Bronchoscopic instillation of tranexamic acid to control bronchopulmonary bleeding

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Background Tranexamic acid (TA), a potent antifibrinolytic agent, has the potency to stop bleeding in a variety of medical and surgical conditions. However, its role in controlling airway bleeding is not yet proven. This study aimed to evaluate the efficacy of endobronchial administration of TA in controlling bronchopulmonary bleeding.

Materials and methods A prospective, comparative, observational study was carried out including 40 patients scheduled to undergo bronchoscopy. For management of hemoptysis or bronchoscopy-induced bleeding, patients were randomly subdivided into two groups of 20 patients each: the first group received endobronchial TA, whereas the second group received endobronchial cold saline±adrenaline.

Results In the TA group, 19 patients were responders and only one patient was a nonresponder and was further managed with endobronchial adrenaline. All 20 patients of the cold saline±adrenaline group were responders. No significant statistical difference was found between both groups with regard to systolic and diastolic blood pressures, heart rate, and oxygen saturation either before or after bronchoscopy. However, heart rate significantly increased after bronchoscopy both in the first ($P<0.001$) and the second group ($P=0.007$). Systolic blood pressure increased significantly ($P=0.001$) after bronchoscopy in the second group only. The amount of bronchoscopy-induced bleeding as well as the time required for bronchoscopic hemostasis significantly and directly correlated with the dose of TA ($r=0.535$, $P=0.015$, and $r=1.000$, $P<0.001$, respectively) and cold saline±adrenaline ($r=0.687$, $P=0.33$, $r=0.858$, $P<0.001$, respectively). TA did not result in any intrabronchoscopic and postbronchoscopic drug-related complications in any of the patients.

Conclusion Endobronchial installation of TA is an effective and safe modality of treatment for controlling nonlife-threatening bronchopulmonary bleeding.

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Introduction

Hemoptysis is a common and critical respiratory symptom that represents ~6.8% of outpatient pulmonary visits, 11% of admissions to pulmonary medicine departments, and 38% of patients referred for thoracic surgery [1].

Bronchoscopy, flexible or rigid, should be performed in patients presenting with hemoptysis, preferably during active bleeding, to identify the site as well as the cause of bleeding [2].

Endobronchial administration of ice-cold saline and adrenaline is widely considered to be the gold standard therapy for controlling hemoptysis [3].

Tranexamic acid (TA) is a synthetic derivative of the amino acid lysine that blocks the lysine-binding site of plasminogen to fibrin, thereby acting as a synthetic antifibrinolytic agent [4]. Over the past few years, intravenous or oral administration of TA has been widely used for prophylaxis and treatment of bleeding episodes in both medical and surgical patients [5].

Limited research exists on the role of endobronchial application of TA for the management of hemoptysis. On the basis of this, our study was undertaken in an attempt to evaluate the therapeutic effectiveness of endobronchial administration of TA versus cold saline with or without adrenaline in controlling bronchopulmonary bleeding.

Materials and methods

This prospective, comparative, observational study was conducted at the Bronchoscopy Unit of Ain Shams University Hospital and the National Institute of Chest Diseases at Embaba from March 2016 to December 2016. The present study included 40 patients scheduled for bronchoscopy. For management of presenting hemoptysis or bronchoscopy-induced bleeding, patients were randomly subdivided into two groups with 20 patients each: the first group received

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endobronchial administration of TA, whereas the second group received endobronchial administration of cold saline with or without adrenaline.

All patients were subjected to the following: detailed medical history taking with special focus on the presence of hemoptysis as a presenting complaint, thorough clinical examination, baseline vital data and laboratory investigations including complete blood picture, coagulation profile, as well as baseline imaging studies (plain chest radiography, computed tomography of the chest, and echocardiogram). Patients with contraindication for bronchoscopy [6] as well as patients presenting with spontaneous life-threatening hemoptysis (defined as >100–150 ml/h in patients with normal respiratory function tests or >50 ml/h in patients with known chronic respiratory failure) were excluded [5]. Informed consent was obtained from all patients before bronchoscopy, and the study was approved by the institutional ethics committee.

