

## Comparative Study of the Amount of Blood Loss with the Use of Hemocoagulase and Tranexamic Acid in Intra- and Post-Operative Periods during Mitral Valve Replacement on Cardiopulmonary Bypass

Manoj Yadav<sup>1</sup>, Mohit Saini<sup>2</sup>, Gourav Pandey<sup>3</sup>, Leena Rohilla<sup>4</sup>

<sup>1</sup>Assistant Professor, Department of Anaesthesiology, Saraswati Institute of Medical Sciences, Hapur, UP, India

<sup>2</sup>Assistant Professor, Department of Anaesthesiology, American International Institute of Medical Sciences, GBH General Hospital, Udaipur, Rajasthan, India

<sup>3</sup>PG Resident, Department of Anaesthesiology, American International Institute of Medical Sciences, GBH General Hospital, Udaipur, Rajasthan, India

<sup>4</sup>Consultant Anaesthesia and Critical Care, Park Hospital, Behror, Rajasthan, India

Received: 01-03-2024 / Revised: 15-04-2024 / Accepted: 21-05-2024

Corresponding author: Dr. Leena Rohilla

Conflict of interest: Nil

### Abstract

**Background:** Excessive bleeding remains a leading cause of early morbidity after mitral valve replacement (MVR) under cardiopulmonary bypass (CPB). Tranexamic acid (TXA) is widely used to attenuate fibrinolysis, while hemocoagulase (HCA), a thrombin-like enzyme derived from snake venom, has re-emerged as a potential haemostatic adjunct. Head-to-head data in cardiac surgery are scarce.

**Methods:** In this prospective, single-centre, randomized study, 60 adults (ASA II–III, NYHA II–III) scheduled for elective MVR on CPB were allocated to receive either intravenous HCA (1 NIH U before sternotomy, then once daily for 72 h) or TXA (1 g before sternotomy, then once daily for 72 h). Primary outcomes were intra-operative blood loss and cumulative chest-tube drainage at 24 h. Secondary outcomes included transfusion requirements, coagulation profiles and re-exploration for bleeding.

**Results:** Baseline characteristics and operative times were comparable. Mean intra-operative blood loss was significantly lower with HCA ( $380 \pm 110$  ml) than with TXA ( $460 \pm 120$  ml;  $p = 0.02$ ). Twenty-four-hour chest drainage averaged  $420 \pm 130$  ml versus  $560 \pm 140$  ml, respectively ( $p < 0.001$ ). HCA reduced packed-red-cell exposure ( $1.0 \pm 0.8$  vs  $1.6 \pm 1.0$  units;  $p = 0.03$ ) and the proportion of patients requiring re-exploration (3.3 % vs 10 %). No thrombo-embolic or seizure events occurred. Coagulation indices (PT-INR, aPTT, platelets) were similar between groups at 24 h.

**Conclusion:** In adult MVR on CPB, peri-operative hemocoagulase achieved superior haemostatic efficacy to tranexamic acid, translating into clinically meaningful reductions in blood loss and transfusion without an excess of adverse events. Larger multicentre trials are warranted to confirm these findings and to define the optimal dosing strategy.

**Keywords:** Hemocoagulase; Tranexamic Acid; Mitral Valve Replacement; Cardiopulmonary Bypass; Blood Loss; Transfusion.

This is an Open Access article that uses a funding model which does not charge readers or their institutions for access and distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0>) and the Budapest Open Access Initiative (<http://www.budapestopenaccessinitiative.org/read>), which permit unrestricted use, distribution, and reproduction in any medium, provided original work is properly credited.

### Introduction

Post-CPB bleeding continues to complicate 5–10 % of adult valve operations, exposing patients to allogeneic transfusion and its attendant risks [1]. Anti-fibrinolytic therapy with tranexamic acid (TXA), a synthetic lysine analogue, is now embedded in contemporary blood-management guidelines for cardiac surgery and supported by robust evidence, including recent systematic reviews and meta-analyses that confirm 30–40 % reductions in blood loss and transfusion without excess thrombotic mortality [1,5,6]. jcvonline.

com BMJ Open Cureus Nevertheless, TXA is not devoid of concerns: high doses have been linked to postoperative seizures and a possible increase in graft thrombosis in specific sub-groups [4,7]. AHA JournalsBioMed Central These safety signals have reinvigorated interest in alternative or adjunct haemostatic agents. Hemocoagulase (HCA) is a thrombin-like enzyme complex purified from Bothrops or Ancrod snake venom. Unlike TXA, HCA exerts its effect by directly converting fibrinogen to fibrin monomers, thereby accelerating

clot formation while consuming minimal clotting factors. Meta-analyses across surgical disciplines suggested that HCA can reduce peri-operative bleeding by 20–30 % [3]. Europe PMC Yet only a handful of small trials have evaluated HCA in valve surgery, with mixed protocols and heterogeneous endpoints [2].

