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REVIEW

HEMOPTYSIS

Nebulized Tranexamic Acid in the Management of Hemoptysis: An Integrative Review

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Abstract

Objective This integrative review aims to evaluate the efficacy and safety of nebulized tranexamic acid (TXA) in managing hemoptysis, assessing its potential as a non-invasive alternative to traditional invasive procedures.

Methods An integrative review was conducted in accordance with PRISMA guidelines and was registered on PROSPERO (CRD42024584812). The search included databases such as PubMed, EMBASE, Web of Science, and the Cochrane Central Register of Controlled Trials, encompassing studies published up to August 7, 2024. The inclusion criteria focused on human studies that utilized nebulized TXA for hemoptysis, with reported outcomes on bleeding cessation, recurrence, and adverse effects. Extracted data included patient demographics, underlying conditions, TXA dosing, administration methods, clinical outcomes, and reported adverse events.

Results Fourteen studies met the inclusion criteria: five original research studies, and nine case reports involving 13 patients. The majority of patients were older adults with underlying conditions such as chronic obstructive pulmonary disease (COPD), acute respiratory distress syndrome (ARDS), and infections. Nebulized TXA demonstrated high efficacy in controlling hemoptysis across studies, with most patients experiencing rapid cessation of bleeding. In a randomized controlled trial, 96% of patients receiving TXA achieved complete resolution of hemoptysis within five days, compared to 50% in the placebo group. TXA use was also associated with shorter hospital stays and a decreased need for invasive interventions. The safety profile of nebulized TXA was favorable. However, the long-term safety of nebulized TXA, remains unexplored.

Conclusion Nebulized tranexamic acid appears to be an effective and safe non-invasive treatment option for hemoptysis, particularly in non-massive cases. It provides rapid control of bleeding and may reduce the requirement for invasive procedures. However, further large-scale randomized controlled trials are necessary to confirm these findings and to establish optimal dosing regimens.

Keywords Hemoptysis · Nebulized tranexamic acid · Respiratory bleeding management · Non-invasive therapy · Integrative review

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Introduction

Hemoptysis, defined as the expectoration of blood from the respiratory tract, can result from various conditions, including chronic obstructive pulmonary disease (COPD), bronchiectasis, infections, vasculitis, and malignancies. The severity of hemoptysis ranges from mild, self-limiting episodes to life-threatening events, necessitating a spectrum of management strategies [1]. Mild cases often respond well to conservative treatments such as bed rest, oxygen therapy, and antibiotics. In contrast, severe cases may require more aggressive interventions like bronchial artery embolization, bronchoscopy, or surgical resection to control the source of bleeding. Although these invasive techniques can be effective, they carry inherent risks and may not be appropriate for all patients, particularly those with significant comorbidities or critical illnesses [1]. The complexity and urgency involved in managing hemoptysis highlight the need for treatment options that are both effective and minimally invasive [1].

Tranexamic acid (TXA), an antifibrinolytic agent, has recently garnered interest as a potential therapeutic option for hemoptysis, especially when administered via nebulization [2, 3]. TXA works by inhibiting fibrinolysis through the blockade of lysine-binding sites on plasminogen, thereby stabilizing blood clots and reducing further bleeding. Although TXA has been widely used systemically in various conditions, its nebulized form allows for direct, localized delivery to the lungs. This localized administration offers the potential to manage hemoptysis effectively while minimizing the risk of systemic clot formation [4].

This integrative review aims to evaluate the evidence on the use of nebulized TXA in the management of hemoptysis, focusing on its clinical effectiveness, safety profile, and potential benefits. Assessing its role in practice will help determine whether nebulized TXA can be established as a first-line treatment or serve as an adjunct to more invasive procedures in patients with hemoptysis.

Methods

This integrative review was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [5]. The protocol was registered on PROSPERO (Registration No: CRD42024584812), ensuring transparency and adherence to a pre-specified methodology.

