Official Title: A Comparison between the Efficacy of Tranexamic Acid and Adrenaline to Control Endobronchial Bleeding – A Randomized Controlled Trial

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Abstract

Objective: To compare the efficacy of topical administration of tranexamic acid versus adrenaline for controlling endobronchial bleeding during flexible bronchoscopy.

Study Design: Randomized controlled trial.

Setting: Department of Pulmonology, Shaikh Zayed Hospital, Federal Postgraduate Medical Institute Lahore, Pakistan.

Period: Twelve months from 3 January 2022 to 2 January 2023.

Material and Methods:

A total of 76 patients developing moderate bleeding during diagnostic bronchoscopy for endobronchial biopsy for benign or malignant lesions were enrolled and randomized equally into two groups (n=38 per group). Group A received topical endobronchial adrenaline (1 mg in 20 mL normal saline), whereas Group B received topical tranexamic acid (500 mg in 20 mL normal saline). The primary endpoints were immediate hemostasis and rebleeding within 30 minutes. Data analysis was performed using SPSS version 24.0; intergroup comparison was done using Chi-square test, with $p \leq 0.05$ taken as significant.

Results: Mean age was 56.66±10.87 years in tranexamic acid group and 55.89±15.31 years in adrenaline group. Immediate hemostasis was achieved in 38 (100%) patients receiving tranexamic acid compared to 33 (86.8%) patients receiving adrenaline (p=0.021). Rebleeding was significantly lower with tranexamic acid [2 (5.3%)] than with adrenaline [9 (23.7%), p=0.022]. On subgroup analysis, tranexamic acid showed significantly superior hemostasis in males, smokers, patients with body mass index (BMI) <25 kg/m², and those with symptom duration of 1-3 weeks ($p<0.05$ for each).

Conclusion: Topical endobronchial tranexamic acid is significantly more effective than adrenaline in achieving immediate hemostasis and preventing early rebleeding for bleeding following endobronchial forceps biopsy during flexible bronchoscopy.

Keywords: Adrenaline, bronchoscopy, bronchial bleeding, endobronchial biopsy, tranexamic acid.

Material and Methods

This randomized controlled trial (RCT) was conducted in the out-patients department (OPD) and indoor wards, at the Department of Pulmonology, Shaikh Zayed Hospital, Federal Postgraduate Medical Institute, Lahore, over a 12-month period, from 3 January 2022 to 2 January 2023, following approval from the Institutional Review Board (IRB ID SZMC/Internal/0097/2021 dated 25 September 2021). Informed consent was obtained from all participants, and the study conformed to the Helsinki Declaration of 1975, as revised in 1983.

Sample size of 76 patients (38 per group) was calculated using 95% confidence level and 90% power. The expected requirement of second-line medication for adrenaline was 32% and that for TXA was 4%.[9] Patients fulfilling the inclusion criteria were enrolled. Demographic information including age, gender, BMI, smoking status, duration of pulmonary symptoms, and comorbidities such as diabetes mellitus, hypertension and coronary artery disease was documented on a predesigned structured proforma.

Adult patients of any age and gender who underwent diagnostic flexible bronchoscopy for any suspected benign or malignant disease and required endobronchial forceps biopsy were considered for enrollment. Only those who developed moderate endobronchial bleeding post-biopsy were included. Moderate bleeding was operationally defined as bleeding that obscured the bronchoscopic view and required repeated suctioning to clear the airway and endoscopic intervention for hemostasis, but remained hemodynamically stable. Mild bleeding was simple oozing from the biopsy site not obscuring the view. Severe bleeding was defined as bleeding requiring instillation of ice-cold saline, bronchoscopic tamponade for control, application pf electrocautery or argon plasma coagulation (APC) to the bleeding site and life-threatening bleeding was defined as bleeding requiring endotracheal intubation, or spontaneous hemoptysis of more than 100 to 150 ml per hour. Patients with severe or life-threatening bleeding, contraindications to bronchoscopy such as cardiac arrhythmias, oxygen saturation below 90% on supplemental oxygen, acute respiratory failure with hypercapnia, or tracheal obstruction, bleeding diathesis with raised INR or platelet count less than 50,000 per mm3, and patients with unstable coronary artery disease or hypersensitivity to TXA or adrenaline were excluded.

