Original Article

A Comparative Study of the Efficacy and Safety Profile of Topical Application of Tranexamic Acid in the Form of Mist to Reduce Postoperative Bleeding in on-Pump CABG Procedures

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ABSTRACT

Background: Postoperative bleeding is a major concern in cardiovascular surgery, leading to an increased need for blood transfusions and a longer hospital stay. Between 30% and 70% of open-heart surgery patients will require blood product transfusion. The use of the cardiopulmonary bypass machine (CPB) often leads to bleeding due to complement activation, platelet activation, and hyperfibrinolysis. Antifibrinolytic drugs, like ε-aminocaproic acid, aprotinin, and tranexamic acid (TXA) are used to decrease postoperative bleeding in cardiac surgery. According to the Society of Thoracic Surgeons guidelines, TXA is class I recommendation to reduce the risk of bleeding.

Aims: Compare the efficacy and safety of TXA in the mist form to reduce postoperative bleeding.

Settings and Design: Prospective, Randomized, Single-Centre, Interventional Study.

Material and Methods: The study included sixty participants undergoing on-pump CABG randomized into two groups. Group T and Group C received topical TXA and 20 mL NS in mist form, respectively. The mist was blown over the pericardium, LIMA bed, and sternotomy sites before chest closure. The primary objectives were to compare the 48th hour drain collection and need for blood transfusion.

Statistical Analysis Used: Simple *t*-test, Chi-square test and Mann–Whitney U test.

Results: The experimental group had significantly less 48-hour drain (*P* value 0.001), reduced need of blood and blood products (*P* value 0.001) and less duration of postoperative ventilation (*P* value 0.001).

Conclusion: The topical application of TXA in mist form significantly reduced postoperative bleeding, the necessity for blood transfusion, and the duration of mechanical ventilation in on-pump CABG procedures.

Keywords: Blood transfusion, mister blower, on-pump CABG, postoperative bleeding, tranexamic acid

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INTRODUCTION

Postoperative bleeding is a significant issue in cardiovascular surgery, potentially leading to an increased need for blood transfusions and longer hospital stays.[1] Studies indicate that 30% to 70% of patients undergoing open-heart surgery will need blood product transfusions.[2] The use of the cardiopulmonary bypass (CPB) machine during on-pump coronary artery bypass graft (CABG) surgery often results

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in bleeding due to complement and platelet activation, as well as hyperfibrinolysis, which is a major factor in such bleeding.[3] Antifibrinolytic drugs, such as ε-aminocaproic acid, aprotinin, and tranexamic acid, have been utilized to minimize blood loss during CABG surgery.[4]

Massive blood loss is a leading cause of death in cardiovascular surgery. The extent of bleeding can be evaluated by the volume of drainage from chest tubes and the necessity for transfusion of blood components. According to the Society of Thoracic Surgeons guidelines from 2011, intravenous tranexamic acid (TXA) is recommended to mitigate bleeding risks in cardiac surgery.[5]

Tranexamic acid (TXA) is an antifibrinolytic agent administered either by injection or topical application. TXA, which resembles lysine, binds to lysine receptor sites on plasminogen and plasmin, thereby inhibiting fibrinolysis. However, its antifibrinolytic properties may increase the risk of thromboembolic events such as coronary vessel occlusion, deep vein thrombosis, myocardial infarction, cerebral infarction, and pulmonary embolism. Additionally, high doses of intravenous TXA have been associated with seizures.[5]

Topical TXA is expected to have a localized effect, reducing systemic complications. While studies on topical TXA in cardiac surgery are limited and generally show results comparable to intravenous administration, there is a tendency toward reduced postoperative bleeding with topical application. This study aims to compare the efficacy and safety of TXA administered as a mist in reducing postoperative bleeding during on-pump CABG procedures.

MATERIAL AND METHODS

This was a prospective, randomized, single-center, double-blinded, interventional trial conducted from 2022 to 2024. It was approved by the relevant institutional governing bodies (Institutional Ethics Committee no. 280/2022) and registered with the Clinical Trial Registry of India (CTRI No: CTRI/2023/05/052353). The study was conducted in compliance with the Declaration of Helsinki (2013) and Good Clinical Practice guidelines. Informed consent was obtained in writing from all participants prior to their involvement in the study, as well as for the use of their data for research and educational purposes.

The study included sixty-two patients, aged 40 to 75 years, undergoing elective on-pump coronary artery bypass grafting (CABG). Exclusion criteria were known allergy to TXA, previous surgery, coagulopathy (INR >1.5), renal failure (serum creatinine >2 mg/dL), emergency procedures, and left ventricular ejection fraction (LVEF) <35%. Two patients were excluded from the study due to change in plan to do combined mitral valve repair with CABG.