Search Strategy

A comprehensive and integrative search was conducted across four major electronic databases: PubMed, EMBASE, Web of Science, and the Cochrane Central Register of Controlled Trials. Keywords and Medical Subject Headings (MeSH terms) related to “tranexamic acid” and “hemoptysis” were used to identify relevant studies. The search was limited to publications up to August 7, 2024, to encompass the most recent evidence. The strategy was designed to include a broad spectrum of study designs, such as randomized controlled trials (RCTs), retrospective studies, reviews, and case reports. Studies published in non-English languages or available only in abstract form were excluded. Additionally, manual searches of reference lists from identified studies and pertinent review articles were conducted to ensure a thorough inclusion of relevant literature.

Inclusion and Exclusion Criteria

Studies were included if they involved human participants with hemoptysis, utilized nebulized TXA as the intervention, and provided outcome data on bleeding cessation, recurrence of hemoptysis, or adverse effects. Exclusion criteria encompassed studies that administered TXA via non-nebulized routes (e.g., intravenous or oral), those not focused on hemoptysis, animal or in vitro studies, and publications unavailable as full-text articles or written in languages other than English. Conference abstracts, commentaries, letters to the editor, and studies lacking sufficient outcome data were also excluded from the review.

Study Selection

The study selection process was conducted by two independent reviewers who screened titles and abstracts to identify eligible studies. Full-text articles were obtained for potentially relevant studies, and the same reviewers independently assessed each study for final inclusion based on predefined criteria. Any disagreements were resolved through discussion, and if necessary, by consulting a third senior reviewer. A flowchart of the study selection process was created in accordance with PRISMA guidelines to illustrate the identification, screening, and inclusion of studies.

Data Collection Process

Data were independently extracted by two reviewers using a standardized extraction form. The extracted data included patient demographics (such as age, gender, and underlying conditions), study characteristics (such as study design, sample size, and country), details of the intervention (including TXA dose, administration frequency, and duration), and clinical outcomes. The primary outcome of interest was the cessation of hemoptysis. Secondary outcomes included the recurrence of hemoptysis, the need for additional interventions (e.g., bronchoscopy or angiographic embolization), the duration of hospital stay, and any reported adverse events, such as bronchospasm and thromboembolic complications.

Assessment of the Quality of the Data

For randomized controlled trials, the Cochrane Risk of Bias Tool was employed to assess bias, focusing on random allocation, blinding, and the completeness of outcome data [6]. The Joanna Briggs Institute (JBI) quality assessment tool was used to evaluate case reports [7]. For other non-RCT studies, the ROBINS-I tool was applied to assess bias [8].

Results

From the initially pool of 2120 articles, 119 duplicates were removed, and 1,962 studies were excluded based on the title and abstract screening. The full texts of 39 articles were then assessed for eligibility. Of these, six were comments or letters, six were conference abstracts, one did not involve nebulization, five were not accessible, five studies focused on post-tonsillectomy hemorrhage, and two reviews. Consequently, 14 studies were included in this analysis: five original studies [9–13], nine case reports [14–22]. Most patients were older adults, with a higher proportion of males, and common causes of hemoptysis included airway diseases and infections. The study selection process is depicted in Fig. 1.

This paper includes five original studies with a total of 311 patients. Two of the studies are randomized controlled trials, while three are non-RCTs. The patient population consists of both adults and pediatric patients, with TXA doses ranging from 250 to 500 mg, administered through intravenous injection, nebulization, or endotracheal instillation. The treatment duration varied based on patient condition, typically lasting for several days. (Details are shown in Table 1). The cases reviewed demonstrate the broad applicability of nebulized TXA in the management of hemoptysis across various conditions. Patients ranged in age from 14 to 82 and presented with conditions such as COPD, acute respiratory distress syndrome (ARDS), pulmonary embolism, diffuse alveolar hemorrhage, and complications associated with extracorporeal membrane oxygenation (ECMO). Most cases utilized a standard dose of 500 mg of nebulized TXA every 8 h, typically administered for 3 to 5 days (Table 2 provides detailed patient information).

Risk of Bias

Two RCT studies were evaluated using the ROB tool for bias assessment. The results showed that Wand et al.'s study had a low risk of bias, while Gopinath et al.'s study had a high risk of bias, primarily due to performance and allocation concealment bias (Table 3). Clinical studies were evaluated using the ROBINS-I tool, where Alkazemi et al.'s study and Bafaqih et al.'s study were categorized as having a serious risk of bias, mainly due to confounding biases, while O'Neil et al.'s study showed a moderate risk of bias, particularly in confounding and measurement biases (Table 4). The JBI tool was applied to assess case reports, revealing that most reports provided sufficient descriptions of patient characteristics and treatment; however, several reports lacked details on adverse events, resulting in moderate reporting bias (Table 5).