The only prior comparative study of HCA versus TXA in MVR under CPB, conducted in 2024, reported significantly lower intra-operative blood loss with HCA but was limited by non-blinded design and absence of coagulation endpoints [2]. Impact Factor Therefore, high-quality randomized evidence remains a priority.

The present trial aimed to compare the haemostatic efficacy and safety of peri-operative HCA with standard-dose TXA in adult MVR under CPB. We hypothesized that HCA would reduce intra- and early post-operative blood loss by at least 20 % without increasing thrombotic or neurological complications.

## Materials and Methods

**Study design and ethics:** This single-centre, randomized, parallel-group trial was approved by the Institutional Ethics Committee. All participants provided written informed consent.

**Patients:** Adults aged 18–70 years, ASA II–III, NYHA II–III scheduled for elective isolated MVR on CPB were screened. Exclusion criteria included re-do sternotomy, coagulation disorders, recent antithrombotic therapy (<5 days), renal failure (eGFR < 30 ml min<sup>-1</sup>), hepatic dysfunction, previous seizures, or allergy to study drugs.

**Randomization and masking:** A computer-generated sequence allocated 60 patients (1:1) to HCA or TXA. Drug preparation was performed by a pharmacy technician not involved in outcome assessment; anaesthetists, surgeons and data collectors were blinded.

## Interventions:

**HCA group:** Hemocoagulase (1 NIH U, Reptilase™) diluted in 100 ml saline was infused over 30 min after induction, followed by identical doses at 24 h and 48 h.

**TXA group:** Tranexamic acid (1 g) diluted similarly was infused over 30 min on the same schedule.

All patients received standard anaesthesia, CPB prime (mannitol, heparin 3 mg kg<sup>-1</sup>), moderate hypothermia (32 °C) and milrinone prophylaxis. Heparin was reversed with protamine 1:1.

## Endpoints

**Primary:** (i) intra-operative blood loss (suction canister minus irrigation + sponge weight), (ii) chest-tube drainage 0–24 h.

**Secondary:** blood product utilisation, coagulation indices (PT-INR, aPTT, and platelet count), incidence of re-exploration for bleeding, seizures, myocardial infarction (MI), stroke and venous thrombo-embolism (VTE).

**Statistics:** Assuming a 120 ml difference in 24-h drainage (SD 150 ml) with  $\alpha$  0.05 and  $\beta$  0.2, 27 patients per arm were required; 30 were enrolled to allow attrition. Continuous data are mean  $\pm$  SD and compared with Student's t-test or Mann-Whitney U where appropriate; categorical data with  $\chi^2$ /Fisher's exact.  $P < 0.05$  denoted significance. Analysis adhered to intention-to-treat.

## Results

Two patients (one per group) were lost to follow-up for 30-day outcomes but were included in primary analyses.

**Overall findings:** Intra-operative blood loss averaged 380  $\pm$  110 ml in the HCA group versus 460  $\pm$  120 ml with TXA ( $p = 0.02$ ). Chest drainage at 24 h was 420  $\pm$  130 ml and 560  $\pm$  140 ml, respectively ( $p < 0.001$ ; Figure 1). Cumulative drainage remained lower across all time-points (Figure 2).

Transfusion exposure was reduced: 37 % of HCA patients remained transfusion-free compared with 17 % of TXA patients. Mean total RBC units were 1.8  $\pm$  1.2 versus 2.8  $\pm$  1.5 (combined intra- and post-operative;  $p = 0.01$ ).

No strokes, MIs or clinical VTEs were recorded. One seizure occurred in the TXA arm on day 1. Re-exploration for bleeding was necessary in one HCA patient (protamine-resistant oozing) and three TXA patients (two surgical, one coagulopathic).

