CHEST

Inhaled Tranexamic Acid for Hemoptysis Treatment

A Randomized Controlled Trial

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BACKGROUND: Tranexamic acid (TA) is an antifibrinolytic drug currently used systemically to control bleeding. To date, there have been no prospective studies of the effectiveness of inhaled TA for the treatment of hemoptysis.

OBJECTIVES: The goal of this study was to prospectively assess the effectiveness of TA inhalations (ie, nebulized TA) for hemoptysis treatment.

METHODS: This analysis was a double-blind, randomized controlled trial of treatment with nebulized TA (500 mg tid) vs placebo (normal saline) in patients admitted with hemoptysis of various etiologies. Patients with massive hemoptysis (expectorated blood > 200 mL/24 h) and hemodynamic or respiratory instability were excluded. Mortality and hemoptysis recurrence rate were assessed at 30 days and following 1 year.

RESULTS: Forty-seven patients were randomized to receive TA inhalations (n = 25) or normal saline (n = 22). TA was associated with a significantly reduced expectorated blood volume starting from day 2 of admission. Resolution of hemoptysis within 5 days of admission was observed in more TA-treated patients than in those receiving placebo (96% vs 50%; $P < .0005$). Mean hospital length of stay was shorter for the TA group (5.7 ± 2.5 days vs 7.8 ± 4.6 days; $P = .046$), with fewer patients requiring invasive procedures such as interventional bronchoscopy or angiographic embolization to control the bleeding (0% vs 18.2%; $P = .041$). No side effects were noted in either group throughout the follow-up period. In addition, a reduced recurrence rate was noted at the 1-year follow-up ($P = .009$).

CONCLUSIONS: TA inhalations can be used safely and effectively to control bleeding in patients with nonmassive hemoptysis.

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KEY WORDS: fibrinolysis; hemoptysis; tranexamic acid

ABBREVIATIONS: LOS = length of stay; RCT = randomized controlled trial; TA = tranexamic acid

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Hemoptysis may be a symptom of diverse respiratory conditions. The severity of hemoptysis can also vary, ranging from minimal blood-streaked sputum to immediate life-threatening hemorrhage. Effective management of significant hemoptysis includes several interventional procedures, consisting of angiographic bronchial artery embolization and various endobronchial interventions to control bleeding.[1] However, there is no effective medical therapy for hemoptysis, other than treatment of the specific cause (eg, antibiotics for infection).

Tranexamic acid (TA) is a synthetic lysine analogue with antifibrinolytic activity manifested by inhibiting the activation of plasminogen to plasmin and by blocking the action of plasmin on fibrin.[2,3] Systemic administration of TA may reduce surgical blood loss, improve abnormal uterine bleeding, and control traumatic hemorrhage (as reviewed elsewhere[2,3]). Topical application of TA is also effective in reducing surgical blood loss and the need for blood transfusions.[4]

Nebulized TA was described as a treatment for hemoptysis in several case reports and in a small case series[1] but has not, to the best of our knowledge, ever been assessed in a formal study. The goal of the present study was to evaluate the effectiveness of TA in patients admitted with hemoptysis in a prospective, double-blinded, placebo-controlled, randomized controlled trial (RCT).

Patients and Methods

Patient Selection

Adult patients (aged ≥ 18 years) were screened for the study if they were admitted to our department with hemoptysis during the previous 24 h. Exclusion criteria included: massive hemoptysis (expectorated blood > 200 mL/24 h), respiratory or hemodynamic instability, pregnancy, renal failure (defined as creatinine level > 3 mg/dL or need for renal replacement therapy), hepatic failure (bilirubin level > 2 mg/dL or aspartate aminotransferase > 3 times the upper limit of normal), coagulopathy (international normalized ratio > 2), known hypersensitivity to TA, or treatment with TA prior to screening.

Study Groups

Patients were randomized to treatment with nebulized TA 500 mg/5 mL or normal saline 0.9% 5 mL as the placebo control, three times daily. The treatment samples were prepared by the Meir Medical Center's pharmacy and provided to the Pulmonary Department in identical unmarked vials, to allow blinding of the treating team, as well as the patients, to the trial group allocation. Inhaled therapy with the trial drugs was given for up to 5 days from admission (with the duration of therapy determined by the treating physician). Anticoagulant and antiaggregant therapy was stopped until resolution of bleeding. Additional evaluation and therapy were chosen by the treating physicians who were blinded to the trial group allocation.