Efficacy of Nebulized TXA

Several studies demonstrated the efficacy of nebulized TXA in controlling hemoptysis. In a RCT by Wand et al., 96% of patients treated with nebulized TXA (500 mg three times a day) achieved complete resolution of hemoptysis within five days, compared to 50% in the placebo group ($p < 0.0005$) [9]. Sanghvi et al. reported a case in which a 78-year-old patient experienced rapid bleeding control after receiving 2 g of nebulized TXA, leading to successful extubation on the third day [16]. The review further emphasizes that nebulized TXA effectively resolves non-massive hemoptysis, making it a viable first-line treatment or an adjunct to other therapies [23]. Favorable outcomes were also observed in ARDS patients on ECMO, with TXA contributing to stabilization and successful decannulation [17].

However, some patients experienced only temporary relief. For example, an 82-year-old female with diffuse alveolar hemorrhage initially responded to TXA, but her hemoptysis recurred, leading to a transition to comfort care [14]. This suggests that while TXA provides immediate benefits, its long-term effectiveness may be limited in severe or irreversible conditions.

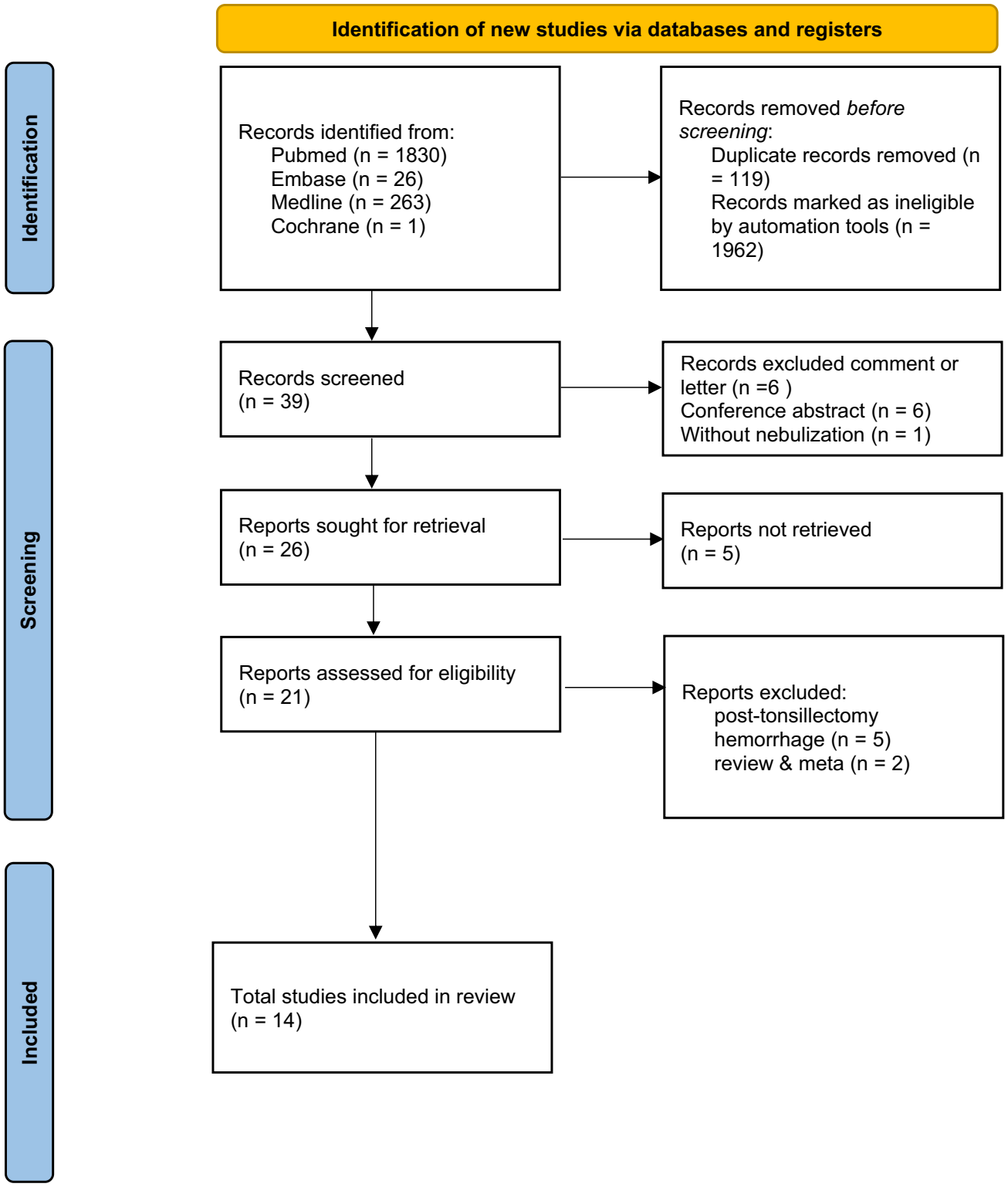

Fig. 1 Flow diagram for search and selection of included studies

Table 1 Characteristics of included studies

Study	Study design	Sample size	TXA dose	Duration	Clinical outcomes