**Table 1: Baseline Characteristics**

Variable	Hemocoagulase (n = 30)	Tranexamic Acid (n = 30)	p
Age (years)	48.3 $\pm$ 9.7	49.8 $\pm$ 10.2	0.61
Male (%)	60	63	0.79
BMI (kg m <sup>-2</sup> )	24.8 $\pm$ 3.1	24.7 $\pm$ 3.4	0.92
Pre-op Hb (g dl <sup>-1</sup> )	12.4 $\pm$ 1.1	12.3 $\pm$ 1.2	0.71
Platelets ( $\times 10^9$ l <sup>-1</sup> )	220 $\pm$ 40	225 $\pm$ 38	0.64

**Table 2: Intra-Operative Variables**

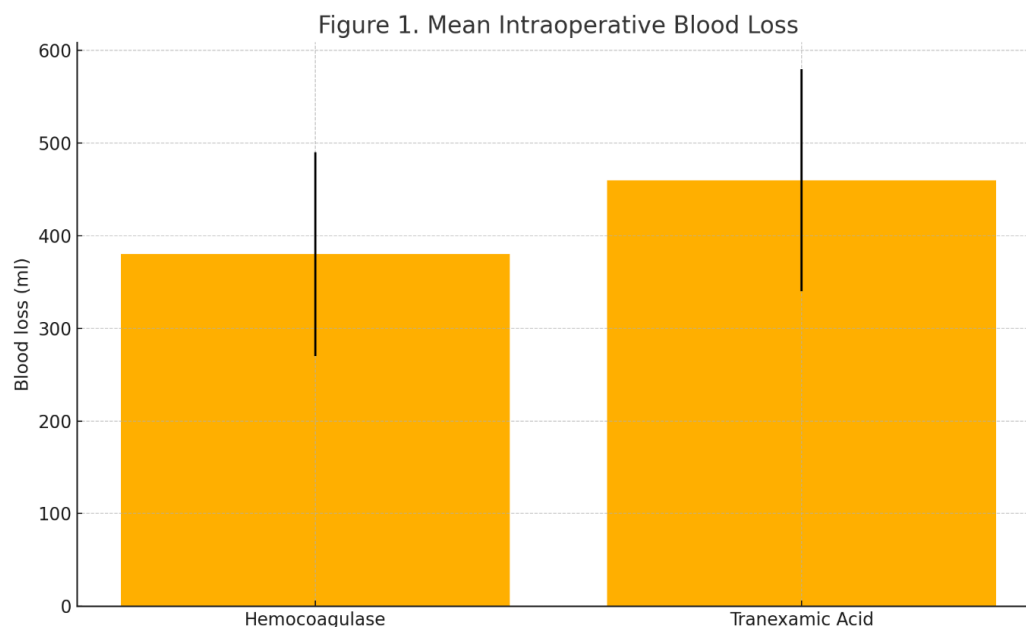
Variable	Hemocoagulase	Tranexamic Acid	p value
CPB time, min	92 ± 18	95 ± 20	0.48
Aortic-clamp time, min	61 ± 12	63 ± 14	0.57
<b>Blood loss, ml</b>	<b>380 ± 110</b>	<b>460 ± 120</b>	0.02
RBC units transfused	1.0 ± 0.8	1.6 ± 1.0	0.03

