Use of endoscopic fibrinogen–thrombin in the treatment of severe hemoptysis

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Summary Bronchial artery embolization (BAE) is the treatment of choice in the majority of patients with severe hemoptysis. However, this procedure may be unavailable and even fail or be counterindicated in 4–13% of cases. In these cases, the efficacy of fibrinogen–thrombin (FT) instilled endoscopically as treatment for massive hemoptysis was assessed. Between August 1993 and February 1996 a prospective clinical study was performed. FT instillation was indicated in all patients with severe hemoptysis (>150 ml/12 h) in whom BAE had failed, was counterindicated or not available. FT was instilled endoscopically. Patients were followed up until June 2001. Eleven of 101 patients (11%) with hemoptysis >150 ml/12 h in whom BAE was not possible or proved ineffective were included. The severe hemoptysis was controlled immediately in all cases. During the follow-up period (mean: 39.4 months), early relapse of the severe hemoptysis occurred in two patients (18%) and a long-time relapse in one. Mean procedure duration was 3 min and no attributable complications were observed in any case. In conclusion, these results suggest that topical treatment with FT could be considered in the initial endoscopic evaluation of patients with severe hemoptysis while awaiting BAE or surgery, or as alternative treatment to arterial embolization when the latter is not available, has proved ineffective or is counterindicated.

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Introduction

Severe hemoptysis constitutes a medical emergency, with mortality between 7 and 10%. The most frequent causes of death are asphyxia and intractable hypoxemia due to the inundation of blood within alveoli. Because of the unpredictable course of severe hemoptysis, maintenance of airway patency and control of the bleeding are the primary immediate goals.

The ideal time for bronchoscopy is controversial. Whereas delayed bronchoscopy, within 24–48 h of admission, is preferred in stable patients before performing computed tomography in severe hemoptysis, bronchoscopy is the initial procedure of choice for most authors, particularly during active bleeding, since it permits the bleeding lung to be displaced to one side, the exact bleeding point to be located, and to be obtained an etiologic diagnosis in some cases. Furthermore, the exact location of the bleeding point will be of inestimable value as a guide for applying topical therapeutic measures, possible surgical treatment or bronchial artery embolization (BAE) that may be urgently indicated if the bleeding persists or worsens.
Morbidity and mortality are high when urgent surgery is performed;\textsuperscript{5,6,10-11} thus, BAE, in recent years, has become the treatment of choice in severe hemoptysis as a palliative procedure preparing the patient for elective surgery of localized disease or continued antimicrobial therapy if indicated.\textsuperscript{12-17} In patients deemed too ill to undergo elective surgery, BAE may be repeated successfully for recurrent hemoptysis. However, this technique is not always available in emergencies in all hospital centers; even when available, it is ineffective,\textsuperscript{18-21} not possible to perform or counterindicated in 4–13% of cases.\textsuperscript{22} In such situations, additional bronchoscopic techniques to tamponade the bleeding bronchial segment including thrombin or fibrinogen–thrombin (FT) combination,\textsuperscript{23-24} Fogarthy balloon-tipped,\textsuperscript{25-26} right-heart balloon catheters,\textsuperscript{27} endobronchial electrosurgery or laser therapy\textsuperscript{28} may be helpful in preserving gas exchange to a great extent.

The aim of the present study was to assess the efficacy of endoscopic FT administration in the short-, medium- and long-term control of severe hemoptysis in patients in whom BAE could not be performed for the reasons stated above.

Materials and methods

Study population

From August 1993 to February 1996, a prospective study was conducted using FT instillation via fiberoptic bronchoscopy (FOB) in all patients with severe hemoptysis (150 ml/12 h) in whom BAE could not be performed either because of unavailability, ineffectiveness (in case of early relapse after the first embolization attempt or if no anomalous bronchial artery branch is found) or because it was counterindicated (anticoagulant treatment, pregnancy or previous vascular injury).