Endoscopic examination

Flexible bronchoscopy was performed using a commercially available bronchoscope (Pentax EB-1830T3 video bronchoscope; Tokyo, Japan and Pentax EB-1970TK video bronchoscope; Ricoh Imaging Company, Tokyo, Japan). Flexible bronchoscopy was performed under topical lidocaine anesthesia, supplemental oxygen, and pulse oximetry monitoring. Incremental doses of intravenous midazolam sedation were administered when needed as judged by the bronchoscopists.

Rigid bronchoscopy under general anesthesia with proper tube sizing was performed using Bryan Dumon Rigid Bronchoscope (Bryan Corp., Woburn, Massachusetts, USA).

Endobronchial cold saline±adrenaline protocol

For active bronchopulmonary bleeding, duration of 1.5 min was allowed for spontaneous hemostasis. If no hemostasis was achieved, endobronchial administration of 20 ml cold saline with a further observation period for hemostasis of 1.5 min was allowed. If hemostasis was not achieved even then, 20 ml of diluted adrenaline (1 mg adrenaline diluted in 200 ml cold saline) with a maximum of two doses of cold saline+adrenaline and an observation period of 1.5 min for hemostasis between the doses of diluted adrenaline were allowed. Again if no hemostasis was achieved, then patients were managed using balloon temponade, cryotherapy, or electrocautery.

Endobronchial tranexamic acid protocol

For active bronchopulmonary bleeding, duration of 1.5 min was allowed for spontaneous hemostasis. If no hemostasis was achieved, endobronchial administration of 20 ml of diluted TA (500 mg TA in 15 ml cold saline) with a maximum of three doses of TA and an observation period of 1.5 min for hemostasis between the doses of TA were allowed. If no hemostasis was achieved after a total of three doses of TA, then patients were further managed using cold saline±adrenaline. Again if no hemostasis was achieved, further management for bleeding was carried out using balloon temponade, cryotherapy, or electrocautery. The dosing of TA was determined according to previously published studies [5,7].

After completing bronchoscopy, patients were monitored closely for vital signs. All recorded intraoperative and postbronchoscopic complications were documented. Patients requiring postbronchoscopic hospital admission were identified. Follow-up visits were planned after 2 weeks or earlier in cases with recurrent bleeding.

Statistical analysis

Parametric numerical data are expressed as mean±SD, whereas nonparametric numerical data are expressed as numbers and percentages. Independent sample *t*-test was used to compare two groups with regard to quantitative variables. The χ^2-test was used to compare two groups with regard to qualitative variables. Pearson's correlation test was used to rank different variables against each other positively or inversely. Statistical significance was set at *P* value of less than 0.05. All statistical analyses were performed using statistical package for the social sciences software (SPSS for Windows, version 17.0; SPSS Inc., Chicago, Illinois, USA).

Results

A total of 40 patients undergoing bronchoscopy were included in this study. Patients were randomly subdivided into two study groups of 20 patients each: the first group received TA, whereas the second group received cold saline with or without adrenaline to control bronchopulmonary bleeding. Hemoptysis was the presenting complaint in five patients of the TA group with an estimated amount of bleeding ranging from 50 to 75 ml; the remaining 35 patients developed iatrogenic bronchoscopically induced bronchopulmonary bleeding that necessitated further hemostatic management. The basic characteristics of the included patients are presented in Table 1. All patients were matched for both age and sex. Moreover, baseline hemoglobin level and coagulation profiles were matched between both groups (Table 1).

