CHEST

Tranexamic Acid vs Adrenaline for Controlling Iatrogenic Bleeding During Flexible Bronchoscopy

A Double-Blind Randomized Controlled Trial

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BACKGROUND: The most commonly used topical hemostatic agents during flexible bronchoscopy (FB) are cold saline and adrenaline. Data on use of other agents such as tranexamic acid (TXA) for this purpose are limited.

RESEARCH QUESTION: Is TXA effective and safe in controlling iatrogenic bleeding during FB compared with adrenaline?

STUDY DESIGN AND METHODS: We conducted a cluster-randomized, double-blind, single-center trial in a tertiary teaching hospital. Patients were randomized in weekly clusters to receive up to three applications of TXA (100 mg, 2 mL) or adrenaline (0.2 mg, 2 mL, 1:10000) after hemostasis failure after three applications of cold saline (4 ° C, 5 mL). Crossover was allowed (for up to three further applications) before proceeding with other interventions. Bleeding severity was graded by the bronchoscopist using a visual analog scale (VAS; 1 = very mild, 10 = severe).

RESULTS: A total of 2,033 FBs were performed and 130 patients were randomized successfully to adrenaline (n = 65) or TXA (n = 65), whereas 12 patients had to be excluded for protocol violations (two patients from the adrenaline arm and 10 patients from TXA arm). Bleeding was stopped in 83.1% of patients (54/65) in both groups ($P = 1$). The severity of bleeding and number of applications needed for bleeding control were similar in both groups (adrenaline: mean VAS score, 4.9 ± 1.3 [n = 1.8 ± 0.8]; TXA: mean VAS score, 5.3 ± 1.4 [n = 1.8 ± 0.8]). Both adrenaline and TXA were more successful in controlling moderate bleeding (86.7% and 88.7%, respectively) than severe bleeding (40% and 58.3%, respectively; $P = .008$ and $P = .012$, respectively) and required more applications for severe bleeding (3.0 ± 0 and 2.4 ± 0.5, respectively) than moderate bleeding (1.7 ± 0.8 and 1.7 ± 0.8, respectively) control ($P = .006$ and $P = .002$, respectively). We observed no drug-related adverse events in either group.

INTERPRETATION: We found no significant difference between adrenaline and TXA for controlling noncatastrophic iatrogenic endobronchial bleeding after cold saline failure, adding to the body of evidence that TXA can be used safely and effectively during FB.

TRIAL REGISTRY: ClinicalTrials.gov; No.: NCT04771923; URL: www.clinicaltrials.gov

CHEST 2023; 163(4):985-993

KEY WORDS: adrenaline; bronchoscopy; endobronchial bleeding; tranexamic acid

FOR EDITORIAL COMMENT, SEE PAGE 751

ABBREVIATIONS: FB = flexible bronchoscopy; SAE = serious adverse event; TBB = transbronchial biopsy; TXA = tranexamic acid; VAS = visual analog scale

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Take-home Points

Study Question: Is tranexamic acid (TXA) effective and safe in controlling iatrogenic bleeding during flexible bronchoscopy (FB) compared with adrenaline?

Results: No differences were found in the bleeding control rate between TXA and adrenaline. Bleeding was stopped in 83.1% of patients (54/65) in both groups ($P = 1$).

Interpretation: We found no significant difference between adrenaline and TXA for controlling non-catastrophic iatrogenic bleeding after cold saline failure, thus adding to the body of evidence that TXA can be used safely and effectively during FB.

Flexible bronchoscopy (FB) is one of the most fundamental diagnostic procedures for airway examination and sampling. The procedure is safe with a reported mortality between 0% and 0.1% and a complication rate ranging from < 0.1% to 11%.[1-3] The most common complication of diagnostic FB is bleeding, which can occur in 0.26% to 5% of patients, mostly depending on the procedures performed and patient characteristics.[4] The most widely used topical hemostatic agents for bleeding during diagnostic FB are cold saline and adrenaline. The proposed mechanism of action of both drugs is vasoconstriction of pulmonary vessels with consequent blood flow reduction and hemostasis promotion.[5]