Measured Variables

Variables collected during the trial included patient data, age, sex, smoking status, medical history such as known pulmonary diseases and medications, and results of imaging and laboratory studies. Patients were instructed to collect the expectorated blood in a measuring cup daily during the trial to measure the amount of bleeding. The cause of hemoptysis was determined by the treating physicians and authors based on clinical, laboratory, and imaging data.

Outcome

There were two primary outcomes: the rate of patients with a complete resolution of hemoptysis during the first 5 days from admission, and the difference in the daily volume of expectorated blood between the two study groups. Secondary outcomes included rates of interventional bronchoscopy; angiographic embolization, or surgery between the groups; and the mean hospital length of stay (LOS). The rate of side effects associated with the treatment in each group served as a safety outcome. Follow-up data (30 days and 1 year) were collected for analysis of mortality and recurrence rates.

Statistical Analysis

Based on the assumption that resolution of bleeding will be achieved in 90% of the patients in the TA group and 55% of the placebo group, the sample size was estimated to be equal to 25 in each group. We added 10% to cover for dropouts for any reason to reach a total of 60 patients.

Continuous variables are presented as mean or median with SDs, or as numbers and percentages for nominal parameters. Comparisons between the two study groups were made by using the Student *t* test, the Mann-Whitney test, the Fisher exact test, or the Pearson χ^2 test according to the scale-measured variables. The difference between the groups was considered statistically significant at a two-sided *P* value of < .05. All statistical analyses were conducted by using SPSS version 23 (IBM SPSS Statistics, IBM Corporation).

Ethical Approval

This study was conducted in accordance with the amended Declaration of Helsinki. Local institutional review boards or independent ethics committees approved the protocol, and written informed consent was obtained from all patients. The study was approved by the Meir Medical Center Institutional Review Board in accordance with the Declaration of Helsinki and with the Good Clinical Practice Guideline (0096-11-MMC). The study was registered in the United States National Institutes of Health database.[5]

Results

Patient Characteristics

Fifty-five patients were screened for the study. Following an internal analysis, the study was terminated after the successful recruitment of 47 patients when the perceived superiority of the TA therapy was noted. In total, the TA group included 25 patients, and the placebo group included 22 patients (Fig 1). The mean age of the participants was 66 ± 11 years. Most of the patients

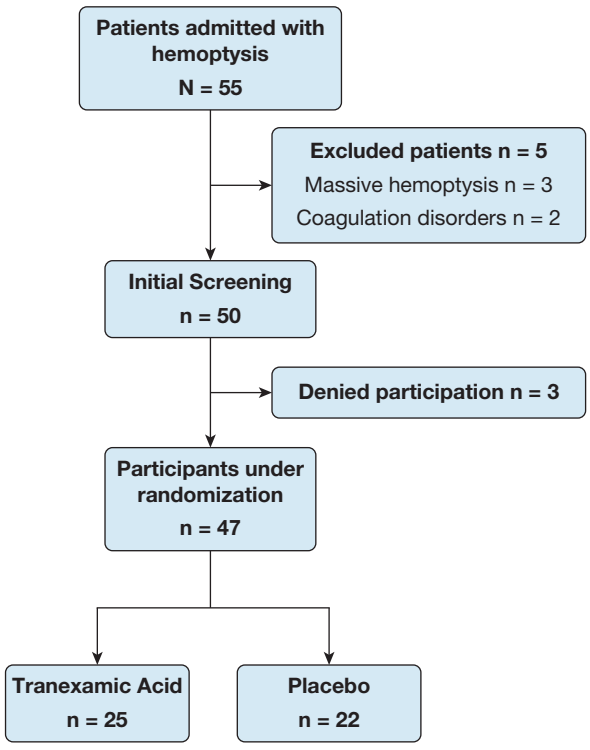

Figure 1 – *Flowchart of participants' recruitment.*

were male (74%) and smokers (64%) with a history of lung disease (66%). Nine patients in each group had lung malignancy, comprising 36% and 41% of the TA and placebo groups, respectively. More than one half of the patients were treated with anticoagulant or antiplatelet drugs at admission. There was no difference between the groups in the administration of antibiotics (71% and 73% in the control and TA groups). There were no significant differences in admission characteristics between the two study groups (Table 1) or in the causes of hemoptysis ($P = .20$) (Table 2).