Wand et al. [9]	Randomized Controlled Trial	47	500 mg, three times daily	5 days	96% of patients in the TXA group achieved hemostasis within 5 days, compared to 50% in the placebo group. The TXA group had a shorter hospital stay (5.7 vs. 7.8 days) and none required invasive procedures, while 18.2% in the placebo group did
Alkazemi et al. [11]	Single-center retrospective matched cohort study	TXA: 14 Ctrl: 58	500 mg, every 6–8 h	Based on patient condition	There was no significant difference in the need for invasive intervention between the TXA (35.7%) and control (56.9%) groups, but the TXA group achieved hemostasis faster, with no serious adverse events reported
Bafaqih et al. [13]	Prospective non-randomized pilot study	18 pediatric patients	<25 kg: 250 mg/dose; >25 kg: 500 mg/dose	Every 6 h for 3–4 doses, followed by rFVIIa if needed	55.6% of patients achieved hemostasis with TXA alone, while the rest did so after adding rFVIIa, with no treatment-related complications
Gopinath et al. [10]	Open-label, cluster-randomized, single-center pilot trial	Inhal.: 55 IV: 55	500 mg, three times daily (nebulized and IV groups)	Based on patient condition	The nebulized group had higher hemostasis success at 30 min (73% vs. 51% for IV group) and reduced hemoptysis at 6, 12, and 24 h, with fewer requiring bronchial artery embolization
O'Neil et al. [12]	Retrospective observational study	19 pediatric patients	100 mg/mL, nebulized or endotracheally instilled	Based on patient condition	95% of patients achieved hemostasis with nebulized TXA, with no major adverse events

Ctrl: control; TXA: tranexamic acid; Inhal.: inhalation; IV: injection of vein; rFVIIa: recombinant activated factor VII