Tranexamic acid (TXA) is an antifibrinolytic drug that competitively inhibits the activation of plasminogen. Both parenteral and topical TXA are used widely for hemostasis in trauma and various surgical settings after several randomized controlled trials confirmed their efficacy and safety.[6,7] A large retrospective Japanese nationwide study concluded that IV TXA may reduce the mortality, length of hospital stay, and health-care costs of patients with hemoptysis.[8] Furthermore, several small prospective studies investigated the use of TXA in airway bleeding with mostly positive results. TXA was used in a wide range of different forms, from prophylactic intratumoral injection and application via FB for airway bleeding after topical cold saline and adrenaline failure to TXA inhalations for hemoptysis.[9-12] To our knowledge, only one small randomized trial evaluated the role of TXA for bleeding control during FB. A total of 50 patients with hemoptysis or iatrogenic bleeding during diagnostic FB were randomized to either adrenaline or TXA after hemostasis failure of cold saline lavage. Although no significant difference was found in time to bleeding control between the two groups, only one patient in the TXA group vs eight patients in the adrenaline group required additional medication for bleeding control.[13]

Based on these data, we hypothesized that topical TXA is a safe and effective therapy for bleeding management during diagnostic FB. The aim of our study was to evaluate the effectiveness of topical TXA in iatrogenic airway bleeding and compared it with topical adrenaline in a prospective, double-blind, cluster randomized controlled trial.

Study Design and Methods

We conducted a pragmatic, cluster-randomized, double-blind, single-center trial in a tertiary teaching hospital during a 1-year period from February 22, 2021, through February 4, 2022. The trial was approved by the University Hospital Centre Zagreb institutional ethical review board (approval no.: 8.1-21/20-2; 02/21AG) and is registered with ClinicalTrials.gov (Identifier: NCT04771923) before the trial start. No changes to trial protocol, materials, or methods occurred after trial commencement.

Participants

All patients requiring diagnostic FB during the study period were assessed for eligibility and signed informed consent before the start of diagnostic FB. Patients requiring mediastinal staging with convex probe endobronchial ultrasound or peripheral bronchoscopy with radial probe endobronchial ultrasound were also screened and included in the study. Exclusion criteria included all relevant relative and absolute contraindications for FB and topical use of adrenaline and are described in detail in e-Appendix 1. All patients first received three applications of 5 mL of cold (4 °C) saline as the standard of care at our institution. Only patients with persistent bleeding were randomized, thus excluding patients with the mildest bleeding.

Interventions

Patients with bleeding during FB that was not controlled successfully after three applications of 5 mL of cold (4 °C) saline were randomized to receive up to three applications of TXA (2 mL of 50 mg/mL

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The abstract was presented at the European Respiratory Society International Congress, September 4-6, 2022, Barcelona, Spain and World Congress for Bronchology and Interventional Pulmonology, October 6-9, 2022, Marseille, France.

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DOI: https://doi.org/10.1016/j.chest.2022.10.013

solution; a total of 100 mg of TXA per application) or adrenaline (2 mL of 1:10,000 solution; a total of 0.2 mg of adrenaline per application). The adrenaline concentration and dose were determined as per usual institution protocol because no official consensus exists among different guidelines and publications on the optimal dose of adrenaline.[14] The drug solutions were prepared and prefilled into identical 2-mL syringes and labelled 1 and 2, depending on the weekly randomization. Each drug application was at least 60 s apart to allow time for visual assessment of clot formation and to standardize workflow between different bronchoscopists. If bleeding persisted, crossover was allowed (for up to three further applications 60 s apart) before proceeding with other interventions, thus ensuring that all patients receive adrenaline as the current standard of care at our institution. At the end of each procedure, the bronchoscopist noted the number of drug applications and severity of bleeding in the written bronchoscopy report.

Outcomes

The primary outcome was proportion of patients with successfully controlled bleeding in each arm. Bleeding control was assessed by the bronchoscopist by visual confirmation of clot formation. Secondary outcomes included the mean number of TXA or adrenaline applications necessary to control bleeding, number of recurrent bleeding episodes in each group, proportion of successfully controlled bleeding episodes in relationship to the severity of bleeding, indications for diagnostic FB, sampling methods during FB, and the number of adverse events in each group. The bleeding severity was graded by the bronchoscopist at the end of the procedure using a visual analog scale (VAS; 1 = very mild, 10 = very severe). An investigator meeting with the bronchoscopy staff was carried out on scaling the bleeding before the study start.