Sixty patients were randomized into two groups using a computer-generated random allocation method, and group allocation concealment was achieved using sealed opaque envelopes. A nursing officer not involved in the study prepared the study drug, ensuring blinding of the anesthesia provider, cardiac surgeon, and the patients to the intervention. Those in Group T received 2 g of TXA, while those in Group C were given 20 mL of normal saline (NS), both administered as mist using a mister blower (Medtronic Clearview, Minneapolis, MN, USA).

The procedure began with standard ASA monitoring, including an arterial line, a central line, and transesophageal echocardiography, followed by anesthesia induction in accordance with the standard institutional protocol. After a median sternotomy was performed, conduits including the left internal mammary artery and saphenous vein grafts were harvested. Following heparinization, cardiopulmonary bypass was initiated, and the heart was arrested with cardioplegia for graft anastomosis. After completing grafting, the patient was weaned off bypass, and heparin was reversed with protamine sulfate.

Depending on group allocation, either TXA (2 g) or 20 mL of NS was administered as a mist over the pericardium, LIMA bed, and sternotomy sites just before closing the sternum. This was done by the surgeon using a mister blower, as shown in Figure 1. This was prepared by nursing staff and given by the consultant anesthesiologist (observer 1) through the infusion pump at a rate of 200 mL/h with oxygen flow of 3-4 L/min with the aid of mister blower without the knowledge of the drug allocation. In all patients, two drainage tubes, one mediastinal and one plural drain were put to ensure drainage

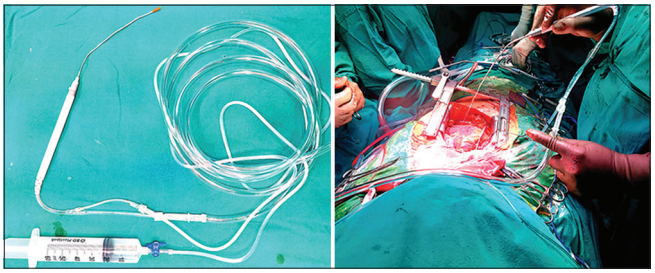


Figure 1: Mister-Blower and spraying the tranexamic acid using the Mister-blower

of collection postoperatively. After ensuring proper graft function and checking for bleeding or complications, the surgeon closed the chest with sternal wires. The patient was then transferred to the intensive care unit (ICU) for monitoring of heart function, blood pressure, and other vital signs.

Postoperative drain outputs were recorded by postgraduate student (observer 3) at 4, 8, 12, 24, and 48 hours, along with details of blood transfusions and coagulation profiles. Blood transfusion decisions were based on hemoglobin levels (<9 g%), bleeding rate, and hemodynamic status, as determined by the cardiac surgeon (observer 2). Hemoglobin and hematocrit levels, as well as activated clotting time (ACT), were recorded by postgraduate student (observer 3) at 4, 8, 12, 24, and 48 hours. Coagulation profiles, including prothrombin time and INR, were assessed at 24 and 48 hours. Weaning from ventilation was performed once the patient was stable and awake. In all patients, drainage tubes were removed by third postoperative day. The patient, the anesthesiologist (Observer 1), the cardiac surgeon (Observer 2), and the postgraduate students (Observer 3) remained blinded to the study. The anesthesiologist was not involved in postoperative assessments to mitigate potential bias.

Statistical analysis

The sample size calculation was based on data from a pilot study involving five participants in each group. The primary outcome measured was the total drain collection over 48 hours. In the control (C) group, the mean drain collection was 358 mL with a standard deviation (SD) of 119 mL, while in the tranexamic acid (T) group, the mean was 278 mL with an SD of 66.6 mL. The average SD was determined to be 185 mL, and the anticipated clinical difference between the groups was estimated at 150 mL.

Using standard statistical methods, the required sample size to detect this difference with 80% power at a 5% significance level was calculated to be 24 participants per group. To account for a 20% dropout rate, the final sample size was set at 30 participants per group.

Data analysis was performed using SPSS (Statistical Package for Social Sciences) version 21. An independent sample *t*-test was used to evaluate associations between continuous variables and the groups, while the Chi-square test and Mann–Whitney U test were applied to assess associations between qualitative variables. A significance level of less than 0.05 was considered statistically significant.

RESULTS

Sixty-two patients were assessed for eligibility and 60 patients were included for the study. Two patients were excluded because of change in surgical plan to do mitral valve replacement concomitantly as shown in consort diagram [Figure 2].