Table 2 Summary of patient cases from 9 studies

No	Study	Age	Gender	Diagnosis	TXA dose	Administration	Outcome
1	Grant-Sittol [14]	82	Female	Diffuse alveolar hemorrhage secondary to vasculitis	500 mg every 8 h for 3 days	nebulized	Temporary resolution followed by recurrent hemoptysis; patient died after comfort care
2	Eltahir [15]	63	Male	COPD/bronchiectasis on rivaroxaban with non-massive hemoptysis	500 mg every 8 h for 48 h	nebulized	Complete resolution of hemoptysis, no recurrence
3	Sanghvi [16]	78	Female	Pulmonary hemorrhage post-tPA administration	2 g over 20 min	nebulized	Bleeding controlled; patient extubated on day 3, discharged on day 10
4	Cabanilla [17]	45	Male	ARDS on ECMO complicated by pulmonary hemorrhage	500 mg every 8 h for 5 days	nebulized via ETT	Stabilized hemodynamics, discharged to LTAC
5	Cabanilla [17]	68	Male	ARDS with severe necrotizing pneumonia on ECMO	500 mg every 8 h for 5 days	nebulized via ETT	Successfully decannulated, no further complications
6	Cabanilla [17]	34	Male	Lemierre's disease with multiple pulmonary aneurysms and ARDS	500 mg every 8 h for 5 days	nebulized via ETT	Controlled bleeding, tolerated decannulation, discharged to LTAC
7	Komura [18]	N/A	N/A	Hemoptysis	N/A	nebulized	Positive response to treatment, outcome not detailed
8	Hankerson [19]	N/A	N/A	Cancer-related hemoptysis	N/A	nebulized	Effective in controlling hemoptysis, outcome not detailed
9	Dhanani [20]	65	Male	Submassive PE and moderate hemoptysis	500 mg every 6 h	Inhaled (nebulized)	Treatment successful, no further complications
10	Cutshall [21]	61	Male	COPD with pulmonary hemorrhage	500 mg every 8 h for 3 days	Inhaled (nebulized)	Hemoptysis controlled, stable condition
11	Alabdrabalnabi [22]	31	Female	SLE with pulmonary hemorrhage and lupus nephritis	500 mg every 8 h for 1 day	Nebulized	Improved, stable hemoglobin, discharged
12	Alabdrabalnabi [22]	14	Female	G6PD, nephrotic syndrome, vasculitis with diffuse alveolar hemorrhage	500 mg every 8 h for 3 days	Nebulized	Bleeding reduced, no further need for TXA, stabilized
13	Alabdrabalnabi [22]	66	Female	Rheumatic heart disease, post-valvuloplasty and valve replacement, on warfarin	100 mg every 8 h for 2 days	Nebulized	Bleeding reduced, improvement, discharged after 12 days

TXA tranexamic acid, *ETT* endotracheal tube, *COPD* chronic obstructive pulmonary disease, *ARDS* acute respiratory distress syndrome, *ECMO* extracorporeal membrane oxygenation, *LTAC* long-term acute care facility, *SLE* systemic lupus erythematosus, *G6PD* glucose-6-phosphate dehydrogenase

Table 3 Risk of bias assessment with the cochrane assessment tool

Author	Bias from randomization	Bias from allocation	Bias from performance	Bias from detection	Bias from attrition	Bias from reporting	Bias from other	Overall risk of bias
Wand et al. [9]	Low	Low	Low	Low	Low	Low	Low	Low
Gopinath et al. [10]	Low	Some	High	Low	Low	Low	Low	High

Table 4 Risk of bias assessment with the ROBINS-I tool

Study	Confounding bias	selection bias	Classification bias	Intervention bias	Missing data bias	Measurement bias	Reporting bias	Overall risk of bias
Alkazemi et al. [11]	Serious	Low	Low	Moderate	Low	Moderate	Moderate	Serious
Bafaqih et al. [13]	Serious	Low	Low	Low	Low	Moderate	Moderate	Serious
O'Neil et al. [12]	Moderate	Low	Low	Moderate	Low	Moderate	Moderate	Moderate

Table 5 The quality evaluation of 9 case reports by the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Case Reports

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8
Alabdrabalnabi et al. [22]	Y	Y	Y	Y	Y	Y	N	Y
Cabanilla et al. [17]	Y	Y	Y	Y	Y	Y	N	Y
Cutshall et al. [21]	Y	Y	Y	Y	Y	Y	N	Y
Dhanani et al. [20]	Y	Y	Y	Y	Y	Y	N	Y
Eltahir et al. [15]	Y	Y	Y	Y	Y	Y	N	Y
Grant-Sittol et al. [14]	Y	Y	Y	Y	Y	Y	Y	Y
Hankerson et al. [19]	Y	Y	Y	U	Y	Y	N	Y
Komura et al. [18]	Y	Y	Y	Y	Y	Y	N	Y
Sanghvi et al. [16]	Y	Y	Y	Y	Y	Y	N	Y

Y Yes, *n* No, *U* Unclear

Q1: Were patient's demographic characteristics clearly described?

Q2: Was the patient's history clearly described and presented as a timeline?

Q3: Was the current clinical condition of the patient on presentation clearly described?

Q4: Were diagnostic tests or assessment methods and the results clearly described?

Q5: Was the intervention(s) or treatment procedure(s) clearly described?