Sample Size

A previously published randomized trial comparing endobronchial TXA with adrenaline reported a 96% (24/25 patients) bleeding control rate in the TXA group and 68% (17/25 patients) in the adrenaline group.[13] Based on these data, a group sample size of 40 patients is required to detect this difference with 90% power and a significance level of 5%. However, given our previous clinical experience with adrenaline, we hypothesized that the bleeding control rate of adrenaline is at least 75%, thus requiring a group sample size of 61 patients to detect the difference with the same power and significance level.

Randomization

To minimize workflow interruption, instead of randomizing each patient separately, we randomized patients in weekly clusters. Each week during the study period was assigned randomly to TXA or adrenaline as the first medication to be used during that week. All patients with hemostasis failure after three applications of cold saline during the given week received the same first medication and the same second medication in case of hemostasis failure. The random allocation sequence was generated and supervised by a medical doctor in our institution who has no contact with the bronchoscopy suite and communicated to the supervising nurse. The supervising nurse prepared the drug solutions during the entire week and prefilled identical 2-mL syringes with adrenaline and TXA, labelling them with the number 1 or 2. If the week was assigned randomly to TXA, syringes containing TXA were labelled 1 and those containing adrenaline were labelled 2, and vice versa if the week was assigned randomly to adrenaline. When bleeding requiring drug application occurred, the bronchoscopist ordered drug 1 up to three times and, if necessary, drug 2 for up to three further applications, as described previously.

Blinding

The operating bronchoscopists, bronchoscopy nurses, patients, and the staff collecting data and assessing outcomes were blinded. The allocation was available only to the supervising medical doctor and nurse, who were not involved in performing the bronchoscopies or administering patient care in any way. The treating bronchoscopist could break blinding and continue hemostasis as per usual institutional protocol (repeated instillations of 5-mL aliquots of cold saline, up to five instillations of 2-mL 1:10,000 adrenaline solution, wedging of the bronchoscope and intubation with insertion of a balloon blocker, if indicated) at his or her own discretion if concerned about patient safety during the procedure, and those patients were excluded from the analysis.

Statistical Methods

Microsoft Excel (Microsoft) was used to tabulate data and calculate frequencies and percentages. MedCalc version 20.027 software (MedCalc Software) was used to calculate summary statistics as well to perform χ^2 tests, t tests, and Mann-Whitney U tests as appropriate. P values of $< .05$ were considered statistically significant.

Results

A total of 2,033 FBs were performed during the study period between February 22, 2021, and February 4, 2022, with 575 bleeding episodes with a mean VAS score of 3.6 ± 1.3. Bleeding was stopped successfully with cold saline in 432 patients (75.1%). One patient declined further treatment and was excluded, whereas the remaining 142 patients were randomized to either TXA or adrenaline (75 and 67 patients, respectively). Final analysis was performed in 130 patients; 11 patients were excluded from the final analysis because of protocol violations before unblinding and one patient was unblinded during the procedure by the operating bronchoscopist because of the severity of bleeding (Fig 1). Patient and procedure characteristics were similar for both groups (Table 1).

No significant difference was found in the primary outcome between TXA and adrenaline. Bleeding was stopped successfully in 54 of 65 patients (83.1%) in both groups (Fig 2). Additionally, the sensitivity analysis that was performed because of the disproportionate number of patients excluded from each group showed no significant change in the primary outcome (e-Appendix 2). The severity of bleeding and number of applications needed for bleeding control were similar in both groups (Fig 3). However, more severe bleeding episodes occurred in the TXA group (12/65 patients [18.5%]) than in the adrenaline