Nebulized TA Treatment Reduced the Amount of Expectorated Blood

Resolution of bleeding was achieved by 5 days in 96% of the patients in the TA group vs 50% in the placebo group ($P < .0005$) (Fig 2A). In addition, TA treatment was associated with significantly reduced amounts of expectorated blood, starting from day 2 of admission through day 5 ($P < .01$) (Fig 2B).

Nebulized TA Treatment Reduced LOS and Additional Interventional Procedures

Chest CT imaging was performed in 84% and 78% ($P = .56$) of the patients, and bronchoscopy in 40% and 45% ($P = .3$), in the TA and placebo groups, respectively. In two patients in the placebo group (9.1%), interventional bronchoscopy was required, whereas it was unnecessary in the TA group. The two interventional bronchoscopies were performed because

TABLE 1] Patient Characteristics

Parameter	Tranexamic Acid (n = 25)	Placebo (n = 22)	*P* Value
Age, median (range), y	68 (49-86)	69 (30-84)	.89
Male sex	18 (72%)	17 (77%)	.68
History of smoking	14 (56%)	16 (73%)	.31
History of TB	4 (16%)	0	.11
Malignancy	9 (36%)	9 (41%)	.73
Lung diseases			
COPD	4 (16%)	9 (41%)	
Bronchiectasis	9 (36%)	6 (27%)	
Asthma	2 (8%)	0	
Pulmonary fibrosis	1 (4%)	0	
Total	16 (64%)	15 (68%)	.23[a]
Anticoagulation			
Warfarin	3 (12%)	1 (4.5%)	
LMWH	2 (8%)	1 (4.5%)	
NOAC	1 (4%)	0	
Antiplatelets	8 (32%)	11 (50%)	
Total	14 (56%)	13 (59%)	.59[a]
Volume of bleeding at admission, mean ± SD, mL	51 ± 47	35 ± 29	.34

LMWH = low-molecular-weight heparin; NOAC = novel oral anticoagulants.
[a]The $\chi 2$ test for the group of lung diseases and anticoagulation treatments.

TABLE 2] Causes of Hemoptysis

Cause	Tranexamic Acid (n = 25)	Placebo (n = 22)
COPD	0	3 (14%)
Bronchiectasis	11 (44%)	5 (23%)
Infection	3 (12%)	2 (9%)
Malignancy	9 (36%)	8 (36%)
Unknown	2 (8%)	4 (18%)

The χ^2 test for cause of bleeding was $P = .2$.

of severe bleeding; one also involved intubation. Urgent angiographic embolization was required to control bleeding in two noncancer patients in the placebo group (9.1%), and in none of the patients in the TA group. No surgical procedures were performed in either group. In total, 18.2% of the patients in the placebo group vs none in the TA group required an interventional procedure to control bleeding ($P = .041$) (Fig 3A). The average hospital LOS for the placebo group was 7.8 days; for the TA group, it was 5.7 days ($P = .046$) (Fig 3B).

No bronchospasms or any other adverse effects from the nebulized therapy occurred in either group.

Long-term Effects of Nebulized TA Treatment of Hemoptysis Outcome

We summarized the follow-up patient data regarding mortality rates and the recurrence of hemoptysis at 30 days and 1 year following the event. The TA group showed significantly improved 30-day outcomes compared with the placebo group (χ^2 analysis of the combined outcomes was $P = .04$) (Table 3). Following 1 year, although there was no difference in the mortality rates, the recurrence rate was significantly lower in the TA group ($P = .0092$).

Discussion

The present study compared nebulized TA with placebo for the treatment of hemoptysis; TA was associated with higher rates of hemoptysis resolution and a quicker decrease in the amount of bleeding starting from the second day of therapy. No adverse effects of treatment were noted in either group. The advantages of TA therapy translated into clinical benefits of a shorter hospitalization term and a reduced need for interventional procedures to control bleeding.

