controversy surrounds the efficacy of intrapericardial topical TXA in CPB cardiac surgery. Recent high-quality evidence, including the 2024 DEPOSITION randomized controlled trial [17] and several meta-analyses [18-19], suggests that topical TXA fails to demonstrate significant advantages in reducing transfusion requirements, leading to uncertainty regarding its optimal clinical implementation.

Existing studies on topical TXA in cardiac surgery primarily focus on clinical endpoints, with limited mechanistic data on coagulation function changes. Additionally, most investigations are conducted in Western populations, resulting in a lack of evidence for Asian/Chinese patients. Given the clinical need for alternative antifibrinolytic strategies for patients intolerant to intravenous TXA, the present single-center, large-sample randomized controlled trial (RCT) was designed to evaluate the non-inferiority of topical TXA versus standard intravenous TXA in CPB cardiac surgery, using allogeneic RBC transfusion rate from postoperative to discharge as the primary efficacy endpoint. We aimed to explore the effects of topical TXA on coagulation dynamics via multi-time-point coagulation parameters and TEG measurements, providing mechanistic evidence to inform clinical antifibrinolytic strategies for Chinese cardiac surgery patients.

Materials and methods

This study adheres to the CONSORT 2025 guidelines [20], and a completed CONSORT checklist is provided as an additional file (Supplementary material 1). The trial was registered with the Chinese Clinical Trial Registry (approval number: ChiCTR2500113718) and approved by the institutional ethics committee. Written

informed consent was obtained from all participants or their legal guardians.

Study Population and Group Allocation

This RCT was conducted at our tertiary cardiac surgery center from September 2022 to December 2024, enrolling patients scheduled for elective CPB cardiac surgery.

Inclusion criteria: (1) age 18–65 years; (2) any gender; (3) elective cardiac surgery with planned CPB. Exclusion criteria: (1) active coagulation disorders; (2) documented epilepsy or seizure history; (3) hypersensitivity or contraindications to TXA; (4) terminal illness (anticipated survival <3 months); (5) pregnancy or lactation; (6) cognitive or legal incapacitation; (7) CPB duration exceeding 3 hours.

The age limitation (≤65 years) and exclusion of prolonged CPB (>3 hours) were implemented to reduce confounding factors for mechanistic analysis: elderly patients often have multiple organ dysfunction and abnormal coagulation, which would interfere with TXA pharmacodynamic interpretation; patients with prolonged CPB receive intensified antifibrinolytic regimens in our center, leading to non-uniform TXA dosing. A computer-generated randomization sequence was used to assign eligible patients to the experimental (topical TXA) or control (intravenous TXA) group in a 1:1 ratio, with no stratification factors.

Therapeutic Interventions

Experimental group (topical TXA): 2.5 g of TXA was reconstituted in 50 mL of 0.9% normal saline. After completion of the primary cardiac procedure, achievement of surgical hemostasis, and sternal closure, the TXA solution was administered via the pericardial drainage catheter. The drainage system was clamped for 30 minutes to enhance local drug exposure, then unclamped for routine drainage.

Control group (intravenous TXA): the regimen followed standard clinical antifibrinolytic guidelines for CPB cardiac surgery. After general anesthesia induction and central venous catheterization, an intravenous loading dose of 10 mg/kg TXA was administered, followed by a continuous maintenance infusion of 2 $mg \cdot kg^{-1} \cdot h^{-1}$ until the end of surgery. An additional 1 mg/kg TXA was added to the CPB priming solution before CPB initiation.

Observation Indicators

We clearly defined primary and secondary outcomes to ensure the clarity of the study's clinical and mechanistic endpoints. All endpoint data were collected from surgery initiation to patient discharge via the hospital electronic medical record system, with 30-day postoperative follow-up for adverse events.

(1) Primary endpoints: ① primary efficacy endpoint: Rate of allogeneic RBC transfusion from postoperative to hospital discharge (the core endpoint for perioperative bleeding in cardiac surgery). ② primary safety endpoint: 30-day composite adverse event rate, including all-cause mortality, cardiac surgery-associated acute kidney injury (CSA-AKI), stroke, myocardial infarction, lower extremity venous embolism, and seizures. (2) Secondary endpoints: ① efficacy secondary endpoints: Allogeneic RBC transfusion volume, postoperative 24-hour drainage volume, re-exploration rate for bleeding, duration of mechanical ventilation, ICU length of stay, postoperative hospital stay, total hospitalization costs, transfusion rates of plasma and platelets. ② safety secondary endpoints: Single 30-day adverse event rates, coagulation parameters [prothrombin time (PT), activated partial thromboplastin time (APTT), thrombin time (TT), fibrinogen (FIB), platelet count (PLT)], and TEG parameters (R, K, EPL, LY30, CI, G) at multiple time points.

Standardized Transfusion Criteria

Allogeneic RBC transfusion was guided by institutional standardized thresholds: (1) postoperative hemoglobin <70 g/L for asymptomatic patients; (2) postoperative hemoglobin <80 g/L for patients with ischemic symptoms (chest pain, palpitations, dyspnea). All transfusion decisions were made jointly by two or more attending anesthesiologists to exclude subjective discretion of a single clinician.