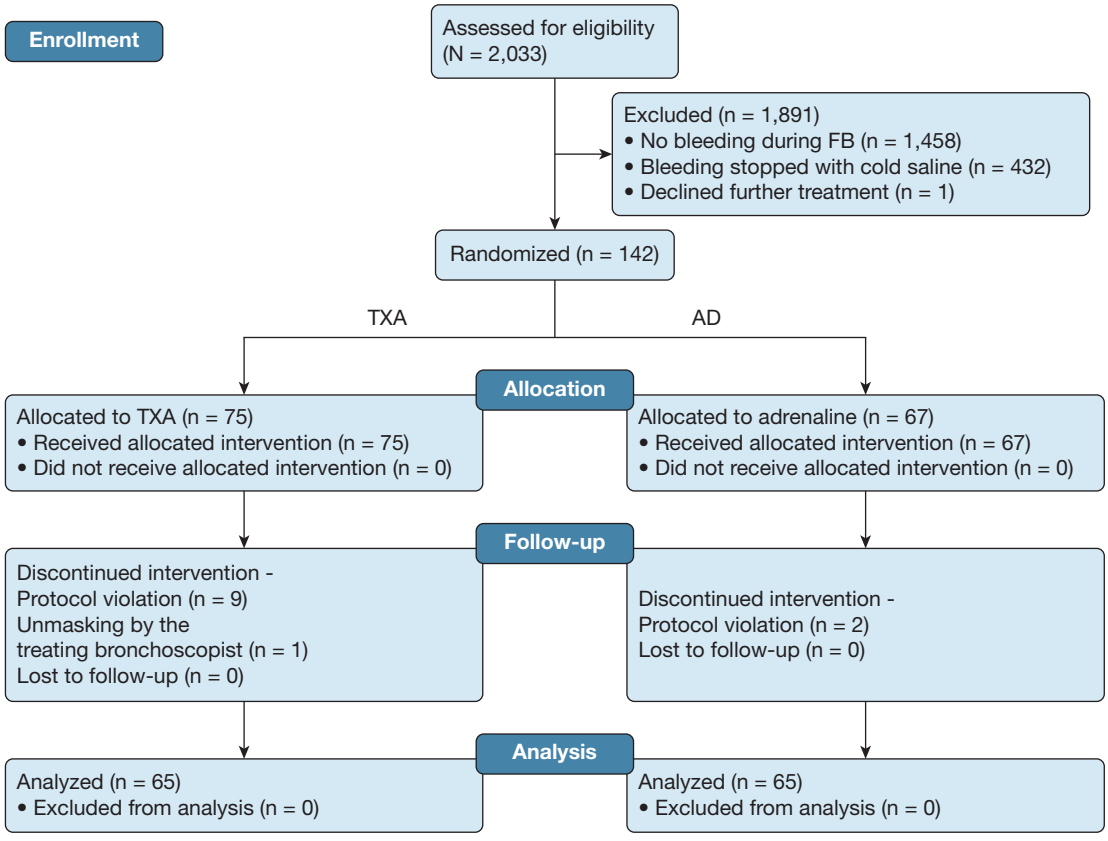

Figure 1 – *Consolidated Standards of Reporting Trials flow diagram. AD = adrenaline; FB = flexible bronchoscopy; TXA = tranexamic acid.*

group (5/65 patients [7.7%]; $P = .069$). Of the overall 575 bleeding episodes, 367 episodes (63.8%) were scored as mild (VAS score, 1-3), 184 bleeding episodes (32.0%) were scored as moderate (VAS score, 4-6), and 24 bleeding episodes (4.2%) were scored as severe (VAS score, 7+). No significant difference in the bleeding control rate was found between the adrenaline and TXA arms in patients with moderate (VAS score, 4-6; $P = .75$) and severe (VAS score, 7+; $P = .50$) bleeding. Both drugs were significantly more successful in controlling moderate bleeding than severe bleeding and required more applications for severe bleeding control (Fig 4). Overall, hemostasis was achieved successfully with cold saline in 367 of 367 patients (100%) with mild bleeding (VAS score, 1-3), 62 of 184 patients (33.7%) with moderate bleeding (VAS score, 4-6), and three of 24 patients (12.5%) with severe bleeding (VAS score, 7+; $P < .0001$). Most bleeding in the finally examined groups (n = 130) occurred after endobronchial biopsy (59.2%), followed by transbronchial biopsy (TBB; 16.9%), brushing (16.2%), and transbronchial needle aspiration (7.7%).

A total of nine serious adverse events (SAEs) occurred during the study period among the 2,033 FBs performed. Patients randomized to adrenaline experienced a total of three SAEs: the first patient experienced acute respiratory failure, the second experienced a transitory ischemic attack, and the third patient demonstrated recurrent bleeding after early termination of the procedure on patient request. Patients randomized to TXA experienced two SAEs; both required hospitalization because of recurrent bleeding, but were excluded from the analysis because of study protocol violation. Other SAEs that occurred during the study period were one episode of new-onset atrial fibrillation, one respiratory arrest during FB with successful resuscitation, and one episode of recurrent bleeding after initial successful hemostasis with two cold saline applications. Only one patient required ICU admission because of massive bleeding after renal cell carcinoma endobronchial metastasis biopsy, but was not included in the study at the operator's discretion.