Demographic data, preoperative coagulation profiles [Table 1], and intraoperative parameters [Table 2] for all participants were comparable, with no statistically significant differences observed between the two groups. Table 3 and Figure 3 show the postoperative drain collection over the first 48 hours, with the T group recording 302.41 ± 95.53 mL and the C group 582.5 ± 252.93 mL, a difference that was statistically significant (*P* value 0.001). In the T group, only 4 patients (13.3%) required PRBC transfusion, compared to 13 patients (43.3%) in the C group, a statistically significant difference (*P* value 0.01). However, there was no statistically significant difference in the requirement for other blood products such as platelets and FFP between the two groups. The duration of mechanical ventilation was significantly shorter in the T group (7.1 ± 3.19 hours) compared to the C group (10.1 ± 3.68 hours). There was one instance of re-exploration on postoperative day 0 in the C group due to bleeding and cardiac tamponade. There were no incidents

Table 1: Comparison of the demographic data and preoperative coagulation parameter

Parameters	T group (*n*=30)	C group (*n*=30)	*t* test *P*
Age in years Mean±SD	57.7±7.96	61.50±9.60	0.081
Gender (M/F)	25/5	27/3	0.448
BMI in kg/m^2 (Mean±SD)	25.32 – 3.22	24.00 – 2.97	0.108
Smoking (yes) (N%)	3 (10)	6 (20)	0.566
DM (yes)(*n*%)	21 (70)	14 (46.6)	0.722
HTN (yes) (*n*%)	22 (73.3)	22 (73.3)	0.813
PT (Mean±SD) Sec	10.98±0.53	11.12±0.69	0.369
INR (Mean±SD)	0.95±0.07	0.96±0.07	0.565
APTT (Mean±SD) Sec	30.43±10.14	28.09±2.01	0.220
Platelets (Mean±SD) L/micro-L	2.49 0.56	2.81±0.92	0.150

Table 2: Comparison of the intraoperative parameters in group T and group C

Parameter	T group Mean±SD	C group Mean±SD	Mann Whitney *U* test *P*
Baseline ACT (Sec)	152.50±23.20	163±64.52	0.399
Number of grafts	2.97±0.41	2.90±0.48	0. 567
ACT after protamine (Sec)	149.10±17.59	166.50±14.19	0.371
Pump time (min)	107.77±28.46	117.73±32.68	0.213
Cross clamp time (min)	71.67±21.80	77.83±30.00	0.366
Duration of surgery (hours)	5.12±1.02	5.53±0.79	0.085

Table 3: Postoperative drain collection in first 48 hours

Time	T group			C group			Mann Whitney *U* test *P*
	Mean±Sd	Median	IQR (lower/upper)	Mean±Sd	Median	IQR (lower/upper)	
4th hour (ml)	48.46±31.46	45	20/62	104±77.89	80	50/130	0.001
8th hour (ml)	96.43±51.01	100	50/137	200±109.23	170	127/282	0.001
12th hour (ml)	120±56.32	125	70/150	330.4±247.66	270	160/412	0.001
24th hour (ml)	213.67±96.63	205	150/282	480±302.41	400	310/602	0.001
48th hour (ml)	302.41±95.53	310	220/340	582.5±252.93	540	402/707	0.001

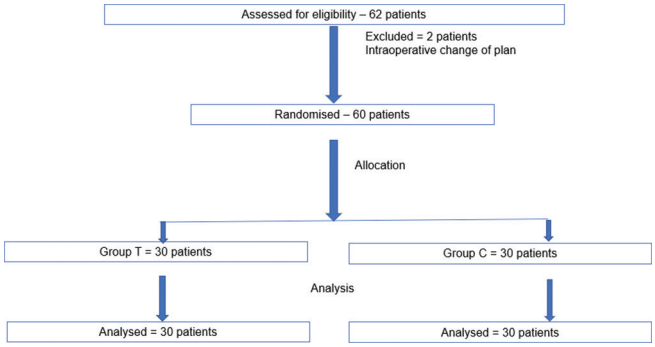


Figure 2: Consort diagram

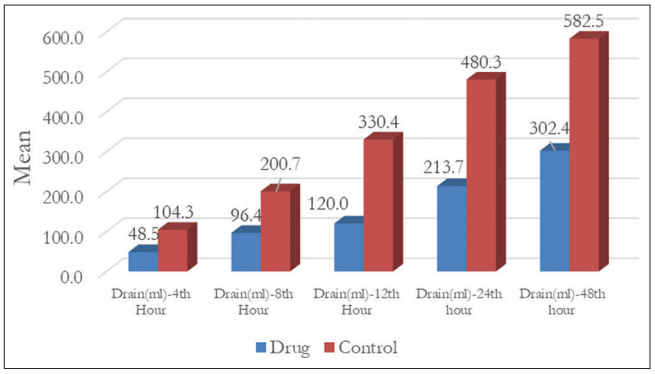


Figure 3: Histogram showing the mean postoperative drain in group T and group C

of complications like seizure, ST segment elevation, stroke, or thromboembolic events in either of groups.