Bronchoscopy technique

FOB was performed in all cases by expert bronchoscopists trained in performing the technique, using Pentax 18X or 19TX (Asahi Optical Co. Ltd., Tokyo, Japan) bronchoscopes. Fifteen minutes before insertion, 0.5 mg of atropine was injected subcutaneously. The upper airway was anesthetized with 5 ml of 1% lidocaine solution administered orally by nebulization, and additional small quantities of lidocaine were instilled through the bronchoscope as required to control coughing.\textsuperscript{29} In patients with assisted mechanical ventilation and endotracheal intubation, the FOB was inserted through the same. Oxygen saturation was monitored in all patients by digital pulsoxymetry (Minolta Pulsox TS-7\textsuperscript{R}, Japan), together with cardiac frequency and ECG registry (Cardiolife TEC-7200\textsuperscript{R}, NIHON KOHDEN Corp., Japan). Non-intubated patients received oxygen supplements by nasal probe or by mouth. Following FOB insertion, remains of blood were carefully aspirated from the airways. Once the bleeding site was identified, local hemostasis measures were applied using instillation via the FOB aspiration channel of cold sterile 0.9% saline solution, epinephrine solution (diluted at 1:20,000 in cold sterile 0.9% saline solution) or by collapse of the bleeding bronchial orifice by applying continuous aspiration with the FOB.\textsuperscript{30,31} The FT solution was instilled immediately after these measures and after drying of the airway with oxygen, administered directly through the FOB channel (connecting an O\textsubscript{2} probe directly to the suction channel, at a flow of 3–4 l/min and a pressure of 5 bar). Endoscopic revision of the whole bronchial tree was made once the bleeding had been controlled. Samples of bronchial washings were obtained in all cases for cytology study and \textit{Mycobacterium tuberculosis} and aerobic bacteria identification.

Fibrinogen–thrombin instillation

The FT solution used (Tissucol\textsuperscript{R}, Baxter AG, Vienna) consisted of two vials. The first contained a fibrinogen solution (70–110 mg/ml), fibronectin (2–9 mg/ml), factor XIII (10–50 U/ml), plasminogen (0.04–0.12 mg/ml), and aprotin (3000 KIU/ml). The second contained a Cl\textsubscript{2} Ca solution (40 mmol/L) and human thrombin (500 IU/ml). The two components were instilled simultaneously into the bleeding bronchial orifice using syringes connected to a double-syringe system (Duploject\textsuperscript{R}, Baxter AG, Vienna) and a double-channel, 180 cm long, 0.17 cm external diameter catheter (Duplocath\textsuperscript{R} 180, Baxter AG, Vienna). This catheter was passed through the bronchoscope channel and placed inside the bleeding bronchial segment or subsegment.

BAE and surgery

Within 5 days post-FT instillation, BAE was reconsidered if it had previously been counterindicated or was not available. BAE or lung surgery was considered if episodes of severe hemoptysis recurred after FT instillation.
Table 1 Patient characteristics, FT indications and hemoptysis evolution.*

