Pulmonary hemorrhage: A novel mode of therapy

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Summary
Major hemoptysis a potentially life-threatening condition in pulmonology and can originate from both identifiable and unidentifiable sites. Identifiable bleeding sites can be controlled locally by iced saline, vasopressors, laser, electrocautery and balloon tamponade. Bleeding from an unidentifiable source, on the other hand, is much more difficult to control as the bleeding site is not accessible by the bronchoscope. Tranexamic acid (TA), a synthetic anti-fibrinolytic agent, is approved for treatment or prophylaxis of bleeding episodes in hemophilia or following major operative procedures via intravenous or oral routes. Its efficacy in controlling bleeding from mucosal tissue led us to apply it to patients with pulmonary bleeding. Six patients with significant hemoptysis, two who bled during bronchoscopy biopsy and four with spontaneous bleeding (lung cancer, diffuse alveolar hemorrhage, idiopathic pulmonary bleeding, metastatic thyroid carcinoma) were treated with TA. For the two who bled during bronchoscopy, we used a bolus of 500 mg/5 mL through the bronchoscope working channel, while the latter four received aerosolized TA 500 mg/5 mL 3–4 times a day. In all cases, the bleeding stopped with the first dose of TA, and the treatment was well tolerated without adverse events. While limited due to the small number of patients, these data show that TA administered either as a bolus through the bronchoscope or via inhalation seems to be effective in controlling severe hemoptysis from both identifiable and unidentifiable bleeding sites. Further clinical studies are needed to evaluate the use of the TA in this set-up.

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Introduction
Hemoptysis, a frequent symptom in pulmonary diseases, refers to identifiable bleeding from major airways or to unidentifiable bleeding from the lung parenchyma. Identifiable bleeding originates mostly from endobronchial...
lesions, either spontaneously or following diagnostic or therapeutic procedures. Unidentifiable bleeding originates mostly from vascular injury to more distal vessels and tends to be spontaneous. Regardless of the etiology, pulmonary bleeding can be severe and life-threatening, requiring prompt intervention to stop the bleeding. Identifiable bleeding sites are managed with the instillation of cold water and/or vasopressors and/or balloon tamponade through the bronchoscope. In selected, equipped medical centers, laser coagulation or electrocautery and bronchial artery embolism (if an abnormal vessel can be recognized) are performed.\textsuperscript{1–7}

The therapeutic options for unidentifiable bleeding, on the other hand, for example, diffuse alveolar hemorrhage, are limited and include correction of coagulation defects (if present) along with supportive treatment.\textsuperscript{8–10} There is no doubt that further treatment modalities for pulmonary bleeding are needed.

Tranexamic acid, a synthetic anti-fibrinolytic agent, has been approved for many years for the treatment or prophylaxis of bleeding episodes in patients with bleeding disorders or following major operative procedures via intravenous or oral routes. Its effectiveness in controlling local bleeding from mucosal tissue in the nose, colon, rectum and mouth led us to evaluate its activity in pulmonary bleeding.\textsuperscript{11–13} This report summarizes our preliminary experience with tranexamic acid to treat pulmonary bleeding of varying etiologies.

Methods

Following are the results of the experimental treatment of patients with severe pulmonary bleeding not responding to conventional medical therapy. Usual measures included steroids and antibacterial agents in cases of diffuse alveolar hemorrhage and topical application of iced saline with adrenaline in cases of identifiable bleeding during bronchoscopy. Six patients hospitalized in Rambam Health Care Campus, a 900-bed tertiary care-center, university-affiliated hospital, who experienced severe pulmonary hemorrhage unresponsive to conventional treatment during their hospital stay, received experimental treatment with TXA. The present case series describes 6 patients in whom permission to administrate TXA either by inhalation or by topical application was given by the local ethical committee as an off-label treatment. A protocol that was approved by the local ethical committee ensured that all patients with uncontrolled bleeding encountered during clinical practice would be eligible to this compassionate treatment without informed consent.