All procedures were performed as diagnostic flexible fibreoptic bronchoscopy using a Fujinon® flexible video bronchoscope (EB-270S system) under topical airway anesthesia with 2%

lignocaine, with supplemental oxygen and continuous pulse oximetry, heart rate and blood pressure monitoring. Endobronchial biopsies were obtained from visible lesions or abnormal mucosa as clinically indicated, using 2.2 mm flexible cupped biopsy forceps. Patients who developed moderate post-biopsy bleeding were randomly allocated into two groups by lottery method. In Group A, 1 mg adrenaline diluted in 20 mL normal saline to achieve a concentration of 0.05 mg/mL was used, while in Group B, 500 mg TXA diluted in 20 mL normal saline to achieve a concentration of 25 mg/mL was used. The allocated study drug was instilled directly onto the bleeding site through the working channel of the bronchoscope in 5 mL aliquots. Administration could be repeated up to three times at 30-second intervals if bleeding persisted.

Immediate bleeding control, the primary outcome, was defined as direct bronchoscopic observation of cessation of oozing and/or formation of a stable clot at the bleeding site within 90 seconds of drug instillation. Rebleeding, the secondary outcome, was assessed by close clinical observation and repeat inspection with flexible bronchoscopy performed 30 minutes after initial hemostasis, with pulse oximetry monitoring to ensure clot stability and adequate ventilation. Any fresh bleeding from the same site within this period was labeled as rebleeding. If bleeding persisted beyond 90 seconds despite maximal administration of the trial drug, it was defined as treatment failure, and rescue hemostatic measures were adopted including topical cold saline instillation, crossover instillation of adrenaline or TXA, prolonged wedge tamponade of the involved segment, and other standard interventions like application of electrocautery or APC were implemented to ensure hemostasis.

Statistical Analysis

All statistical analyses were performed using SPSS for Windows, version 24.0 (SPSS Inc., Chicago, Illinois, USA). Quantitative variables including age, body mass index and duration of pulmonary symptoms were expressed as mean and standard deviation. Qualitative variables such as gender, diabetes mellitus, hypertension, smoking history, immediate hemostasis and rebleeding were presented as frequencies and percentages. The efficacy of TXA versus adrenaline in terms of immediate hemostasis and rebleeding was compared between the two groups using Chi-square test. Post-stratification analysis was performed to control for effect modifiers including age, gender, body mass index, duration of disease, diabetes, hypertension and smoking history, and

Chi-square test was applied within each stratum. A p-value of less than or equal to 0.05 was considered statistically significant.

Results

A total of 76 patients who developed moderate endobronchial bleeding after biopsy were enrolled and randomized equally into TXA (n=38) and adrenaline (n=38) groups. The baseline demographic and clinical characteristics were largely comparable. Mean age was 56.66 ± 10.87 years in the TXA group and 55.89 ± 15.31 years in the adrenaline group. Male predominance was observed in both groups [84.2% vs 60.5%]. The prevalence of diabetes mellitus was identical in both groups [26.3% each], while hypertension was more frequent in the adrenaline group [57.9% vs 26.3%]. Smoking history was present in 73.7% of patients in the TXA group and 55.3% in the adrenaline group. Mean BMI (23.29 ± 3.97 kg/m²) in both groups and mean duration of pulmonary symptoms (2.58 ± 1.49 weeks) in both groups were similar.

Primary Outcome

Immediate hemostasis within 90 seconds was achieved in all patients in the tranexamic acid group (100%, n=38) compared to 86.8% (n=33) in the adrenaline group, a difference that was statistically significant (p=0.021). Rebleeding within 30 minutes of initial hemostasis (table 1) was significantly lower in the TXA group (5.3%, n=2) compared to the adrenaline group (23.7%, n=9; p=0.022).