Q6: Was the post-intervention clinical condition clearly described?

Q7: Were adverse events (harms) or unanticipated events identified and described?

Q8: Does the case report provide takeaway lessons?

Reduction in Hospital Stay and Invasive Procedures

The use of nebulized TXA was associated with shorter hospital stays and a reduced need for invasive procedures. In the study by Wand et al., patients treated with TXA had an average hospital stay of 5.7 days compared to 7.8 days in the placebo group ($p = 0.046$). Notably, none of the patients in the TXA group required invasive procedures such as bronchoscopy or embolization, while 18.2% of the placebo group did [9]. Previous research also reported a reduction in hospital stay by nearly two days and a decreased need for further interventions (risk ratio = 0.38, 95% CI: 0.16–0.87) [2].

Safety Profile

Nebulized TXA demonstrated a favorable safety profile across the included studies. For instance, a 63-year-old male with COPD and bronchiectasis experienced complete resolution of hemoptysis within 48 h of TXA administration, with no recurrence [15]. Similarly, a 70-year-old male with pulmonary embolism and bleeding responded well to nebulized TXA (500 mg every 8 h for 3 days) without complications [21]. TXA was also linked to a reduction in short-term mortality (risk ratio = 0.78, 95% CI: 0.72–0.85) and a decrease in bleeding duration by an average of 24.61 hours [2].

Notably, across all ten case reports, no significant adverse events were directly attributed to nebulized TXA. This consistent safety profile suggests that TXA is a well-tolerated option for managing hemoptysis, even in patients with complex medical conditions.

Discussion

Nebulized TXA shows potential as a non-invasive treatment for hemoptysis and may serve as an alternative to invasive methods such as bronchial artery embolization and bronchoscopy. This review provides an overview of

the available evidence regarding TXA's use in various clinical settings, including COPD, ARDS, vasculitis, and malignancies. However, most of the included studies are small in scale and many are case reports, which limits the strength of the evidence. Consequently, the conclusions drawn must be considered preliminary, given the limited scope of the available research.

The reviewed studies suggest a trend indicating that nebulized TXA may be effective, but further investigation is required, particularly regarding its role in different severities and etiologies of bleeding. While existing randomized controlled trials and observational studies suggest that nebulized TXA may help control non-massive hemoptysis, the quality of the evidence varies, and further high-quality research is needed to confirm these findings. For instance, Wand et al. found that 96% of patients treated with TXA experienced cessation of bleeding within five days, compared to 50% in the placebo group, suggesting that nebulized TXA might effectively stabilize patients [9]. Gopinath et al. also found that nebulized TXA might reduce hemoptysis volume and the need for invasive procedures compared to intravenous TXA, though larger trials are necessary to substantiate these results [10]. Preliminary case reports suggest that TXA may serve as both a non-invasive therapy and a bridge to definitive treatment. In complex cases, such as patients with ARDS on ECMO described by Cabanilla et al., TXA appeared to control pulmonary bleeding, allowing for stabilization and weaning from mechanical support without surgery [13, 17]. However, these findings are based on small-scale studies and require confirmation through more robust research. Similarly, in resource-limited settings where access to interventional procedures is restricted, TXA may provide an initial option to control bleeding, but more research is needed to validate its efficacy in such scenarios. Nebulized TXA might reduce the need for invasive interventions in pediatric patients with hemoptysis, as demonstrated in the study by Bafaqih [13]. However, these findings are based on limited sample sizes and study designs, highlighting the need for more robust research. O'Neil et al. suggested that nebulized TXA could be both effective and safe for managing pulmonary hemorrhage in critically ill pediatric patients, but the lack of control groups limits the strength of these conclusions [12].

The potential for nebulized TXA to reduce healthcare resource utilization is promising. Wand et al. found that patients treated with TXA had shorter hospital stays (5.7 vs. 7.8 days) and required fewer invasive interventions [9]. However, these findings should be interpreted cautiously until confirmed by larger studies. While nebulized TXA may offer economic benefits by reducing the need for invasive procedures, further cost-effectiveness studies are needed to support these claims.