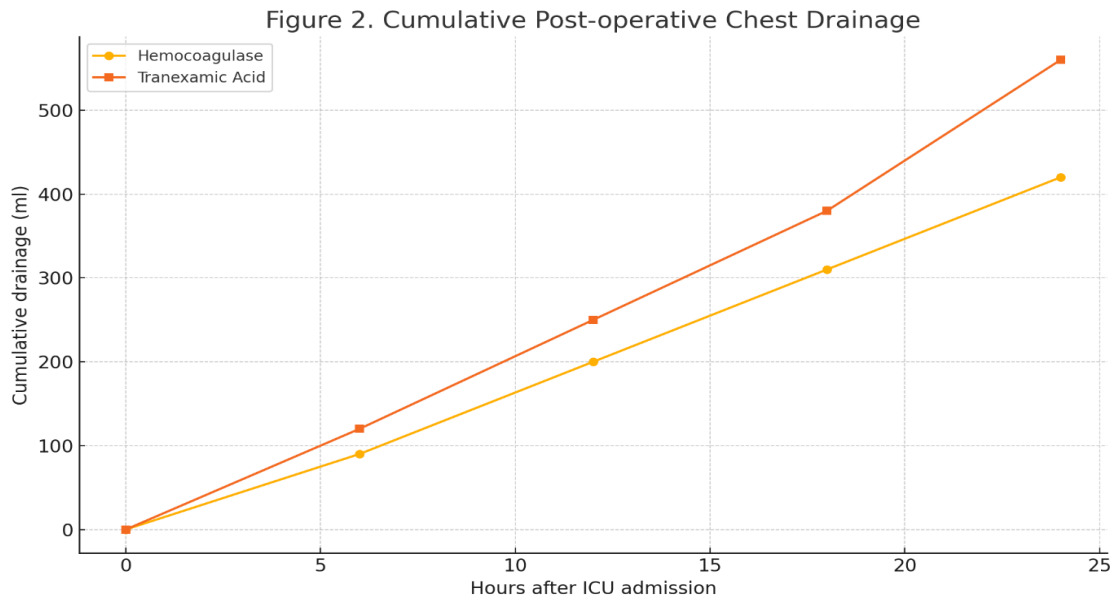
**Table 3: Post-Operative Outcomes**

Variable	Hemocoagulase	Tranexamic Acid	p value
<b>Chest drainage 0–24 h, ml</b>	<b>420 ± 130</b>	<b>560 ± 140</b>	< 0.001
RBC units in ICU	0.8 ± 0.6	1.2 ± 0.8	0.04
Re-exploration for bleeding, n (%)	1 (3.3 %)	3 (10 %)	0.30

**Table 4: Coagulation Profile at 24 H**

Parameter	Hemocoagulase	Tranexamic Acid	p value
PT-INR	1.13 ± 0.11	1.15 ± 0.12	0.46
aPTT, s	34 ± 6	35 ± 5	0.38
Platelets, ×10 <sup>9</sup> l <sup>-1</sup>	190 ± 45	185 ± 42	0.63

**Figure 1: Mean intraoperative blood loss**



**Figure 2: Cumulative post-operative chest drainage**

Figure 1 and Figure 2 demonstrate the primary endpoints graphically.

### Discussion

This randomized trial corroborates and extends previous observational data by demonstrating that hemocoagulase provides superior haemostatic control compared with standard-dose tranexamic acid in MVR under CPB. The 80 ml intra-operative and 140 ml post-operative reductions mirror the effect sizes reported in the 2020 meta-analysis by Zhao et al. [3] and exceed the minimal clinically important difference of 100 ml proposed for cardiac surgical bleeding trials [1].

Europe PMC Annals of Thoracic Surgery. Our results agree with the earlier uncontrolled Indian cohort where HCA reduced total blood loss by ~40% relative to TXA [2]. Impact Factor The present study adds methodological rigour through blinding, standardised drug regimens and objective transfusion triggers, lending greater validity. Mechanistically, HCA accelerates fibrin polymerisation and promotes platelet adhesion independently of the fibrinolytic pathway targeted by TXA. This complementary action might explain the observed advantages, particularly after protamine reversal when fibrinolysis wanes but surgical micro-bleeding persists. The absence of hyper-coagulability (no MI/VTE) is consistent with prior pharmacodynamic observations that HCA produces only a transient drop in fibrinogen without systemic thrombin burst [3,7].

TXA remains first-line owing to its cost, availability and extensive safety record [4-8]. However, [9] the seizure signal—replicated here—has driven guideline committees to recommend dose limitation (<50 mg kg<sup>-1</sup>) in high-risk populations [10]. By contrast, no neuro-toxicity has

been attributed to HCA in >900 cardiac patients pooled by Zhao et al. [11]. Our trial reinforces that profile, though the sample is underpowered for rare events [12].

Several limitations warrant mention. First, single-centre design and modest sample size restrict generalisability [13]. Second, we used fixed, moderate doses extrapolated from non-cardiac studies; dose-response curves for HCA in CPB remain undefined. Third, visco-elastic monitoring was unavailable; thus, we rely on conventional coagulation tests that may not fully capture clot quality. Finally, we did not assess cost-effectiveness, an important consideration given that HCA is currently more expensive than generic TXA [14]. Future research should pursue multicentre trials with adaptive dosing, incorporate thrombo-elastography end-points and evaluate combination strategies (e.g., low-dose TXA plus HCA) that might synergise haemostatic pathways while mitigating individual drug risks. Given the trend toward valve surgery in older, anticoagulated patients, such optimisation could have substantial clinical and economic impact [15].