Discussion

We found no significant difference between TXA and adrenaline for controlling noncatastrophic bleeding during FB after cold saline failure in this randomized

TABLE 1] Patient and Procedure Characteristics

Variable	Total (N = 130)	Adrenaline (n = 65)	Tranexamic Acid (n = 65)
Patient characteristics			
Age, y	67 (61-75)	68 (63-77)	67 (56-75)
Sex			
Female	47 (36.2)	24 (36.9)	23 (35.4)
Male	83 (63.8)	41 (63.1)	42 (64.6)
BMI, kg/m^2	26.2 ± 5.1	25.7 ± 5.3	26.7 ± 4.8
Comorbidities			
Arterial hypertension	70 (53.8)	36 (55.4)	34 (52.3)
Diabetes mellitus	24 (18.5)	12 (18.5)	12 (18.5)
Atrial fibrillation	11 (8.5)	8 (12.3)	3 (4.6)
End-stage CKD (eGFR < 30 mL/min)	1 (0.8)	1 (1.5)	0
CKD (eGFR 30-60 mL/min)	8 (6.2)	4 (6.2)	4 (6.2)
Liver cirrhosis	0	0	0
Abnormal LFT results	7 (5.4)	2 (3.1)	5 (7.7)
Thrombocytopenia ($< 100 \times 10^9$/L)[a]	1 (0.8)	1 (1.5)	0
Pulmonary hypertension[b]	1 (0.8)	1 (1.5)	0
Laboratory values			
Hemoglobin, g/L	129.9 ± 19.8	130.3 ± 22.4	129.4 ± 16.8
Platelet count, $\times 10^9$/L	303.1 ± 115.0	299.7 ± 107.9	308.6 ± 123.4
INR	1.01 ± 0.1	1.01 ± 0.11	1.02 ± 0.06
APTT, s	24.1 ± 3.8	23.8 ± 4.4	24.34 ± 2.93
Fibrinogen, g/L	4.85 ± 1.68	4.78 ± 1.43	4.91 ± 1.93
BUN, mM	6.4 ± 3.0	6.7 ± 3.1	6.0 ± 2.9
Creatinine, μM	78.6 ± 35.5	78.7 ± 39.8	78.6 ± 30.8
Indication for bronchoscopy			
Lung cancer	116 (89.2)	59 (90.8)	57 (87.7)
ILD	13 (10)	5 (7.7)	8 (12.3)
Other	1 (0.8)	1 (1.5)	0 (0)
Procedure characteristics			
Operator experience			
IP	58 (44.6)	28 (43)	30 (46.2)
Non-IP	72 (55.4)	37 (56.9)	35 (53.8)
General anesthesia[c]	4 (3.1)	2 (3.1)	2 (3.1)
Procedure leading to bleeding			
EBB	77 (59.2)	40 (61.5)	37 (56.9)
TBB	22 (16.9)	12 (18.5)	10 (15.4)
TBNA	10 (7.7)	6 (9.2)	4 (6.2)
Brush	21 (16.2)	7 (10.8)	14 (21.5)

Data are presented as No. (%), median (interquartile range), or mean ± SD. APTT = activated partial thromboplastin clotting time; CKD = chronic kidney disease; EBB = endobronchial biopsy; eGFR = estimated glomerular filtration rate; ILD = interstitial lung disease; INR = international normalized ratio; IP = interventional pulmonologist; LFT = liver function test; TBB = transbronchial biopsy; TBNA = transbronchial needle aspiration.
[a]Patients with a platelet count of $< 50 \times 10^9$/L were excluded as noted in e-Appendix 2.
[b]Patients with uncontrolled pulmonary hypertension were excluded as noted in e-Appendix 2.
[c]All other patients received topical anesthesia and conscious sedation.

clinical trial. This finding is in concurrence with those of previous studies, further strengthening the evidence base indicating that TXA could be a valid therapeutic option in bleeding control during FB.[12,13] In addition, no significant differences were found between the drugs in the secondary outcomes, including the number of