Time Points for Coagulation and TEG Measurements

Coagulation parameters and TEG were measured at three predefined time points to evaluate dynamic changes: (1) T0: After anesthesia induction, before CPB initiation;

(2) T1: After CPB completion, before sternal closure; (3) T2: 24 hours postoperatively, during routine ICU laboratory review.

Sample Size Estimation

The sample size was primarily calculated based on the primary efficacy endpoint (allogeneic RBC transfusion rate) (safety endpoint as secondary reference), consistent with the study's core objective of evaluating hemostatic efficacy. The calculations were performed using PASS 20.0 software, with the following assumptions based on our center's 2020–2022 retrospective CPB cardiac surgery data and existing literature: (1) Efficacy endpoint: Control group RBC transfusion rate = 23.4%; statistical power = 90%; one-sided $\alpha = 0.025$; non-inferiority margin = 15% (per the 2023 Guidelines for Perioperative Antifibrinolytic Therapy in Cardiac Surgery and Shi et al. [10]). The initial calculated sample size was 211 patients per group; after adjustment with the Lan-DeMets alpha-spending function (α=0.0245) for one interim analysis, the sample size increased to 212 per group. (2) Safety endpoint: Control group 30-day composite event rate = 42.0%; clinically meaningful reduction = 15% (per Habbab et al. [18]); the same statistical power and α were applied, with an initial sample size of 222 patients per group (223 after adjustment).

Considering an estimated 10% dropout rate, the final sample size was set at 246 patients per group (total n=492), which met the sample size requirements for both efficacy and safety endpoints.

Statistical Analyses

Data were analyzed using SPSS 26.0 (IBM Corp., Armonk, NY, USA), and figures were generated with GraphPad Prism 8.0.2 (GraphPad Software, La Jolla, CA, USA). Non-inferiority tests were used for the primary endpoints, with 95% CIs reported to assess non-inferiority. For other analyses: (1) normally distributed continuous variables were presented as mean ± standard deviation (SD) and compared using independent samples t-tests (between groups) and paired t-tests (within groups); (2) non-normally distributed continuous variables were presented as median (interquartile range, IQR) and compared using the Mann–Whitney U test (between groups) and Wilcoxon signed-rank test (within groups); (3) categorical variables were presented as frequency (percentage) and compared using the chi-square test or Fisher's exact test

(as appropriate); (4) repeated measures data (coagulation parameters) were analyzed with two-way analysis of variance (ANOVA) to assess time-by-group interaction effects and main effects (group, time). A two-sided P-value < 0.05 was considered statistically significant. Sensitivity analyses of non-inferiority were performed using a more conservative non-inferiority margin of 10% for all safety endpoints (composite and individual adverse events) and for the primary efficacy endpoint (RBC transfusion rate). The differences in event rates and their 95% confidence intervals were calculated using the Newcombe method [11]. Non-inferiority was concluded if the upper limit of the 95% CI did not exceed the non-inferiority margin of 10%.

Results

Baseline Characteristics

A total of 492 patients were enrolled and randomly assigned to the experimental group (n=246) or control group (n=246), with no dropouts or loss to follow-up during the study. Baseline demographic and clinical characteristics, including gender distribution, age, preoperative hemoglobin, and operative duration, were well balanced between the two groups with no statistically significant differences (all P>0.05) (Table 1). This confirmed the adequacy of randomization and the comparability of the two groups.

Primary Endpoints

(1) Primary efficacy endpoint (RBC transfusion rate): The allogeneic RBC transfusion rate was 35.0% (86/246) in the experimental group and 27.6% (68/246) in the control group. The difference did not reach statistical significance (χ^2=3.062, P=0.080, 95%CI: -1.2% to 16.0%), and the 95% CI did not cross the predefined 15% non-inferiority margin (Table 2). The median RBC transfusion volume was 0 (0, 2.5) units in the experimental group and 0 (0, 1.5) units in the control group, with no significant difference (Z=1.894, P=0.058).

(2) Primary safety endpoint (30-day composite adverse event rate): The 30-day composite adverse event rate was 9.8% (24/246) in the experimental group and 15.4%

(38/246) in the control group. No significant between-group differences were observed for individual adverse events (χ^2=3.617, P=0.057, 95%CI: -11.2% to 0.0%) (Table 3). Notably, seizures occurred in 1.2% of the topical group and 2.0% of the intravenous group; CSA-AKI occurred in 2.0% and 2.8%, respectively; thromboembolic events occurred in 2.0% and 2.8%, respectively, with no statistical differences (all P>0.05).

(3) Sensitivity analysis (10% margin): For RBC transfusion rate, the upper 95%CI (16.0%) exceeded 10%, so efficacy non-inferiority was not confirmed. For composite and individual safety endpoints, all upper 95%CIs were below 10%, confirming safety non-inferiority.

Coagulation Parameters

At T2 (24 hours postoperatively), the experimental group had a significantly prolonged TT (P<0.001) and decreased FIB levels (P<0.05) compared with the control group (Table 4). PT showed a significant time effect in both groups (P<0.001), with a numerically longer PT in the experimental group at T2 (Table 4). APTT and PLT counts exhibited no significant between-group differences at any time point (all P>0.05). All coagulation parameters passed the Mauchly's sphericity test (P<0.001) (Figure 1).