<table>
<thead>
<tr>
<th>Patient</th>
<th>Gender (M/F)</th>
<th>Age (yr)</th>
<th>Previous condition</th>
<th>Previous hemoptysis</th>
<th>Quantity of bleeding (ml)</th>
<th>$\frac{PaO_2}{PaCO_2}$/Sat $O_2$% (mmHg)</th>
<th>Cause of hemoptysis</th>
<th>Follow-up (months)</th>
<th>Clinical evolution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>M</td>
<td>71</td>
<td>COPD, BCh</td>
<td>No</td>
<td>1000/48 h</td>
<td>45/51/82</td>
<td>Bilateral BCh.</td>
<td>9</td>
<td>Deceased (COPD exacerbation)</td>
</tr>
<tr>
<td>Patient 2</td>
<td>M</td>
<td>58</td>
<td>TB, COPD</td>
<td>No</td>
<td>950/72 h</td>
<td>69/39/93</td>
<td>Calcified granuloma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient 3</td>
<td>M</td>
<td>66</td>
<td>TB, Asbestosis Hemophilia B.</td>
<td>No</td>
<td>500/24 h</td>
<td>67/31/94</td>
<td>BCh.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient 4</td>
<td>M</td>
<td>74</td>
<td>TB, BCh</td>
<td>4 mo.</td>
<td>200/24 h</td>
<td>87/42/93</td>
<td>BCh.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient 5</td>
<td>F</td>
<td>30</td>
<td>COPD, MS</td>
<td>No</td>
<td>150/12 h</td>
<td>-/-/97</td>
<td>Infiltrate LLL</td>
<td>48</td>
<td>Alive. Simple hemoptysis 4 days post-FOB</td>
</tr>
<tr>
<td>Patient 6</td>
<td>M</td>
<td>57</td>
<td>COPD, MS</td>
<td>No</td>
<td>600/12 h</td>
<td>68/38/93</td>
<td>Bilateral BCh.</td>
<td>74</td>
<td>Alive. Simple hemoptysis 7 mo. post-FOB</td>
</tr>
<tr>
<td>Patient 7</td>
<td>F</td>
<td>84</td>
<td>BCh</td>
<td>No</td>
<td>200/24 h</td>
<td>83/43/93</td>
<td>BCh</td>
<td>6 days</td>
<td>Deceased (lung cancer)</td>
</tr>
<tr>
<td>Patient 8</td>
<td>M</td>
<td>69</td>
<td>COPD, TB</td>
<td>6 days</td>
<td>250/12 h</td>
<td>75/31/96</td>
<td>BCh.: LLL</td>
<td>39</td>
<td>Deceased (from mitral valve surgery). Embolization 3 days post-FOB. Minor hemoptysis 14 and 34 mo. post-BAE.</td>
</tr>
<tr>
<td>Patient 9</td>
<td>F</td>
<td>30</td>
<td>CF</td>
<td>6 days</td>
<td>500/48 h</td>
<td>73/30/95</td>
<td>Bilateral BCh.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient 10</td>
<td>M</td>
<td>76</td>
<td>COPD</td>
<td>4 mo.</td>
<td>250/24 h</td>
<td>77/35/90</td>
<td>BCh.: RUL</td>
<td>11</td>
<td>Alive. Severe hemoptysis 3 days post-FOB (BAE). Severe hemoptysis 20 mo. post BAE (RUL lobectomy)</td>
</tr>
<tr>
<td>Patient 11</td>
<td>F</td>
<td>45</td>
<td>TB</td>
<td>1 mo.</td>
<td>500/48 h</td>
<td>51/31/86</td>
<td>Infiltrate RUL</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*CT = computed tomography of the thorax; M = male; F = female; COPD = chronic obstructive pulmonary disease; BCh. = Bronchiectasis; TB = tuberculosis; mo. = month; MS = mitral stenosis; CF = cystic fibrosis; LLL = left lower lobe; RML = right middle lobe; RUL = right upper lobe; BAE = bronchial artery embolization; FOB = fiberoptic bronchoscopy.