The causes of hemoptysis in this study were diverse and mostly comprised bronchiectasis, respiratory infections, and malignancy. These results are in accordance with contemporary studies of the causes of hemoptysis in areas with a low prevalence of TB.[6-8] In a retrospective nationwide study from France, no etiology was identifiable for one half of patients admitted for episodes of hemoptysis, which were initially considered cryptogenic.[8] However, a specific diagnosis, mostly lung cancer, was subsequently identified in a significant proportion of these patients, again corresponding to similar reports. In addition, the tendency of patients in the present study to be elderly male subjects who smoked is consistent with previous publications; in the present study, however, patients were on the average older than those of the previous reports.[6-8] More than one half of the patients in our study were treated with antiplatelet drugs or anticoagulation on admission. Because pulmonary infections such as bronchitis could be a major cause for hemoptysis in smokers,[9] and nearly one third of the study patients were presenting with bronchiectasis, most patients were treated with antibiotics during admission. These findings also match the present situation in developed countries. Thus, this

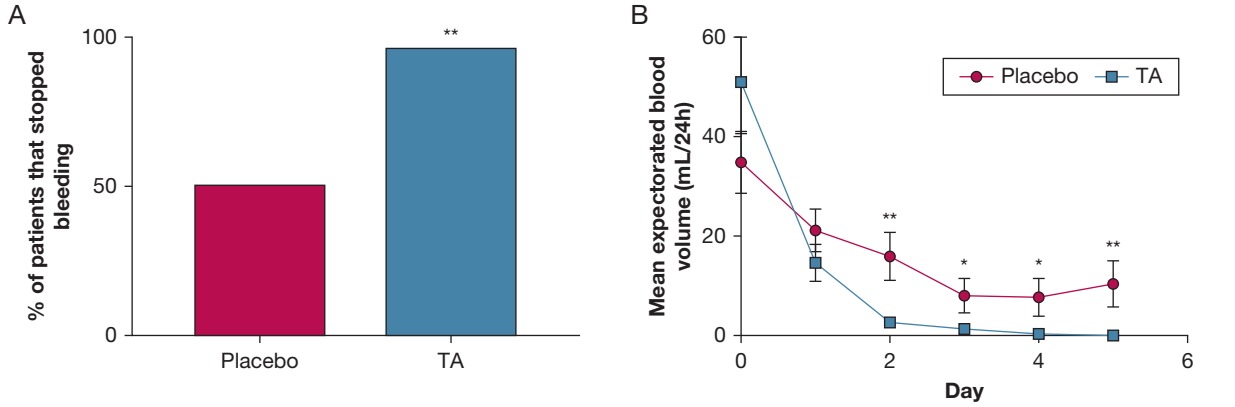

Figure 2 – *Nebulized TA is effective for hemoptysis treatment. A, The total percentage of patients who stopped bleeding in each group. **P < .001, Fisher exact test. B, The amount of expectorated blood (milliliters) measured every 24 h. *P < .05, **P < .01, Student t test. Placebo is normal saline. Error bars represent the error of the mean ± SEM. TA = tranexamic acid.*

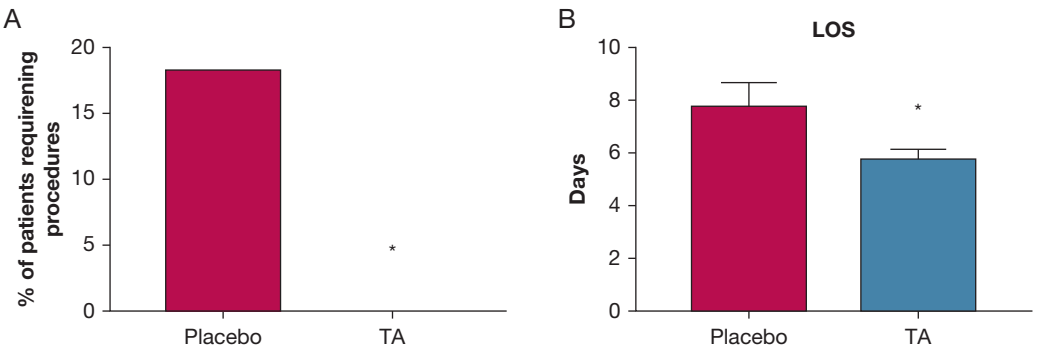

Figure 3 – *Nebulized TA reduced hospital length of stay and additional interventional procedures. A, The total percentage of patients who required either interventional bronchoscopy or urgent angiographic embolization in each group. *P < .05, Fisher exact test. B, The average length of stay of patients in each group. *P < .05, Student t test. Placebo is normal saline. Error bars represent the error of the mean ± SEM. See Figure 1 legend for expansion of abbreviation.*

study population seems to well represent current conditions in regions not endemic for TB, which may make our findings generalized. The average LOS for the placebo group was 7.8 days, which was similar to previously reported studies describing mild to moderate bleeding.[6]