Thromboelastography (TEG) Findings

TEG analysis demonstrated that the R value (coagulation initiation time) was significantly prolonged in the experimental group at T1 compared with the control group (P<0.001), indicating delayed coagulation initiation in the topical TXA group (Table 5). No statistically significant differences were observed in other TEG parameters (K value, EPL, LY30, CI index, G value) at T0 or T1 between the two groups (all P>0.05).

Secondary Clinical Outcomes

The experimental group had a significantly higher postoperative 24-hour drainage

volume than the control group [1063 (941–1209) mL vs. 1032 (857–1161) mL, Z=3.190, P=0.001] (Table 6). No statistically significant differences were found in other secondary efficacy outcomes, including duration of mechanical ventilation, re-exploration rate for bleeding, ICU length of stay, postoperative hospital stay, and total hospitalization costs (all P>0.05). The transfusion rates of plasma and platelets were also comparable between the two groups (P>0.05).

Discussion

The optimal administration route of TXA for CPB cardiac surgery remains an unresolved clinical and academic question. Intravenous TXA is the first-line prophylactic therapy due to its proven efficacy in reducing perioperative bleeding [4], but it carries the risk of systemic adverse effects such as seizures [10-11,21]. Topical TXA has been proposed as a minimally invasive alternative to minimize systemic exposure, but its efficacy and mechanistic effects on coagulation in cardiac surgery are controversial [17-18]. This large-sample RCT evaluated the non-inferiority of topical intrapericardial TXA versus standard intravenous TXA in CPB cardiac surgery, with a focus on coagulation dynamics via multi-time-point measurements. The results provide novel mechanistic evidence for the clinical application of topical TXA, while also highlighting the limitations of the current topical regimen.

Primary Endpoints: No Statistical Difference but with Clinical Numerical Trends

In this study, the primary efficacy and safety endpoints showed no statistically significant differences between the topical and intravenous TXA groups, and the 95% CIs for both endpoints did not cross the predefined 15% non-inferiority margin. This confirms the non-inferiority of topical TXA to intravenous TXA for the primary endpoints under the study's dosing and administration regimen. However, clear numerical trends were observed: the topical group had a 7.4% higher RBC transfusion rate and a 5.6% lower 30-day composite adverse event rate than the control group, with p-values approaching statistical significance (P=0.080 and P=0.057).

These trends suggest a potential Type II error, which may be attributed to the single-center design and sample size limitations. Larger multi-center RCTs with more diverse patient populations are required to validate these findings. Notably, the

numerically higher RBC transfusion rate in the topical group is consistent with the 2024 DEPOSITION trial [17], which reported an 8.3% higher transfusion risk in the topical TXA group. This trend indicates that the hemostatic efficacy of topical TXA is not superior to intravenous TXA, and topical TXA cannot replace the standard intravenous regimen in routine clinical practice.

A non-inferiority margin for the primary efficacy endpoint was set at 15% based on clinical guidelines and previous trials [4,10]. Our primary analysis showed that the 95% CI for the RBC transfusion rate difference (-1.2% to 16.0%) did not exceed this margin, supporting non-inferiority. However, when a more conservative margin of 10% was applied in a sensitivity analysis, the upper limit (16.0%) exceeded 10%, indicating that the conclusion of non-inferiority is sensitive to the choice of margin. This finding underscores the importance of margin selection in non-inferiority trials and suggests that the hemostatic efficacy of topical TXA could be considered inferior to intravenous TXA under stricter criteria. Notably, all safety endpoints—both composite and individual—fell within the 10% non-inferiority margin, with upper 95% CIs well below 10%, reinforcing the robust safety profile of topical TXA. These sensitivity analyses provide additional assurance that topical TXA does not compromise patient safety, even when evaluated against a stringent benchmark.

Coagulation Dynamics: Delayed Coagulation Initiation in the Topical TXA Group

The most important mechanistic finding of this study is that topical intrapericardial TXA was associated with delayed coagulation initiation and altered coagulation dynamics, as evidenced by prolonged TT/PT, decreased FIB levels, and an elevated TEG R-value. These changes are consistent with the coagulation findings of Lamy et al. [17], and our multi-time-point measurements further confirm that these alterations persist into the early postoperative period (T2). It is critical to emphasize that these changes represent coagulation dynamics alterations rather than coagulation function suppression: TXA is an antifibrinolytic agent, not an anticoagulant, and it does not directly inhibit the coagulation cascade [3].

Hypothesis-generating mechanistic explanations for these coagulation changes (based on existing literature, no direct PK/PD measurements in this study) include two key mechanisms: (1) Local high-concentration TXA effects: Intrapericardial administration and 30-minute clamp create a high topical TXA concentration in the

cardiac mediastinal region [22], which may transiently and moderately inhibit platelet activation and key components of the intrinsic coagulation pathway [23]. This results in delayed coagulation initiation (prolonged TEG R-value) and prolonged coagulation times (TT/PT). (2) Low systemic TXA exposure: Topical TXA administration achieves high local tissue concentrations but low systemic blood levels [24], which is insufficient to inhibit the systemic fibrinolytic activation induced by CPB [2]. Persistent systemic fibrinolysis leads to continuous fibrinogen degradation, resulting in decreased FIB levels in the topical group. These two mechanisms synergistically contribute to the observed coagulation dynamics alterations in the topical TXA group, providing a biological rationale for the hemostatic characteristics of topical TXA in CPB cardiac surgery.