Patients with uncontrolled pulmonary hemorrhage either from identifiable or unidentifiable sources were included. For unidentifiable bleeding episodes, we used inhaled tranexamic acid 500 mg/5 ml 3–4 times a day (Hexakapron, TEVA Group, Tel-Aviv, Israel), and for identifiable bleeding episodes we used boluses of tranexamic acid administered through the working channel of the flexible bronchoscope. Each ampoule of 5 ml contained 500 mg of tranexamic acid dissolved in water for injection, sodium hydroxide and hydrochloric acid (for pH adjustment). A quantitative and qualitative (verbal) evaluation of the symptoms was made, such as general clinical evaluation, chest X-ray, and blood tests. Data on the patients are presented in Table 1. Clinical follow-up was until discharge or death and as of writing of this manuscript no patient dropped from follow-up (maximum of follow-up 2 years).

Patient no. 1

A 67-year-old male was admitted with hemoptysis. Renal cell carcinoma has been diagnosed three years earlier for which he underwent radical nephrectomy followed by chemotherapy and immunotherapy. Right upper lobe metastasis diagnosed two years earlier was treated by external radiotherapy. Chest CT revealed a large endobronchial mass in the right upper lobe bronchus. Fiberoptic bronchoscopy confirmed bleeding from this lesion. An attempt to perform bronchoscopic electrocautery resulted in massive bleeding (approximately 750 ml of blood) that did not respond to a bolus of iced saline and instillation of epinephrine through the bronchoscope. At that time, a bolus of 500 mg (vial) of TA was instilled through the bronchoscope working channel with immediate cessation of the bleeding within 30–60 s. The patient remained stable for the next few days, did not bleed, and was discharged.

Patient no. 2

A 43-year-old male presented with recurrent episodes of significant hemoptysis of 3 weeks’ duration followed by a reduction of 5 g% in hemoglobin. He had suffered from multiple, bilateral, inoperable, pulmonary metastases of medullary thyroid carcinoma over the last 10 years for which he underwent surgery, chemotherapy and radiation therapy. He also suffered from right vocal cord and right diaphragmatic paralysis, along with hypoxemia and pulmonary hypertension treated at home with nasal positive pressure ventilation oxygen and Endothelin-1 antagonists. A chest CT showed bilateral masses compressing the main bronchi and bronchoscopy revealed narrowed bronchi to the left and the right sides along with irritated mucosa and signs of blood coming from distal unidentifiable sites on both sides. Aerosolized TA (500 mg/5 ml) four times a day resulted in immediate and complete cessation of the bleeding. The time frame elapsing from application of TXA to cessation of overt bleeding was 15–20 min. An attempt to stop the therapy after 72 h resulted in a new episode of hemoptysis which also responded well to this therapy. The patient continued to inhale a half-vial — 2.5 ml (250 mg) — of TA two to three times a day as preventive therapy. Overall, he received this treatment for three months without side effects. Later, the frequency of the inhalation was gradually reduced to once a day and finally could be stopped.

Patient no. 3

A 49-year-old female with myelofibrosis since 1998 underwent splenectomy in 2005. In 2006 her disease transformed into acute myeloid leukemia and she eventually underwent haploidentical bone-marrow transplantation (BMT) with complete remission of the leukemia. Six months after the BMT she developed idiopathic thrombocytopenic purpura
(ITP) for which she received immune globulins along with corticosteroids with no response. A month later she was admitted to hospital with hemoptysis, shortness of breath, hypoxia, new diffuse bilateral diffuse alveolar infiltrates, and a drop of 2 g% in hemoglobin values with a platelet count of 3000/µL, consistent in this set-up with the diagnosis of diffuse alveolar hemorrhage (DAH). BAL findings were consistent with the diagnosis of DAH and she was treated with immunoglobulin, high-dose steroids, platelet transfusion and CPAP ventilation enriched with 100% oxygen. One day after admission, the platelet counts were 3000/µL, hemoglobin had decreased by a further 1 g% and her respiratory status continued to deteriorate. At this point we put her on inhalations of TA (500 mg) every 6 h. The hemoptysis stopped within a 2–3 h and her respiratory status stabilized. A few days later it had improved significantly along with disappearance of the pulmonary infiltrates. Two days later she was able to walk along the corridor without oxygen. TA was stopped after one week of therapy without recurrence of the bleeding.