Although TA is commonly used to control bleeding in various scenarios, its use in patients with hemoptysis has not been thoroughly investigated. Two review articles evaluated the effectiveness of TA in patients with hemoptysis. The Cochrane review[11] included two RCTs that included systemic TA administration (orally[10] or intravenously[12]) to patients with hemoptysis. Pooled results revealed a significant reduction in bleeding time in patients treated with TA, compared with placebo, although had no effect on remission of hemoptysis. No side effects were noted. The authors concluded that evidence to judge whether antifibrinolytic agents should be used to treat hemoptysis from any cause remains insufficient. A different review by Moen et al[13] assessed studies describing various forms, dosages, and length of treatments with TA in patients with different etiologies for hemoptysis; in addition to previous RCTs, it included observational studies, case series, and case reports. The authors concluded that TA may reduce the duration and volume of bleeding, with a low risk for side effects, but they were reluctant to give strong recommendations.

Following the aforementioned reviews, Bellam et al[14] published another RCT describing patients with submassive hemoptysis who were randomized to receive IV TA or placebo. The severity of hemoptysis decreased in patients treated with TA, with no adverse effects. The authors suggested that TA can be used as a bridging therapy until definitive measures to control the bleeding are undertaken.

Publications regarding nebulized TA treatment, however, were limited to case reports or case series, mostly including patients with advanced malignancies. Nevertheless, in these publications, nebulized TA was found to be highly effective in controlling the bleeding, although results may have been skewed because of publication bias.[15-17]

The inhaled form of administration was shown to be faster and more effective than systemically administered medications in various conditions such as lung cancer.[18] Inhaled aerosolized medications are routinely used for various chronic lung diseases such as COPD, asthma, and bronchiectasis, and were shown to offer several advantages over the systemically administered medications. These include more rapid onset of action

TABLE 3] Follow-up Data: 30 Days and 1 Year

	30 Days			1 Year		
Outcome	Tranexamic Acid (n = 25)	Placebo (n = 22)	*P* Value	Tranexamic Acid (n = 25)	Placebo (n = 22)	*P* Value
Recurrent hemoptysis	2 (8%)	6 (27.3%)	.12	3 (4%)	11 (22.7%)	< .01
Death	0	2 (10%)	.21	4 (16%)	4 (18%)	< .01

for drugs such as β-adrenergic agonists compared with oral medication, high luminal doses for inhaled antibiotics when used to treat endobronchial infection, and an improved therapeutic index compared with systemic delivery for other classes of drugs such as corticosteroids.[19-21] Based on these data, we assumed that the inhaled TA would be at least as effective topically as it was systemically. In addition, we also assumed that side effects such as thrombosis were more likely to occur in the IV form and not in the inhalation type of administration.

To the best of our knowledge, this study is the first prospective RCT to assess the effect of nebulized TA in patients admitted with hemoptysis, and as such, it contributes significantly to the current data. Nonetheless, our study has several limitations. Patients with massive hemoptysis were excluded, as these individuals require emergent interventions to control bleeding. The small number of participants does not allow specific assessment of TA in different scenarios of hemoptysis, such as anticoagulant therapy or varying etiologies. However, as mentioned earlier, the wide inclusion criteria and apparently representative participants seem to lead to generalized results. In addition, the fact that positive effects of nebulized TA were consistent in different measured outcomes, including not only the volume of expectorated blood but also clinical outcomes of hospital LOS and requirements for intervention, supports the efficiency of this therapy.

Conclusions

Nebulized TA is an effective and safe option for patients admitted with nonmassive hemoptysis. It can be used as a sole therapy, as well as an adjunct to other interventions in patients with hemoptysis of various causes.

Acknowledgments

Author contributions: D. S. takes full responsibility for the content of the manuscript, including the data and analysis. O. W., L. I.-S., and D. S. had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis, including and especially any adverse effects. E. G., A. G., G. E. S., and L. I.-S. contributed substantially to the study design, data analysis and interpretation, and the writing of the manuscript.

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