Counterintuitive Finding: Increased Postoperative Drainage in the Topical TXA Group

A counterintuitive finding of this study is the significantly higher postoperative drainage volume in the topical TXA group, despite TXA being a potent antifibrinolytic agent. This finding can be fully explained from clinical and biological perspectives, and is closely linked to the study's dosing and administration regimen: (1) Systemic fibrinolysis in CPB: Unlike orthopedic or spinal surgery (where fibrinolysis is localized to the surgical field), CPB induces systemic fibrinolytic activation [2]. Topical intrapericardial TXA only inhibits fibrinolysis at the local cardiac surgical site, with insufficient systemic exposure to suppress whole-body fibrinolysis. This results in persistent bleeding from the extensive surgical field of cardiac surgery. (2) Delayed administration timing: Topical TXA was administered after sternal closure in this study, at which time CPB-induced fibrinolysis activation had already reached its peak [2]. The delayed timing reduces the antifibrinolytic effect of topical TXA, as early administration is critical for inhibiting fibrinolysis in cardiac surgery [4]. (3) Coagulation dynamics alterations: Delayed coagulation initiation and decreased FIB levels in the topical group further aggravate postoperative bleeding, leading to increased drainage volume. This finding is specific to the dosing and administration timing of the present study and does not indicate a lack of antifibrinolytic activity of topical TXA per se. Optimizing the topical TXA regimen (e.g., earlier administration, higher local dose, or combined low-dose intravenous TXA) may improve its hemostatic efficacy and reduce postoperative drainage volume.

Comparison with Existing Studies

Our study results are generally consistent with recent high-quality studies on topical TXA in cardiac surgery [17-18], which also reported no significant reduction in transfusion requirements with topical TXA. However, this study makes three important incremental contributions to the existing literature: (1) Mechanistic coagulation data: This study is the first to provide detailed multi-time-point coagulation and TEG data for topical TXA in cardiac surgery, elucidating the coagulation dynamics alterations induced by topical TXA and filling the gap in mechanistic evidence (previous studies only focused on clinical endpoints). (2) Asian population evidence: Most previous studies were conducted in Western populations; this study supplements critical evidence for the Chinese/Asian population, where cardiac surgery patient characteristics and TXA pharmacokinetics may differ [24]. (3) Large-sample safety validation: With a sample size of 492 patients, this study provides robust safety data for topical TXA, confirming that it does not increase the risk of 30-day adverse events and may have a numerically lower composite event rate (potentially due to reduced systemic exposure). Furthermore, sensitivity analyses with a 10% non-inferiority margin consistently demonstrated non-inferiority in safety across all endpoints, strengthening the evidence supporting safety.

A small number of studies [18] reported reduced postoperative drainage volume with topical TXA, which is inconsistent with our findings. This discrepancy is primarily attributed to differences in dosing and administration timing: these studies used a higher topical TXA dose (3–5 g) and administered the drug intraoperatively (before sternal closure), whereas our study used a 2.5 g dose with post-sternal closure administration. This highlights the critical importance of regimen optimization for the clinical efficacy of topical TXA.

Clinical Implications

Based on the study results and current clinical guidelines [4], the clinical implications for topical TXA in CPB cardiac surgery are clear: (1) Intravenous TXA remains the first-line therapy: given its proven hemostatic efficacy and the numerical trend of higher transfusion rates with topical TXA, intravenous TXA should remain the standard prophylactic antifibrinolytic regimen for routine CPB cardiac surgery. The sensitivity analyses demonstrating a failure to achieve non-inferiority in efficacy

within a 10% margin support the preference for intravenous TXA in cases requiring optimal hemostasis. (2) Topical TXA as a second-line alternative: Topical TXA may serve as a reasonable alternative for patients intolerant to intravenous TXA, such as those with a history of seizures, severe renal dysfunction (at risk of TXA accumulation), or contraindications to systemic antifibrinolytic therapy. (3) Regimen optimization is required: For topical TXA to be used more widely, optimization of dosing (higher local dose) and administration timing (intraoperative, before sternal closure) is necessary to improve its hemostatic efficacy and reduce postoperative drainage volume.

Study Limitations

This study has several limitations that should be acknowledged when interpreting the results. First, the singlecenter design may limit external validity, as findings could be influenced by institutional clinical practice and a relatively homogeneous patient population. Second, we did not perform direct pharmacokinetic or pharmacodynamic measurements of TXA in pericardial fluid or systemic circulation, so all related interpretations were inferential based on previous literature. Third, the topical TXA regimen used in this study was not optimized, and further research is warranted to assess higher doses, intraoperative administration, and combination therapy with lowdose intravenous TXA. Fourth, we excluded elderly patients and those with prolonged cardiopulmonary bypass, so the efficacy and safety of topical TXA in these highrisk subgroups remain unclear. Finally, we did not investigate novel delivery systems such as hydrogels or nanocarriers that might improve sustained local release and antifibrinolytic efficacy.