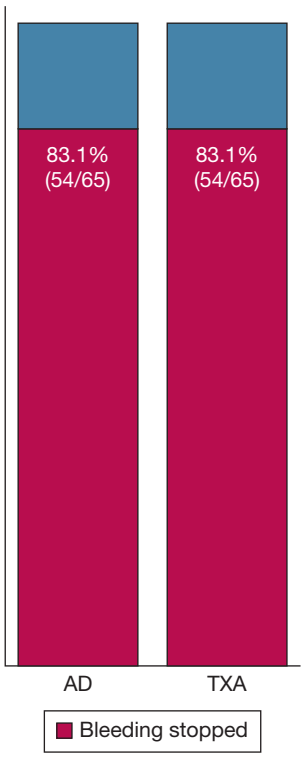

Figure 2 – *Bar graph showing no differences in the bleeding control rate between the groups. Bleeding was stopped in 83.1% (54/65 patients) and 83.1% (54/65 patients) of patients receiving adrenaline or TXA, respectively (P = 1). AD = adrenaline; TXA = tranexamic acid.*

applications needed for bleeding control and severity of bleeding.

Endobronchial bleeding is one of the most common complications of FB. Although most bleeding episodes during FB are mild and self-limiting, serious or fatal bleeding can occur even in the absence of obvious precipitating factors.[15,16] We recorded a total of 575 bleeding episodes during the 2,033 FBs performed, most of which were classified as mild (367/575 [63.8%]) and moderate (184/575 [32.0%]) with a mean VAS score of 3.6 ± 1.3. Of the 2,033 patients, 142 patients (6.98%) required at least one drug application for bleeding control during FB and only 20 patients (0.98%) experienced severe (VAS score, 7+) bleeding. No deaths occurred during the study period, four patients (0.19%) required hospitalization for recurrent bleeding, and only one patient (0.05%) experienced massive bleeding requiring ICU admission. Most moderate and severe bleeding occurred after endobronchial biopsy of visible lesions, followed by TBB, both of which are known to be most associated with clinically significant bleeding. Although the incidence of severe bleeding was similar to the incidence reported in previous studies,[17-19] we observed a higher incidence of mild and moderate bleeding in the present cohort. This could be explained

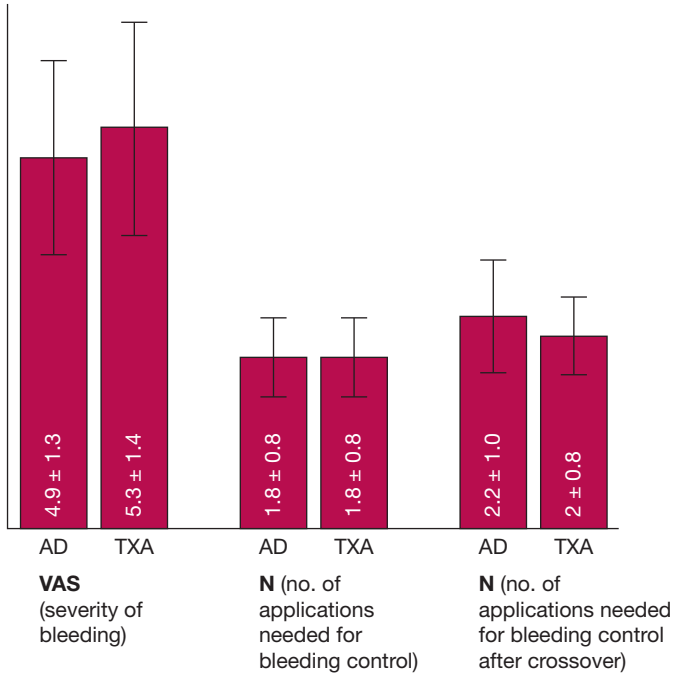

Figure 3 – *Bar graph showing the severity of bleeding and number of applications needed for bleeding control were similar in both groups (AD: mean VAS score, 4.9 ± 1.3 [n = 1.8 ± 0.8]; TXA: mean VAS score, 5.3 ± 1.4 [n = 1.8 ± 0.8]). A nonsignificant difference was found in the number of applications needed after crossover: 2.0 ± 0.8 applications of TXA were needed to control the bleeding after AD failure and 2.2 ± 1.0 applications of AD were needed to control the bleeding after TXA failure* (P = .57). *AD = adrenaline; TXA = tranexamic acid; VAS = visual analog scale.*