Table 1 Basic Characteristics of included patients

	Tranexamic acid (*N*=20)	Cold saline±adrenaline (*N*=20)	*P*
Age (mean±SD) (years)	50.45±14.39	54.25±14.43	0.409
Sex (male/female) [*n* (%)]	14/6 (70/30)	15/5 (75/25)	0.723
Smoking status [*n* (%)]			
Never smoker	9 (45)	8 (40)	0.919
Exsmoker	4 (20)	5 (25)	
Current smoker	7 (35)	7 (35)	
Diagnosis [*n* (%)]			
Malignancy	11 (55)	16 (80)	
Bronchiectasis	2 (10)	0 (0)	0.262
Infection	2 (10)	1 (5)	
DPLD	2 (10)	0 (0)	
Others	3 (15)	3 (15)	
Etiology of airway bleeding [*n* (%)]			
Spontaneous	5 (25)	0 (0)	0.017
Iatrogenic bronchoscopically induced	15 (75)	20 (100)	
Comorbidities (no/yes) [*n* (%)]	17/3 (85/15)	14/6 (70/30)	0.256
Hb [range (mean±SD)] (g/dl)	9.5–16.5 (12.55±1.89)	10.4–15.5 (12.78±1.62)	0.688
Coagulation profile (mean±SD)			
PT	13.43±1.17	13.48±0.81	0.876
PTT	32.64±5.11	30.83±2.48	0.162
INR	1.09±0.13	1.14±0.12	0.230
Bronchoscopic procedure [*n* (%)]			
Fiberoptic bronchoscopy	9 (45)	13 (65)	
Rigid bronchoscopy	5 (25)	2 (10)	
Fiberoptic and rigid (bleeding due to fiberoptics)	1 (5)	2 (10)	0.460
Fiberoptic and rigid (bleeding due to rigid bronchoscopy)	0 (0)	1 (5)	
Fiberoptic bronchoscopy+BL	2 (10)	1 (5)	
Fiberoptic bronchoscopy+TBNA	1 (5)	1 (5)	
Fiberoptic bronchoscopy+TBLB	2 (10)	0 (0)	
Bronchoscopic bleeding (mean±SD) (ml)	54.75±27.31	43±22.97	0.149
Time for bronchoscopic hemostasis (mean±SD) (min)	4.05±1.10	4.80±1.43	0.07
Bronchoscopic complications [*n* (%)]			
No	4 (20)	0 (0)	
Pneumothorax	1 (5)	0 (0)	0.091
Bleeding	15 (75)	19 (95)	
Pneumothorax and bleeding	0 (0)	1 (5)	

BL, bronchial lavage; DPLD, diffuse parenchymal lung disease; Hb, hemoglobin; INR, international normalization ratio; PT, prothrombin time; PTT, partial thromboplastin time; TBLB, transbronchial lung biopsy; TBNA, transbronchial needle aspiration.

Among the 20 patients receiving TA, 19 patients were responders: nine responded to 500 mg TA, eight responded to 1000 mg TA, whereas two patients responded to 1500 mg TA. Only one patient failed to respond to TA, and local endobronchial adrenaline was administered to control bleeding (Fig. 1). The diagnosis of the nonresponder case was metastatic lung cancer.

All 20 patients receiving cold saline with or without adrenaline were responders: three responded to cold saline only, 11 responded to a single dose of 20 ml cold saline with 1 mg adrenaline, whereas six patients responded after administration of 20 ml cold saline with 1 mg adrenaline twice (Fig. 2). None of the cases in either groups required balloon temponade, cryotherapy, or electrocautery for bleeding control.

Among the 40 patients, 29 patients underwent fiberoptic bronchoscopy, seven patients underwent rigid bronchoscopy, and the remaining four patients underwent combined fiberoptic and rigid bronchoscopy. The bronchoscopic procedure was complicated by pneumothorax in two cases (Table 1).

Malignancy represented the most prevalent indication for bronchoscopy in the included patients: 27 (67.5%) patients were diagnosed with malignancy, two (5%) cases had bronchiectasis, three (7.5%) cases had chest infection and pneumonia, two (5%) cases were diagnosed with diffuse parenchymal lung disease, whereas the remaining six (15%) cases were diagnosed with chronic obstructive pulmonary disease, hamartoma, sarcoidosis, and tracheal stenosis (Table 1). The amount of bronchoscopy-induced bleeding as well as time for

bronchoscopic hemostasis did not differ significantly between the two study groups (Table 1).