Conclusion

In this randomized controlled trial, topical intrapericardial TXA (2.5 g administered after sternal closure) was not statistically different from standard intravenous TXA in allogeneic RBC transfusion rate or 30-day composite adverse event rate. Efficacy non-inferiority was confirmed at a 15% margin but not at a stricter 10% margin, whereas safety non-inferiority was consistent across both margins. Topical TXA was associated with delayed coagulation initiation, reduced fibrinogen levels, and significantly higher postoperative drainage volume. Intravenous TXA remains the

first-line prophylactic antifibrinolytic therapy for CPB cardiac surgery. Topical TXA is a safe and reasonable alternative for patients intolerant to systemic administration. Dose and timing optimization are required to improve hemostatic efficacy.

DECLARATIONS

Ethics approval and consent to participate

The present study was approved by the Ethics Committee of People's Hospital of Xinjiang Uygur Autonomous Region (approval number: KJ-2025-382-01). Procedures operated in this research were completed in keeping with the standards set out in the Announcement of Helsinki and laboratory guidelines of research in China. Written informed consent to participate in this study was provided by the participants or legal guardian / next of kin.

Patient consent for publication

Not applicable.

Availability of data and materials

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

Disclosure of conflicts of interest

The authors declare no competing interests with respect to the research, authorship, and/or publication of this article.

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Authors‘ contributions

Conceptualization: Lei Yan.

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Writing—revision, review & editing: Chen-xi Li.

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Formal analysis: Dilnaar Tuerhong, Chen-xi Li, and Lei Yan.

Funding acquisition: Chen-xi Li and Lei Yan.

Investigation: Dilnaar Tuerhong, Chen-xi Li, and Lei Yan.

Methodology: Chen-xi Li, and Lei Yan.

Supervision: Lei Yan.

Validation: Dilnaar Tuerhong, Chen-xi Li, and Lei Yan.

Project administration: Lei Yan.

All authors read and approved the final manuscript. All authors contributed to the article and approved the submitted version.

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References

[1] Sellke FW. Bleeding After Cardiovascular Surgery: A Continuing Problem. Circulation. 2024 Oct 22;150(17):1324-1326. doi: 10.1161/CIRCULATIONAHA.124.071147.

[2] Bartoszko J, Karkouti K. Managing the coagulopathy associated with cardiopulmonary bypass. J Thromb Haemost. 2021 Mar;19(3):617-632. doi: 10.1111/jth.15195.

[3] Park LJ, Marcucci M, Ofori SN, Borges FK, Nenshi R, Kanstrup CTB, et al. Safety and Efficacy of Tranexamic Acid in General Surgery. JAMA Surg. 2025 Mar 1;160(3):267-274. doi: 10.1001/jamasurg.2024.6048.

[4] Gao B, Liu Y, Yao YT; Evidence in Cardiovascular Anesthesia (EICA) Group. Efficacy and safety of tranexamic acid in patients undergoing thoracic surgery: a systematic review and PRISMA-compliant meta-analysis. J Cardiothorac Surg. 2024 Apr 9;19(1):195. doi: 10.1186/s13019-024-02716-9.

[5] Zhang Q, Chen Y, Li Y, Liu R, Rai S, Li J, et al. Enhanced recovery after surgery in patients after hip and knee arthroplasty: a systematic review and meta-analysis. Postgrad Med J. 2024 Feb 15;100(1181):159-173. doi: 10.1093/postmj/qgad125.

[6] Izima C, Sampath SG, Tang AJ, Ambati VS, Chou D, Chan AK. Systematic review and meta-analysis of topical tranexamic acid in spine surgery. Neurosurg Focus. 2023 Oct;55(4):E18. doi: 10.3171/2023.7.FOCUS23363.

[7] Karanicolas PJ, Lin Y, McCluskey SA, Tarshis J, Thorpe KE, Wei A, et al. Tranexamic Acid in Patients Undergoing Liver Resection: The HeLiX Randomized Clinical Trial. JAMA. 2024 Oct 1;332(13):1080-1089. doi: 10.1001/jama.2024.11783.

[8] Li CX, Ma HM, Liu Y, Han JF, Ding MC, Sun JL. Clinical effectiveness assessment of a single dose of tranexamic acid for perioperative blood loss control in patients treated with craniomaxillofacial plastic and cosmetic surgery: a meta-regression analysis of registered randomized controlled trials. Chin J Plast Surg, 2025, 41(01):52-68. doi:10.3760/cma.j.cn114453-20240909-00229.

[9] Buheiri AR, Tveskov L, Dines LM, Bagge JD, Möller S, Bille C. Tranexamic Acid in Breast Surgery - A Systematic Review and Meta-Analysis. Clin Breast Cancer. 2025 Jul;25(5):e496-e510. doi: 10.1016/j.clbc.2025.01.011.

[10] Shi J, Zhou C, Pan W, Sun H, Liu S, Feng W, et al. Effect of High- vs Low-Dose Tranexamic Acid Infusion on Need for Red Blood Cell Transfusion and Adverse Events in Patients Undergoing Cardiac Surgery: The OPTIMAL Randomized Clinical Trial. JAMA. 2022 Jul 26;328(4):336-347. doi: 10.1001/jama.2022.10725.