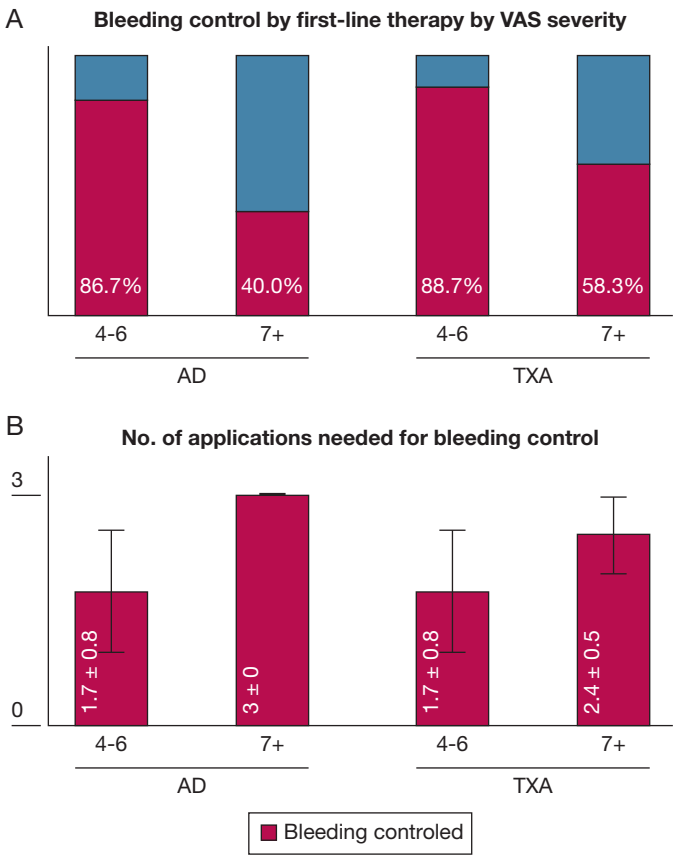

Figure 4 – *A, B, Bar graphs showing that both AD and TXA were significantly more successful in controlling moderate bleeding than severe bleeding (P = .008 and P = .012, respectively) and required significantly more drug applications for controlling severe bleeding than moderate bleeding (P = .006 and P = .002, respectively). AD = adrenaline, TXA = tranexamic acid; VAS = visual analog scale.*

by several factors, including patient, procedure, and operator characteristics and bleeding definitions, which are not standardized in the literature.[20] A standardized bleeding scale was proposed recently to define bleeding severity after TBB by grading the required response, the Nashville bleeding scale. Using this scale, the vast majority of the current randomized patients would be classified as having grade 2 bleeding.[20] Similarly, the Common Terminology Criteria for Adverse Events that was used to assess bleeding in the NAVIGATE study also is based on the intervention needed to control the bleeding.[19] Despite promising attempts, no methods to quantify bleeding objectively are used widely, and definitions of massive bleeding vary in the literature.[5,21] Thus, we decided to use a simple VAS to assess the severity of bleeding from minor (score of 1) to very severe (score of 10). Although subjective, similar subjective assessments of bleeding were used in previous studies and were adapted by the British Thoracic Society guidelines for diagnostic FB.[22,23] The mean VAS score and VAS score distribution were similar in both groups, allowing us to conclude that no significant bias resulting from perceived bleeding severity was present. The groups also were well balanced regarding other important factors such as procedure type, comorbidities, platelet counts, and coagulation parameters. Furthermore, the physician composition is the same every week in our bronchoscopy unit.

Although bleeding is one of the most common complications of FB, strong recommendations from guidelines on bleeding management are lacking. A narrow selection of topical medications is used in everyday practice with evidence from high-quality trials supporting their use missing.[22] The most used substances are cold saline and adrenaline, but despite their widespread use, no standardization of doses and dilutions used during FB exists. The amount of cold saline recommended by the literature ranges from large-volume iced saline lavage using 50-mL aliquots, with an average volume of up to 500 mL in some series,[24] to small aliquots of 5 to 10 mL.[22] Although the control of bleeding after TBB in the lung periphery may require larger volumes of cold saline, we used 5-mL aliquots

according to usual institutional protocol. Although topical therapies usually are considered similar in potency, particularly when grading bleeding,[20] we observed a significant drop in cold saline efficacy with increasing bleeding severity. TXA and adrenaline successfully controlled most bleeding that could not be stopped with cold saline, but the additional time and wedging of the bronchoscope likely also contributed. Additionally, despite reports of successful control of massive bleeding with cold saline,[25] only three of 20 episodes of severe bleeding were controlled by cold saline in this study. This difference could be explained by the smaller volume of saline used in our protocol.