**Patient no. 4**

A 52-year-old male with a history of heavy smoking presented with shortness of breath, fever and purulent sputum of a few days’ duration. He was treated with broad spectrum antibiotics and oxygen mask. In 1999, diffuse mixed small cleaved and large cell lymphoma had been diagnosed. Over the years, he experienced multiple relapses managed with several lines of chemotherapy, including autologous BMT. On the 10th day of the current hospitalization, he developed significant hemoptysis of 500 ml. CBC disclosed thrombocyte count of 70,000/mm³ and normal coagulation studies. Chest CT disclosed a left lower lobe cavitary lesion along with extensive consolidation. Due to the poor respiratory status, BAL was delayed and the patient was put on inhalations of TA 500 mg every 6 h for three days, again with rapid resolution of the hemoptysis. Bronchoscopic biopsy performed three days later demonstrated poorly differentiated squamous cell carcinoma. The patient eventually died during this hospital stay from sepsis without active bleeding.

**Patient no. 5**

A 57-year-old male was admitted to the emergency room with fever, productive cough and dyspnea. His past medical history was unremarkable except for smoking of 60 pack-years until 12 years ago. CT of the chest revealed a 2.5-cm sized mass in the right upper lobe. He was put immediately on broad spectrum antibiotics with resolution of the fever. Bronchoscopy performed one day after admission revealed a normal bronchial tree. During transbronchial biopsy, massive bleeding (600 ml) occurred with a reduction of 2 g% in hemoglobin. Two doses (500 mg/5 ml each) of TA were instilled through the bronchoscope to the affected segment, resulting in the immediate and complete cessation of the bleeding. The biopsy sample showed non-small cell lung carcinoma. The patient was discharged and is scheduled for resection of the lung cancer.

**Patient no. 6**

A 59-year-old previously healthy man with retinal detachment underwent elective left-eye vitrectomy. Following uneventful surgery under general anesthesia he was extubated. A few minutes later, a bloody cough developed. On physical examination he had 30 breaths per minute, pulse of 130/min and O₂ saturation of 85–87% while breathing room air. Urgent chest radiograph followed by chest CT scan confirmed the presence of diffuse, confluent, and bilateral alveolar opacities. No endobronchial mass was observed on bronchoscopy. Subsequent laboratory studies showed a drop in hemoglobin level (12 g%) compared to baseline values (15 g%). Platelet count, coagulation studies and blood chemical values were within normal limits. Oxygen (15 l/min) was given via non-re-breathing mask, resulting in oxygen saturation of 93%. He was put on inhaled TA (500 mg qid) for 48 h with almost instantly stopping of the hemoptysis. Follow-up fiberoptic bronchoscopy performed 48 h later revealed signs of old inactive bleeding in the bronchus to the posterior segment of the left lower lobe and no endobronchial lesion. Abdominal CT revealed an irregular mass in the left kidney, later diagnosed as renal cell carcinoma.
Discussion

This report describes the effectiveness of administering TA to six patients with pulmonary hemorrhage of varying etiologies. Two patients with significant bleeding from malignant tumors during bronchoscopy (one during a transbronchial biopsy) responded immediately to a bolus of TA 500 mg/5 ml injected directly through the bronchoscope working channel to the bleeding site in the patient with the identifiable tumor and to the affected segment in the patient who bled during the transbronchial biopsy. The remaining four patients with spontaneous bleeding of varying etiologies — endobronchial tumor, unidentifiable lung metastasis, DAH and idiopathic pulmonary bleeding — were managed with inhalations of TA (250–500 mg) up to four times a day and responded immediately. Only one patient with non-resectable lung metastasis required three months of therapy.

Tranexamic acid, a synthetic derivative of the amino acid lysine, possesses anti-fibrinolytic activity because it binds to plasminogen, blocks its binding to fibrin, and subsequent activation to plasmin. The pulmonary distribution of oral and IV TA is not known. Sindet-Pedersen’s observation of much higher concentrations of TA in saliva after a mouth rinse with 10 mL of a 5% aqueous TA solution than after oral administration of 1 g of the drug, suggests superior effectiveness of local administration of the drug rather than systemic treatment. This could translate into better inhibition of fibrinolysis that lasts for many hours with minor side effects, even in the patient who received it for three months.