[11] Martin K, Knorr J, Breuer T, Gertler R, Macguill M, Lange R, et al. Seizures after open heart surgery: comparison of ε-aminocaproic acid and tranexamic acid. J Cardiothorac Vasc Anesth. 2011 Feb;25(1):20-5. doi: 10.1053/j.jvca.2010.10.007.

[12] CRASH-2 trial collaborators; Shakur H, Roberts I, Bautista R, Caballero J, Coats T, et al. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. Lancet. 2010 Jul 3;376(9734):23-32. doi: 10.1016/S0140-6736(10)60835-5.

[13] Liu CW, Anih J, Lebedeva V, Gungor A, Wang C, Park L, et al. Kidney disease in trials of perioperative tranexamic acid. J Clin Anesth. 2024 Jun;94:111417. doi: 10.1016/j.jclinane.2024.111417.

[14] Dallaku K, Shakur H, Roberts I, Edwards P, Beaumont D, Delius M, et al. Effects of tranexamic

acid on platelet function and thrombin generation (ETAPlaT): WOMAN trial sub-study. Wellcome Open Res. 2016 Dec 15;1:29. doi: 10.12688/wellcomeopenres.9964.1.

[15] Ling T, Zhang L, Huang L. The efficacy and safety of combined administration of intravenous and intra-articular tranexamic acid in total knee arthroplasty: An update meta-analysis. J Clin Pharm Ther. 2022 Sep;47(9):1312-1321. doi: 10.1111/jcpt.13725.

[16] Fijany AJ, Givechian KB, Zago I, Olsson SE, Boctor MJ, Gandhi RR, et al. Tranexamic acid in burn surgery: A systematic review and meta-analysis. Burns. 2023 Sep;49(6):1249-1259. doi: 10.1016/j.burns.2023.05.009.

[17] Lamy A, Sirota DA, Jacques F, Poostizadeh A, Noiseux N, Efremov S, et al. Topical Versus Intravenous Tranexamic Acid in Patients Undergoing Cardiac Surgery: The DEPOSITION Randomized Controlled Trial. Circulation. 2024 Oct 22;150(17):1315-1323. doi: 10.1161/CIRCULATIONAHA.124.069606.

[18] Habbab LM, Semelhago L, Lamy A. Topical Use of Tranexamic Acid in Cardiac Surgery: A Meta-Analysis. Thorac Cardiovasc Surg. 2020 Apr;68(3):212-218. doi: 10.1055/s-0039-1691748.

[19] Gao B, Liu Y, Yao YT; Evidence in Cardiovascular Anesthesia (EICA) Group. Efficacy and safety of tranexamic acid in patients undergoing thoracic surgery: a systematic review and PRISMA-compliant meta-analysis. J Cardiothorac Surg. 2024 Apr 9;19(1):195. doi: 10.1186/s13019-024-02716-9.

[20] Hopewell S, Chan AW, Collins GS, Hróbjartsson A, Moher D, Schulz KF, et al. CONSORT 2025 statement: updated guideline for reporting randomised trials. Lancet. 2025 Apr 14:S0140-6736(25)00672-5. doi: 10.1016/S0140-6736(25)00672-5.

[21] Ducloy-Bouthors AS, Jeanpierre E, Saidi I, Baptiste AS, Simon E, Lannoy D, et al. TRAnexamic acid in hemorrhagic CESarean section (TRACES) randomized placebo controlled dose-ranging pharmacobiological ancillary trial: study protocol for a randomized controlled trial. Trials. 2018;19(1):149. doi: 10.1186/s13063-017-2421-6.

[22] Fergusson DA, Hébert PC, Mazer CD, Fremes S, MacAdams C, Murkin JM, et al. A comparison of aprotinin and lysine analogues in high-risk cardiac surgery. N Engl J Med. 2008 May 29;358(22):2319-31. doi: 10.1056/NEJMoa0802395.

[23] Tibi P, McClure RS, Huang J, Baker RA, Fitzgerald D, Mazer CD, et al. STS/SCA/AmSECT/SABM Update to the Clinical Practice Guidelines on Patient Blood Management. J Extra Corpor Technol. 202;53(2):97-124. doi: 10.1182/ject-2100053.

[24] Liu Y, Zhou C, Lv H, Tian L, Jiang J, Shi J. Population Pharmacokinetics of Tranexamic Acid in Chinese Population Undergoing Cardiac Surgery with Cardiopulmonary Bypass. Drug Des Devel Ther. 2025 May 26;19:4343-4353. doi: 10.2147/DDDT.S493485.

Table 1. Comparison of baseline characteristics between the two groups.