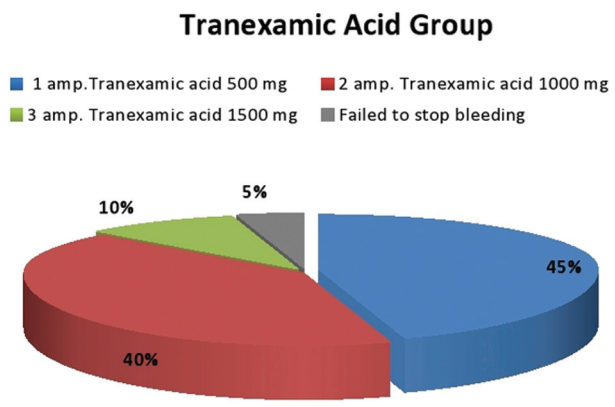
On comparing both groups with regard to systolic and diastolic blood pressures, heart rate, and oxygen saturation either before or after bronchoscopy, no significant statistical difference was found ($P>0.05$). However, on comparing the same variables within the same group before and after bronchoscopy, heart rate significantly increased after bronchoscopy both in the TA group ($P<0.001$) and in the cold saline±adrenaline group ($P=0.007$). Oxygen saturation did not differ significantly either in the TA ($P=0.20$) or in the cold saline±adrenaline group ($P=0.33$) before or after bronchoscopy. Systolic blood pressure increased significantly ($P=0.001$) only in the cold saline ±adrenaline group, whereas it did not differ significantly in the TA group ($P=0.079$). Diastolic blood pressure did not differ significantly either in the TA ($P=0.09$) or the cold saline±adrenaline group ($P=1.00$) before or after bronchoscopy (Table 2).

The amount of bronchoscopy-induced bleeding as well as the time for bronchoscopic hemostasis significantly and directly correlated with the dose of the hemostatic agent used in both the TA group ($r=0.535$, $P=0.015$, and $r=1.000$, $P<0.001$, respectively) and the cold saline±adrenaline group ($r=0.687$, $P=0.001$, $r=0.858$, $P<0.001$, respectively, Table 3).

In all five cases that presented with hemoptysis, TA was applied and resulted successfully in controlling the bleeding; however, the amount of presenting hemoptysis in these cases did not correlate significantly with the dose of TA ($r=0.535$, $P=0.353$, Table 3).

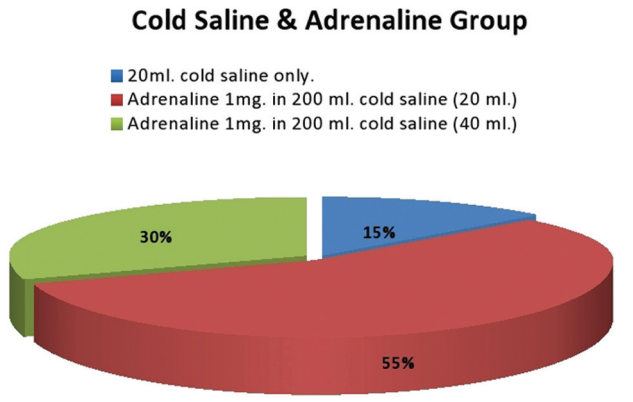
In all cases, bleeding did not recur within 2 weeks after bronchoscopy.

Figure 1



Tranexamic acid group

Figure 2



Cold saline and adrenaline group

Table 2 Comparison between vital signs before and after bronchoscopy

Vital signs	Tranexamic acid ($N=20$)	Cold saline±adrenaline ($N=20$)	P
Heart rate (mean±SD) (beats/min)			
Before	87±13.46	87.20±10.19	0.96
After	95±15.67	101.30±23.66	0.33
P (paired difference)	<0.001	0.007	
SBP (mean±SD) (mmHg)			
Before	123.50±16.23	115.50±14.68	0.11
After	129±23.82	127.50±16.82	0.82
P (paired difference)	0.079	0.001	
DBP (mean±SD) (mmHg)			
Before	74.50±11.86	74±11.88	0.84
After	78.50±14.24	74±11.88	0.29
P (paired difference)	0.09	1.00	
SO_2 (mean±SD) (%)			
Before	95.55±2.16	95.25±1.94	0.65
After	96.15±1.69	94.60±3.20	0.06
P (paired difference)	0.20	0.33	

DBP, diastolic blood pressure; SBP, systolic blood pressure; SO_2, oxygen saturation.

Table 3 Correlation between hemostatic agents and hemostasis, bronchoscopy-induced bleeding, and amount of presenting hemoptysis

	Tranexamic acid		Cold saline±adrenaline	
	r	*P*	*r*	*P*
Bronchoscopy-induced bleeding	0.535	0.015	0.687	0.001
Time for bronchoscopic hemostasis	1.000	<0.001	0.858	<0.001
Amount of presenting hemoptysis	0.535	0.353	–	–

All patients were managed at the outpatient clinics, and only two patients were admitted after bronchoscopy: one case was admitted for 6 days for the management of pneumothorax, whereas the other case was admitted for 4 days to complete the course of parenteral antibiotics.