Similarly, the literature recommends a variety of doses and concentrations of adrenaline (from 0.5 mL up to 20 mL of 1:20,000 solution), with no high-quality data favoring one or the other or supporting the use of adrenaline for endobronchial bleeding in general.[14] We used 2-mL aliquots of 1:10,000 adrenaline according to usual institutional protocol. Adrenaline was effective in bleeding control, stopping 83.1% of bleeding successfully. This success rate was better than we expected based on the study by Fekri et al[13] that reported a success rate of 68%, a difference that could be explained by different doses and dilutions used, study design, and sample size. Adrenaline has the potential of causing arrhythmia and should be used with caution in elderly patients and patients with known heart disease, carcinoid tumors, or a history of arrhythmias. Several existing case reports raise the concern of the safety of adrenaline, even in previously healthy adults with no known risk factors for malignant arrhythmia.[14,26] We observed no SAEs that could be associated definitely with adrenaline and no malignant arrhythmias during the study period. However, all patients with uncontrolled cardiovascular comorbidities and arrhythmia were not eligible to undergo bronchoscopy (e-Appendix 1).

After the affirmation of TXA in different trauma and surgical indications, several small trials explored the role of TXA in the setting of endobronchial bleeding. Márquez-Martín et al[12] conducted a pilot study that included patients with both non-iatrogenic and iatrogenic bleeding. TXA was applied after cold saline and adrenaline failure. All patients in the iatrogenic group (n = 20) achieved hemostasis. In the study by Fekri et al,[13] TXA achieved an equally impressive success rate, stopping 24 of 25 bleeding episodes (96%). We observed a 83.1% total success rate of TXA in this study and a 100% (11/11 episodes) success rate when used after crossover. Although the total success rate was lower, we observed an equally impressive success rate after adrenaline and cold saline failure. This observation is limited by the very small number of patients, but could be a consequence of a synergistic effect of adrenaline and TXA, which have different mechanisms of action. Importantly, in addition to design differences between our and the above-mentioned studies, we used a different dose and dilution of TXA, which also could have contributed to the observed difference in efficacy. The most important concern of TXA use, which was emphasized previously in the literature, is the theoretical increased risk of thrombotic complications.[4] We observed no thrombotic events related to the application of TXA in this study.

Although many potential sources of bias are eliminated from our trial because of the double-blind randomized controlled trial design, it has several limitations. First, the single-center design and the use of the investigated drugs in specific doses and concentrations after cold saline failure according to usual institutional protocol limit the generalizability of our findings. Second, we decided to exclude noniatrogenic bleeding because of concerns for patient safety and inability to provide informed consent for trial participation in emergency situations, thus excluding an important patient group from analysis. Third, we included different bronchoscopic techniques that have different mechanisms for bleeding. TBB, a technique that is associated most commonly with severe bleeding that is difficult to manage, was underrepresented in this cohort. Fourth, a much higher proportion of patients randomized to TXA were excluded for protocol violation. Finally, although a placebo-controlled trial would determine the efficacy and safety of topical TXA in bleeding during FB better, we used adrenaline as a comparator because it is the standard of care at our institution and not providing it could impact patient safety negatively, despite the lack of high-quality evidence supporting its use. Furthermore, we consider using a placebo for a potentially life-threatening complication to be unethical.

Interpretation

We found no significant differences between adrenaline and TXA for controlling noncatastrophic iatrogenic endobronchial bleeding after cold saline failure. Although limited by a select patient population and underrepresentation of some sampling methods, our results add to the body of evidence that topical TXA can be used safely and effectively during FB, providing an important additional therapeutic option, especially for situations when adrenaline raises safety concerns.

Funding/Support

The authors have reported to *CHEST* that no funding was received for this study.

Financial/Nonfinancial Disclosures

None declared.

Acknowledgments

Author contributions: S. B. and G. G. conceptualized and designed the study, collected and analyzed the data, drafted and revised the manuscript, and provided final approval of the version to be published. I. S., F. D., M. J. M., D. B., M. K., F. P., D. S., and M. S. made substantial contributions to the collection and interpretation of data and critical revision of the manuscript and provided final approval of the version to be published. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are investigated appropriately and resolved. S. B. and G. G. take full responsibility for the content of the manuscript, including the data and analysis.

Other contributions: The authors thank the hospital medical staff who performed the procedures as well as the patients who agreed to participate in the study.

Additional information: The e-Appendixes are available online under "Supplementary Data."

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