Metrics	Experimental group (n = 246)	Control group (n = 246)	Test statistic ($t/\chi^2/Z$)	*P* value
Gender, n (%)			0.217	0.642
Male	156	151		
Female	90	95		
Age, year (median, IQR)	51 (39~58)	47.5 (38~56)	1.796	0.073
BMI, kg/m^2 (mean ± SD)	21.65 ± 3.62	21.35 ± 4.52	-0.820	0.412
Preoperative hemoglobin, g/L (mean ± SD)	14.70 ± 1.52	14.39 ± 2.21	-1.798	0.073
Preoperative hematocrit, %	43.79 ± 4.24	43.28 ± 6.01	-1.093	0.275
Operative duration, min (median, IQR)	320 (240, 410)	315 (268.75, 360)	-0.208	0.835

Abbreviations: IQR = interquartile range; SD = standard deviation. No statistically significant differences were observed between the two groups (all $P > 0.05$).

Table 2. Comparison of allogeneic red blood cell transfusion outcomes between the two groups.

Metrics	Experimental group (n = 246)	Control group (n = 246)	Test statistic (χ^2/Z)	95% Confidence Interval	*P* value
Erythrocyte transfusion frequency, n (%)	86 (35.0)	68 (27.6)	3.062	-1.2% ~ 16.0%	0.080*
Erythrocyte transfusion volume, units (median, IQR)	0 (0, 2.5)	0 (0, 1.5)	1.894	-0.1 ~ 2.1	0.058*

Abbreviations: IQR = interquartile range.

*P values are marginally non-significant; the 95% CI for transfusion rate does not cross the predefined 15% non-inferiority margin.

Table 3. Comparison of 30-day composite and individual adverse events between the two groups.

Adverse events	Experimental group (n = 246) n (%)	Control group (n = 246) n (%)	χ^2 value	*P* value
All-cause mortality	3 (1.2)	5 (2.0)	0.127	0.721
CSA-AKI	5 (2.0)	7 (2.8)	0.342	0.559
Stroke	5 (2.0)	8 (3.3)	0.771	0.399
Myocardial infarction	3 (1.2)	6 (2.4)	0.453	0.501
Lower extremity venous embolism	5 (2.0)	7 (2.8)	0.342	0.559
Seizures	3 (1.2)	5 (2.0)	0.127	0.721
Composite adverse events	24 (9.8)	38 (15.4)	3.617	0.057*

Abbreviations: CSA-AKI = cardiac surgery-associated acute kidney injury. No statistically significant differences between groups for any individual or composite adverse event (all P>0.05). *P=0.057 for composite events is marginally non-significant, with a numerically lower rate in the topical TXA group.

Table 4. Comparative analysis of coagulation parameters and platelet counts at T0, T1 and T2.

Metrics	Group	T0 (mean ± SD)	T1 (mean ± SD)	T2 (mean ± SD)	Time effect (P)	Group effect (P)	Time-group interaction (P)
PT (s)	Control group	12.45 ± 1.88	14.00 ± 1.00[a]	13.01 ± 1.11[ab]	< 0.001	0.090	0.357
	Experimental group	12.35 ± 2.34	13.97 ± 1.15[a]	12.72 ± 1.17*[ab]	< 0.001		
APTT (s)	Control group	31.94 ± 3.53	34.68 ± 9.54[a]	30.69 ± 4.90[ab]	< 0.001	0.550	0.670
	Experimental group	32.10 ± 4.64	34.19 ± 11.13[a]	30.34 ± 5.10[ab]	< 0.001		
TT (s)	Control group	14.47 ± 1.57	18.16 ± 4.53[a]	14.35 ± 2.03*[b]	< 0.001	0.170	< 0.001
	Experimental group	14.50 ± 1.95	17.62 ± 4.23[a]	15.59 ± 4.64[ab]	< 0.001		
FIB (g/L)	Control group	2.78 ± 0.78	2.06 ± 0.80[a]	3.21 ± 0.82*[ab]	< 0.001	0.026	0.080
	Experimental group	2.77 ± 0.84	2.00 ± 0.59[a]	2.97 ± 1.07[ab]	< 0.001		
PLT ($\times 10^9$/L)	Control group	241.48 ± 71.96	170.20 ± 54.42[a]	176.72 ± 55.18[a]	< 0.001	0.564	0.498
	Experimental group	243.47 ± 80.97	168.46 ± 56.29[a]	170.05 ± 55.83[a]	< 0.001		

Abbreviations: APTT = activated partial thromboplastin time; FIB = fibrinogen; PLT = platelet count; PT = prothrombin time; TT = thrombin time; T0 = post-anesthesia induction, pre-CPB; T1 = post-CPB completion, pre-sternal closure; T2 = 24 h postoperatively. All parameters passed Mauchly's sphericity test ($P < 0.001$).[a] $P < 0.05$ vs. T0; [b] $P < 0.05$ vs. T1; * $P < 0.05$ vs. control group at the same time point.

Table 5. Comparison of thromboelastography (TEG) parameters at T0 and T1.