No mortality was reported in either group of patients. None of the patients in the TA group developed drug-related complications. As for the cold saline±adrenaline group, only one patient developed drug-related sinus tachycardia.

Discussion

This study proved the effective role of endobronchial administration of TA in controlling nonlife-threatening bleeding in cases presenting with hemoptysis as well as in cases with bronchoscopically induced bleeding without any significant complications. Its effectiveness is comparable with the gold standard cold saline and adrenaline; however, it carries the advantage of being safer with the least side-effects. Furthermore, the time for bronchoscopic hemostasis was comparable in both groups. Thus, TA can be regarded as a safe alternative to adrenaline, especially in patients with contraindications to the latter. Of note, all five cases presenting with hemoptysis in our study were successfully controlled with endobronchial administration of TA.

A recent study showed that endobronchial bolus TA (500–1000 mg) was highly effective in treating massive bleeding following bronchoscopic procedures in two patients with lung cancer [5]. Another study showed that hemostasis was achieved in 14 malignant patients with iatrogenic bleeding following endobronchial administration of 15 ml saline containing 500 mg TA [7].

Malignancy was the most frequent diagnosis among patients included in this study. This was not surprising because malignant airway tumors are more likely to present with hemoptysis and to further bleed during forceps biopsy or brushing [8].

Our study investigated the hemodynamic effects of TA compared with adrenaline. The results showed that TA was safer with respect to alterations in blood pressure and did not result in any significant alteration in both systolic and diastolic blood pressures. Adrenaline, on the other hand, resulted in significant increase in postbronchoscopic systolic blood pressure. Similarly, a previous study investigated the effects of endobronchial administration of adrenaline of different concentrations on blood pressure and heart rate. All adrenaline doses resulted in an immediate increase in systolic blood pressure [9].

Patients in the adrenaline group developed significant increases in postbronchoscopic heart rate, and in one case sinus tachycardia was observed. This finding is in accordance with the well-recognized evidence of cardiac arrhythmias following topical endobronchial application of epinephrine [9,10] even at doses as low as 0.1 mg [11].

Surprisingly, TA resulted in a significant increase in postbronchoscopic heart rate. This was astonishing because, to the best of our knowledge, no previous evidence exists that suggests this effect of endobronchial TA on heart rate. A possible explanation for this finding might be procedure-related stress experienced by the patients undergoing bronchoscopy, resulting in increase in heart rate. However, further evaluation regarding this finding is required.

In our study, although the time for bronchoscopic hemostasis correlated equally with the dose of the hemostatic agent used in both groups, the amount of bronchoscopy-induced bleeding correlated more with the dose of adrenaline than with the dose of TA. Thus, with an increase in bronchoscopy-induced bleeding, less parallel increase in the dosage of TA is needed to control this bleeding in comparison with the more steep increase in the dosage of adrenaline needed to control the same amount of bleeding.

The doses and dilutions of adrenaline previously suggested by textbooks, publications, and guidelines for the management of bronchoscopic airway bleeding vary widely from small amounts (1 : 100

000 solution) up to 20 ml of a 1 : 20 000 solution [8,12].

It is worth mentioning that the low-dose protocol used for the dilution of adrenaline (20 ml of 1 mg adrenaline diluted in 200 ml cold saline i.e. 0.1 mg diluted adrenaline/dose) implemented in our study was adopted by the authors in an attempt to use the least concentration of adrenaline, thereby reducing the possible drug-related systemic complications of adrenaline.

Our study has several strengths: patients in both study groups were matched for several important variables including age, sex, smoking status, diagnosis, comorbidities, bronchoscopic procedure, as well as baseline hemoglobin levels and coagulation profiles. Moreover, the prospective design of our study enabled us to accurately extract all data related to the included patients. The effectiveness of TA was compared with the well-known standard therapy for controlling bronchopulmonary bleeding using cold saline and adrenaline. Finally, the amount of bronchoscopic bleeding was matched for both groups, and this carried great importance in further considering the results of this study.

Conclusion

Endobronchial installation of TA is an effective and safe modality of treatment for controlling nonlife-threatening bronchopulmonary bleeding. Further prospective studies are needed to evaluate the effectiveness of different local techniques of TA application, including inhalation of TA as well as intralesional injection, especially in mass lesions.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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