Safety remains a critical consideration. Gopinath et al. reported two cases of bronchoconstriction, which were promptly managed with short-acting beta-agonists [10]. These incidents highlight the need for careful monitoring in patients with pre-existing respiratory conditions. Additionally, the long-term safety of nebulized TXA, particularly with repeated or prolonged use, remains uncertain. Future pharmacokinetic studies are necessary to evaluate potential systemic absorption and its safety, especially in patients with thrombotic risks.

The effectiveness of nebulized TXA compared with traditional treatments, especially for massive hemoptysis, is still unclear and requires further investigation. While TXA appears effective in non-massive or moderate cases, its role in massive hemoptysis is uncertain due to limited studies. Some case reports, such as those by Komura and Hankerson, suggest that TXA might stabilize severe bleeding before definitive interventions, but these findings are anecdotal and need further validation [9, 18, 19].

Studies have used various regimens, ranging from 500 mg every 8 h to a single 2 g dose. While these regimens have shown effectiveness, the optimal dosing schedule, treatment duration, and patient selection criteria remain unclear. Establishing standardized guidelines through large, multicenter randomized controlled trials is necessary to optimize outcomes and minimize risks.

While this review identifies a potential trend supporting the use of nebulized TXA for hemoptysis, particularly in non-massive cases, the current evidence is insufficient for definitive conclusions. More high-quality studies, including cohort studies and randomized controlled trials, are essential to provide stronger evidence and establish clear guidelines for its use in clinical practice.

Limitations

Despite promising results, current research on nebulized TXA for hemoptysis is limited, primarily consisting of case reports and small-scale trials. This restricts the generalizability of findings and makes it difficult to draw definitive conclusions about TXA's efficacy across diverse populations due to the absence of large, multicenter RCTs. Many studies also have short follow-up periods, focusing on acute bleeding control without long-term data on recurrence rates, patient outcomes, or potential delayed complications.

Another limitation is the heterogeneity in patient populations, underlying conditions, and TXA dosing regimens. Patients had varying etiologies for hemoptysis—ranging from COPD and bronchiectasis to ARDS and malignancies—making it challenging to establish a standardized treatment protocol. The variability in dosing (100 mg to 2 g per session) and treatment duration (single doses to several

days) further complicates determining the optimal therapeutic regimen.

Most studies excluded patients with massive hemoptysis, concentrating on non-massive cases. This raises questions about the safety and effectiveness of nebulized TXA in severe cases requiring rapid and aggressive intervention. The unclear role of TXA in massive hemoptysis warrants further investigation, especially since some studies suggest it might be more effective as a bridging therapy rather than a definitive solution in such scenarios.

Additionally, there is limited data on the potential systemic absorption of nebulized TXA and its long-term safety in patients with coagulation disorders or those on anticoagulant therapy. The risk of thromboembolic events with prolonged or repeated use in high-risk patients has not been fully explored. Further pharmacokinetic and safety studies are needed to assess systemic effects, especially in patients with compromised respiratory function or pre-existing thrombotic risk factors.

In summary, while nebulized TXA shows promise in treating hemoptysis, current evidence is constrained by small sample sizes, variability in treatment protocols, and a lack of long-term outcome and safety data. Future large-scale RCTs are essential to establish standardized guidelines and determine the optimal use of TXA in different clinical scenarios, including massive hemoptysis and high-risk populations.

Conclusion

Nebulized TXA shows promise in treating hemoptysis. Its ability to control bleeding and reduce the need for invasive interventions represents a significant advancement in treatment. While the safety profile is favorable, further research in larger, more diverse populations is needed to confirm these findings and explore potential risks. Nebulized TXA holds promise both as a primary treatment for non-massive hemoptysis and as a bridging therapy in more severe cases. Future well-designed randomized controlled trials with standardized protocols and longer follow-up periods are essential to better define its role and ensure its use is based on high-quality evidence.

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Author contributions HL and YR conceptualized the study; MHY, MFC and CGW performed the selection, data extraction, and risk of bias assessment; YR performed the statistical analysis and drafted the manuscript; ZLJ provided critical appraisal of the manuscript. All authors reviewed and agreed on the final version of the manuscript.

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Data Availability No datasets were generated or analyzed during the current study.

Declarations

Conflict of interests The authors declare no competing interests.

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