DISCUSSION

The results of our study revealed that patients receiving 2 g of tranexamic acid as a mist had an average blood loss of 302 mL within 48 hours after the procedure. In comparison, the control group, which received 20 mL of normal saline, had a significantly higher average blood loss of 583 mL ($P < 0.001$). This indicates that topical application of TXA in mist form effectively reduced postoperative blood loss following on-pump CABG procedures. Additionally, the TXA group required significantly fewer packed red blood cell transfusions compared to the control group ($P = 0.001$). The duration of postoperative mechanical ventilation was also significantly shorter in the TXA group ($P = 0.001$). No significant differences were observed in other parameters such as postoperative hemoglobin levels, transfusions of blood products like Fresh Frozen Plasma (FFP) and platelets, or coagulation profiles. There was one incident of bleeding and cardiac tamponade requiring re-exploration happened in C group, but no such incident was reported in T group. There were no reports of renal failure, cerebrovascular accidents (CVAs), deep vein thrombosis (DVT), or seizures in either group.

A study by Fawzy *et al*.[6] thoroughly investigated the use of tranexamic acid in the mediastinal cavity to reduce blood loss after on-pump CABG surgery. In their study of 36 participants, the group receiving 1 g of tranexamic acid had an average blood loss of 626 mL in the first 24 hours post-surgery, compared to 1040 mL in the control group. Blood transfusion needs were similar between groups, though the rate of platelet transfusion was lower in the tranexamic acid group. These results align closely with those of our study, supporting the effectiveness of topical tranexamic acid in reducing postoperative blood loss without increasing patient risk.

Abul-Azm and Abdullah[7] assessed the impact of topically applied tranexamic acid in the mediastinal cavity on postoperative blood loss in open-heart surgery patients. Their findings indicated that the group receiving 2 g of tranexamic acid had significantly lower blood loss compared to the control group, with fewer transfusions required. Notably, the control group had eight cases of reoperation for bleeding control, whereas none were reported in the tranexamic acid group.

A study by Habibollah Hosseini *et al*.[8] explored the effects of applying 2 g of topical tranexamic acid in off-pump CABG surgery. Their results showed an average blood loss of 366 mL in the tranexamic acid group compared to 788 mL in the control group, a statistically significant difference ($P < 0.001$). However, there were no significant differences in blood transfusion requirements or other blood parameters between the two groups.

Topical tranexamic acid has also been studied in various non-cardiac surgeries, such as orthopedic and gynecological

procedures, by X. Aguilera *et al*.[9] and Sukanya Mitra *et al*.[10] respectively. Mitra's study found that topical tranexamic acid was as effective as intravenous administration in reducing postoperative bleeding in abdominal hysterectomy patients.

Overall, most studies indicate that topical tranexamic acid is effective in reducing postoperative bleeding in both cardiac and non-cardiac surgeries, whether used alone or in combination with intravenous forms. In contrast to previous studies where tranexamic acid was diluted in normal saline and applied to the surgical field, our study utilized a mister blower to apply the undiluted drug uniformly over the thoracic cavity, including the LIMA bed, sternal borders, intercostal space, and proximal anastomotic sites. This method, which adds no extra cost to the procedure, ensures that the drug reaches deep structures that are potential bleeding sites like LIMA bed, left pleural space and sternotomy wiring sites during CABG surgery.

Limitations

The study has several limitations. It is a single-center study, so the results are likely to have limited generalizability but are useful for similar settings. Although the sample size was statistically powered, increasing the sample size in future studies could make the conclusions more robust. The study primarily focused on short-term outcomes, left long-term effects, such as thromboembolic complications, for further investigation. Excluding high-risk patients with significant comorbidities allowed for a more homogeneous sample, though future research could explore broader applicability. Moreover, although efforts were made to standardize protocols, unmeasured factors like surgeon experience might have subtly influenced the outcomes.

CONCLUSION

The topical application of tranexamic acid in the form of mist has been shown to significantly reduce postoperative bleeding, the necessity for blood transfusion, and the duration of postoperative mechanical ventilation in on-pump coronary artery bypass graft procedures.

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Conflicts of interest

There are no conflicts of interest.

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