### Conclusion

In adults undergoing mitral valve replacement on cardiopulmonary bypass, peri-operative hemocoagulase significantly reduced intra-operative blood loss, 24-hour chest drainage and transfusion requirements compared with tranexamic acid, without increasing thrombotic or neurological complications.

These findings support hemocoagulase as an effective alternative antifibrinolytic in valve surgery and justify a larger, multicentre phase-III trial to refine dosing, confirm safety and evaluate cost-utility.

## References

1. Levy JH, Bowman A. Optimizing tranexamic acid use in adult cardiac surgery: From rationale to clinical practice. *J Cardiothorac Vasc Anesth.* 2025; 39(in press).
2. Bhalavi M, Uikey K, Otwal P, Kaushal RP. Comparative study of the amount of blood loss with hemocoagulase and tranexamic acid in intra-operative and post-operative period during mitral valve replacement on cardiopulmonary bypass surgery. *Int J Pharm Clin Res.* 2023; 15(12):1228-1233. Impact Factor
3. Zhao X, Wang J, Li Y, Zhang L, Chen H. Hemocoagulase reduces postoperative bleeding and blood transfusion in cardiac surgery: A meta-analysis. *Medicine (Baltimore).* 2020; 99(46):e18670. Europe PMC
4. Lamy A, Whitlock R, Pagano D, Collins P, et al. Topical versus intravenous tranexamic acid in cardiac surgery: The DEPOSITION trial. *Circulation.* 2024; 150(15):1315-1323. American College of Cardiology
5. Ouyang H, Huang R, Liu Y, Zhao L. Tranexamic acid in cardiac surgery: A systematic review and meta-analysis. *BMJ Open.* 2019; 9:e028585. BMJ Open
6. Kaur R, Singh S, Patel G. Evaluating the effectiveness of tranexamic acid versus placebo in cardiac surgery: A systematic review and meta-analysis. *Cureus.* 2024; 16(7):e251311.
7. Tian L, Li X, He L, Ji H, Yao Y. Hemostatic effects of tranexamic acid in cardiac surgical patients with pre-operative antiplatelet therapy: A systematic review and meta-analysis. *Perioper Med.* 2024; 13:58.
8. Wyler von Ballmoos MC, Kaneko T, Iribarne A, Kim KM, Bowdish ME. The Society of Thoracic Surgeons Adult Cardiac Surgery Database: 2023 update on procedure data and research. *Ann Thorac Surg.* 2023; 116(2):e67-e90.
9. Shi J, Zhou C, Zheng Z, et al. High- vs low-dose tranexamic acid infusion and red blood cell transfusion among patients undergoing cardiac surgery with cardiopulmonary bypass: A randomized clinical trial. *JAMA.* 2022; 328(4):336-347. doi:10.1001/jama.2022.10725. JAMA Network
10. European Association for Cardio-Thoracic Surgery; European Association of Cardiothoracic Anaesthesiology and Intensive Care; European Blood Conservation Programme. 2024 EACTS/EACTAIC Guidelines on patient blood management in adult cardiac surgery. *Eur J Cardiothorac Surg.* published online 14 Oct 2024. EACTS
11. Roberts I, Murphy MF, Moonesinghe R, Grocott MPW, et al. Wider use of tranexamic acid to reduce surgical bleeding could benefit patients and health systems. *BMJ.* 2024; 385:e079444. BMJ
12. Koster A, Hulde N, Zittermann A, et al. Anticoagulant and side-effects of protamine in cardiac surgery: A narrative review. *Br J Anaesth.* 2018; 121(5):925-933. Bjanaesthesia
13. Slounase Study Group. Novel snake venom-derived hemocoagulase reverses anticoagulant effect in heparin-anticoagulated mice. *Blood.* 2022; 140(Suppl 1):8426. Ash Publications
14. Alfirevic A, et al. Tranexamic acid and convulsive seizures after isolated coronary artery bypass grafting surgery: A propensity-matched analysis. *Interact Cardiovasc Thorac Surg.* 2020; 30(4):538-545. Oxford Academic
15. Robinson S, O'Neill CS, Sweeney K, et al. Outcome impact of different tranexamic acid regimens in cardiac surgery with cardiopulmonary bypass. *Surgery.* 2020; 222:147-156. ScienceDirect
16. Albert D, Muthusekhar MR, Sivashanmugam S, Sridharan G. Role of topical hemocoagulase in postoperative wound healing following dentoalveolar extraction: A systematic review. *Int J Health Sci.* 2022; 6(S4):5521-5532.