Stratified Analysis

Post-stratification analysis revealed consistent superiority of TXA in key subgroups. In patients aged 41-60 years, hemostasis was achieved in 100% with TXA versus 71.4% with adrenaline (p=0.025), with rebleeding rates of 0% versus 42.9% respectively (p=0.05). Among male patients, hemostasis was 100% vs 82.6% (p=0.014) and rebleeding was 6.3% vs 26.1% (p=0.04). In smokers, TXA achieved 100% hemostasis versus 81% with adrenaline (p=0.016), with rebleeding rates of 7.1% versus 28.6% (p=0.045). Similarly, in patients with BMI <25 kg/m², hemostasis was 100% vs 79.2% (p=0.016) and rebleeding was 4% vs 29.2% (p=0.017). In patients with symptom duration of 1-3 weeks, hemostasis was 100% vs 84.6% (p=0.024) and rebleeding was 0% vs 26.9% (p=0.002). Among diabetic patients, rebleeding was significantly lower with TXA (0% vs 38.9%; p=0.023), while no significant intergroup differences were observed for hypertension status or in female patients, likely due to small sample size (tables 2).

Table 1: Comparison of Baseline Characteristics and Outcomes between Study Groups

Variable	**Tranexamic Acid Group (n=38)**	**Adrenaline Group (n=38)**	
Age (years), mean ± SD	56.66 ± 10.87	55.89±15.31	
Gender, n (%)			
Male	32 (84.2%)	23 (60.5%)	
Female	6 (15.8%)	15 (39.5%)	
BMI (kg/m²), mean ± SD	23.29 ± 3.97	23.29 ± 3.97	
Disease duration (weeks), mean ± SD	2.58 ± 1.49	2.58 ± 1.49	
Diabetes Mellitus, n (%)	10 (26.3%)	18 (47.4%)	
Hypertension, n (%)	10 (26.3%)	22 (57.9%)	
Smoking, n (%)	28 (73.7%)	21 (55.3%)	
Primary outcomes			**P-value**
Bleeding cessation, n (%)	38 (100%)	33 (86.8%)	0.021
Rebleeding within 30 minutes, n (%)	2 (5.3%)	9 (23.7%)	0.022

Table 2: Stratified Analysis of Bleeding Cessation and Rebleeding Rates by Demographic and Clinical Subgroups

Subgroup	Outcome	Tranexamic Acid (n=38) n (%)	Adrenaline (n=38) n (%)	p-value
Sex				
Male (n=55)	Bleeding cessation	32 (100)	19 (82.6)	**0.014**
	Rebleeding	2 (6.3)	6 (26.1)	**0.040**
Female (n=21)	Bleeding cessation	6 (100)	14 (93.3)	0.517
	Rebleeding	0 (0)	3 (20.0)	0.230
Smoking Status				
Smoker (n=49)	Bleeding cessation	28 (100)	17 (81.0)	**0.016**
	Rebleeding	2 (7.1)	6 (28.6)	**0.045**
Non-smoker (n=27)	Bleeding cessation	10 (100)	16 (94.1)	0.434
	Rebleeding	0 (0)	3 (17.6)	0.159
Body Mass Index				
<25 kg/m² (n=50)	Bleeding cessation	25 (100)	19 (79.2)	**0.016**
	Rebleeding	1 (4.0)	7 (29.2)	**0.017**
≥25 kg/m² (n=26)	Bleeding cessation	13 (100)	13 (100)	—
	Rebleeding	1 (7.7)	2 (14.3)	0.586
Disease Duration				
1–3 weeks (n=57)	Bleeding cessation	31 (100)	22 (84.6)	**0.024**
	Rebleeding	0 (0)	7 (26.9)	**0.002**
>3 weeks (n=19)	Bleeding cessation	7 (100)	11 (91.7)	0.433
	Rebleeding	2 (28.6)	2 (16.7)	0.539
Diabetes Mellitus				
Present (n=28)	Bleeding cessation	10 (100)	14 (77.8)	0.107
	Rebleeding	0 (0)	7 (38.9)	**0.023**
Absent (n=48)	Bleeding cessation	28 (100)	19 (95.0)	0.232
	Rebleeding	2 (7.1)	2 (10.0)	0.724
Hypertension				
Present (n=32)	Bleeding cessation	10 (100)	18 (81.8)	0.149
	Rebleeding	0 (0)	6 (27.3)	0.067
Absent (n=44)	Bleeding cessation	28 (100)	15 (93.8)	0.181
	Rebleeding	2 (7.1)	3 (18.8)	0.243