The prevalence of hemoptysis (mostly identifiable) in patients with primary or secondary lung cancer varies from 24 to 70% with a mortality rate of 10–38%, depending on the etiology and the magnitude of the bleeding. Bronchoscopic-induced bleeding that requires special management occurs in 1.8–5% of patients, mostly in the set-up of bronchial or transbronchial biopsy procedures and during laser or electrocautery treatment of tracheobronchial tumors. While most bleeding episodes are self-limited, some can be fatal.

The management of major hemoptysis includes placing the patient with a bleeding lung in the dependent position, if needed to maintain airway patency, with selective intubation of the non-bleeding lung. Identifiable bleeding sites are managed by instillation of ice-cold saline or with the administration of vasopressors such as epinephrine (1:10,000) through the working channel of the bronchoscope. Of note, about 50% of epinephrine that is systemically absorbed is liable to produce side effects such as tachyarrhythmias and hypertension. Other forms of intervention to control identifiable bleeding include balloon tamponade, laser and/or electrocautery, all of which depend on the availability of trained staff in well-equipped medical centers. A bronchial artery embolism (BAE) applies mainly for local bleeding when an abnormal vessel is documented in medical centers with a stand-by angiographic service. The last resort for significant bleeding is a surgical procedure.

The management of bleeding from an unidentifiable source, on the other hand, is more complicated. For local bleeding from an unidentifiable source, some of the treatments mentioned earlier are applied to the affected bronchus, although with smaller success rates compared to identifiable bleeding. Diffuse alveolar bleeding, either idiopathic or in association with hematological disorders such as BMT, is a devastating entity with a mortality rate of 70–90% on current therapeutic regimens. The exact cause of DAH is unknown but it is considered to represent small vessels abnormality. The effectiveness of TA in DAH is encouraging especially in the face of the high mortality rates of this entity on current therapeutic strategies.

Oral and IV TA have been used adjunct to BAE to control hemoptysis in CF patients. Wong has reported successful management of recurrent minor hemoptysis with oral TA for four years with no apparent toxicity in a patient with collateral vessels after failure of BAE. Chang presented a 6-year-old boy who was successfully treated with TA for five months for hemoptysis that eventually required lobectomy, despite therapy with TA. Graf reported the effective use of TA in a patient with angiographic evidence of significant bronchial artery to spinal artery anastomoses despite multiple BAE procedures. Attempts to withdraw the TA resulted in recurrence of the bleeding.

Tranexamic acid mouthwashes enhance hemostasis after minor oral surgery in warfarinized patients. This approach permits oral surgical procedures without interruption of anticoagulant therapy. In a randomized, double-blind, placebo-controlled trial, administration of TA mouthwash reduced the rate of postoperative bleeding compared with placebo in 93 anticoagulated patients undergoing dental surgery. Local TA therapy (mouth rinse of 10 ml of a 5% solution for 2 min, four times daily) was superior to systemic therapy in controlling spontaneous gingival bleeding or bleeding following subgingival scaling in hemophilia.
Two patients with malignant mesotheliomas who bled to the pleural cavity were successfully treated with oral TA 4 g in four doses in addition to TA 5 g intrapleurally twice daily.28 TA administered directly into the pericardial cavity in patients undergoing coronary bypass operations has been reported to decrease postoperative bleeding.29

These data show that the local application of TA is highly effective in controlling bleeding of different causes. No significant adverse effects have been noted during the local use of tranexamic acid.

The data presented show that TA is an additional effective method of treating patients with significant respiratory bleeding, mostly because this cheap and safe medication is easy to administer and does not require a special set-up. It can be used for identifiable bleeding sites in a bolus directly through the bronchoscope working channel, thus contributing to the management of bleeding in hospitals not equipped with laser or electrocautery. In equipped medical centers it can be administered to patients with identifiable bleeding through a rigid bronchoscope. More importantly, the ability to administer it for both identifiable bleeding from an unidentifiable source through inhalation suggests that it could be considered for pulmonary bleeding in the emergency room and/or in internal medicine departments, instead of or until bronchoscopic procedures are available. While limited due to the small number of patients, these data show that TA application administered either as a bolus through the bronchoscope or via the inhalation seems to be effective in controlling severe hemoptysis from both identifiable and unidentifiable bleeding sites. Further prospective randomized clinical studies are needed to evaluate the use of the TA in this set-up.

Conflict of interest statement

The authors have no conflict of interest to declare.

References