Metrics	Group	T0	T1	Test statistic (*t*/*Z*)	*P* value (vs. T0)	*P* value (group comparison at T1)
R (min)	Control group	6.03 ± 1.68	6.88 ± 1.48	-6.113	< 0.001	< 0.001*
	Experimental group	6.10 ± 0.89	7.43 ± 1.53*	-11.819	< 0.001	
K (min)	Control group	1.52 ± 0.58	1.65 ± 0.58	-2.458	0.015	0.320
	Experimental group	1.56 ± 0.56	1.70 ± 0.57	-2.642	0.009	
EPL (%)	Control group	0.3 (0.0, 0.6)	0.3 (0.1, 0.6)	-0.633	0.527	0.892
	Experimental group	0.3 (0.0, 0.5)	0.3 (0.1, 0.6)	-1.871	0.061	
EPL30 (%)	Control group	0.2 (0.0, 0.5)	0.4 (0.1, 0.7)	-3.813	< 0.001	0.105
	Experimental group	0.2 (0.0, 0.5)	0.3 (0.0, 0.6)	1.780	0.075	
CI	Control group	2.49 ± 1.00	2.10 ± 0.95	4.545	< 0.001	0.418
	Experimental group	2.59 ± 1.05	1.99 ± 0.99	6.277	< 0.001	
G (kPa)	Control group	7.03 ± 1.67	7.43 ± 1.90	-2.332	0.021	0.656
	Experimental group	7.14 ± 1.47	7.24 ± 2.03	-0.650	0.516	

Abbreviations: CI = coagulation index; EPL = estimated percent lysis; G = clot stiffness; K = clot formation time; LY30 = percent lysis at 30 min; R = clot initiation time; T0 = post-anesthesia induction, pre-CPB; T1 = post-CPB completion, pre-sternal closure. Data are presented as mean ± SD for normally distributed variables and median (IQR) for non-normally distributed variables. * $P < 0.05$ vs. control group at the same time point.

Table 6. Comparison of postoperative clinical prognostic indicators between the two groups.

Metrics	Experimental group (n = 246) (median, IQR)	Control group (n = 246) (median, IQR)	*Z* value	*P* value
Transfusion volume of red blood cells, u	0 (0, 2.5)	0 (0, 1.5)	1.894	0.058
Duration of mechanical ventilation, h	28 (15.75, 40)	25 (15.75, 37.25)	1.103	0.270
Postoperative drainage volume, mL	1063 (941, 1209)	1032 (857, 1161)	3.190	0.001**
Incidence of secondary thoracotomy, n (%)	2 (0.8)	1 (0.4)	—	> 0.999
Length of ICU stay, days	2 (2, 4)	2 (2, 3)	1.393	0.163
Postoperative hospital stay, days	12 (9, 13.25)	11.5 (9, 14)	-0.350	0.726
Total hospitalization costs, 10,000 CNY	11.95 (10.73, 13.22)	11.9 (9.6, 14.51)	0.245	0.806

Abbreviations: ICU = intensive care unit; IQR = interquartile range; CNY = Chinese Yuan. **P < 0.01 vs. control group. Fisher's exact test was used for re-exploration rate.

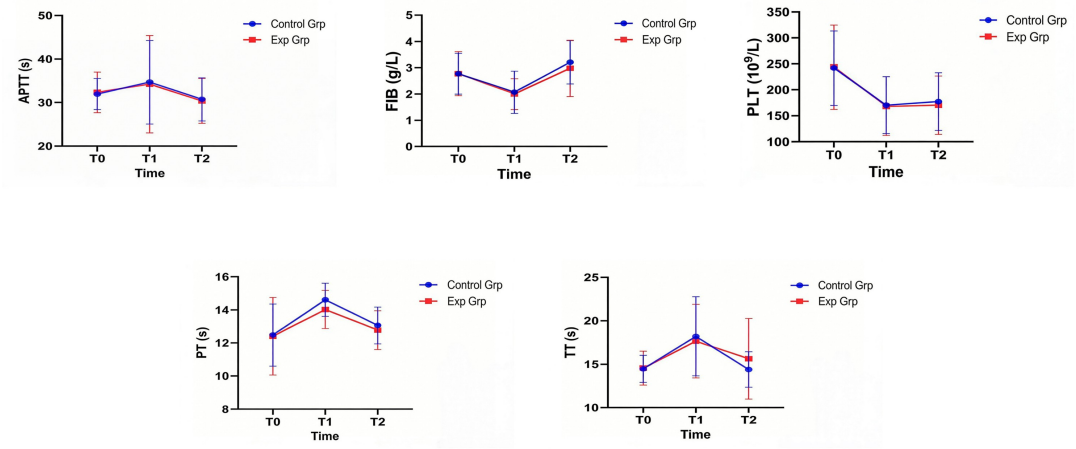

Figure 1. Dynamic changes in key coagulation parameters between the experimental and control groups at T0, T1 and T2.

Dynamic comparison of prothrombin time (PT), thrombin time (TT), fibrinogen (FIB) and platelet count (PLT) in patients receiving topical tranexamic acid (experimental group) and intravenous tranexamic acid (control group) at three time points: T0 (post-anesthesia induction, pre-cardiopulmonary bypass [CPB]), T1 (post-CPB completion, pre-sternal closure), and T2 (24 hours postoperatively). Data are presented as mean ± standard deviation. Statistical notations: [a] $P < 0.05$ vs. T0 at the same group; [b] $P < 0.05$ vs. T1 at the same group; *** $P < 0.05$ vs. control group at the same time point***. The experimental group exhibited significantly prolonged TT at T2, reduced FIB levels at T2, and no significant difference in PLT counts at all time points compared with the control group. PT was numerically longer in the experimental group at T2 without a statistically significant group effect.