1 Bronchial artery aneurysm secondary to bronchial arteriography two months before.
2 Quick time = 18%. 

Bronchial arteriography (FT indication) | Cause of hemoptysis | Follow-up (months) | Clinical evolution |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>Normal</td>
<td>9</td>
<td>Deceased (COPD exacerbation)</td>
</tr>
<tr>
<td>Patient 2</td>
<td>Not effective</td>
<td>Old TB scarring</td>
<td>48</td>
</tr>
<tr>
<td>Patient 3</td>
<td>Not available</td>
<td>Old TB scarring</td>
<td>74</td>
</tr>
<tr>
<td>Patient 4</td>
<td>Counterindicated†</td>
<td>Lung cancer</td>
<td>12</td>
</tr>
<tr>
<td>Patient 5</td>
<td>Not available</td>
<td>COPD</td>
<td>43</td>
</tr>
<tr>
<td>Patient 6</td>
<td>Contraindicated‡</td>
<td>BCh.</td>
<td>39</td>
</tr>
<tr>
<td>Patient 7</td>
<td>Not available</td>
<td>BCh.</td>
<td>11</td>
</tr>
<tr>
<td>Patient 8</td>
<td>Not effective</td>
<td>COPD</td>
<td>72</td>
</tr>
<tr>
<td>Patient 9</td>
<td>Counterindicated‡</td>
<td>BCh.</td>
<td>60</td>
</tr>
<tr>
<td>Patient 10</td>
<td>Not effective</td>
<td>COPD, BCh</td>
<td>66</td>
</tr>
<tr>
<td>Patient 11</td>
<td>Not effective</td>
<td>TB</td>
<td>0.23</td>
</tr>
</tbody>
</table>
Follow-up

After discharge, all patients were followed up every 6 months on an outpatient basis, or by telephone if that were not possible, until June 2001.

Therapy was considered ineffective if hemoptysis recurred within 6 h after treatment. Short-, mid- and long-term recurrent hemoptysis was defined as a further hemoptysis episode occurring between 6 h and 14 days, 14 days and 6 months and more than 6 months, respectively, post-FT treatment.

Results

During the inclusion period, hemoptysis of any extent was the indication for FOB in 360 of 1234 (29.2%) examinations; of these, hemoptysis was severe (>150 ml/12 h) in 101 cases (27.8%). FT administration was indicated in 11 of these 101 (11.11%) patients (7 men; mean age ± SD 55.1 ± 14 years; range: 15–88) in whom BAE could not be performed because it was normal in one case (patient 1), counterindicated in 3 cases (patients 4, 6 and 9), not available in 3 cases (patients 3, 5 and 7) and failed in the other 4 cases. Follow-up ranged from 7 days to 74 months (mean: 39.4 months). Clinical characteristics of the patients, indications for FT treatment, hemoptysis etiology, follow-up period and evolution are shown in Table 1.

FOB with FT instillation was indicated from the Emergency Room in all but three cases (patients 1, 2 and 7) in which it was performed at 48, 72 and 98 h, respectively. It was carried out after admission because of hemoptysis persistence following FOB with local hemostasis (cold normal sterile saline solution, epinephrine instillation and bronchial occlusion) and the impossibility of performing BAE (normal bronchial arteriogram in the first, failure of the procedure in the second and unavailability in the third).

The FT dose required was 2 ml in all but three patients, who required two instillations of 2 ml owing to two different bleeding points (patients 1 and 11) and technical failure in the third (patient 4). The administration of FT extended the FOB examination by a mean of 3 min (range: 2–7 min), with an additional cost of $131 per 2 ml of solution (150.3 €).

FT instillation immediately controlled the active bronchial bleeding in all patients. However, in the short term, severe hemoptysis relapses were observed in two patients (18%) (6 h post-FT treatment in patient 11, and 3 days post-FT treatment in patient 10). Both were treated with BAE, and patient 11 also with left-pneumonectomy 5 days post-embolization, owing to severe hemoptysis. In patient 6, in whom BAE had initially been counterindicated owing to pharmacological anticoagulation, the procedure was applied on the decision of the attending physician 3 days post-FT treatment once the coagulation had been corrected. In the remaining 8 patients, long-term severe hemoptysis relapse was observed in only one (patient 9), 12 months post-FT instillation. Long-term hemoptysis control was 70% (7/10), with the exclusion of patient 6.

FOB examination could be completed in all patients, with no complications that required its suspension; however, in one patient (No. 4) oxygen desaturations <75% were observed and corrected with 100% oxygen administration using a probe connected directly to the FOB aspiration channel. Bronchial bleeding during the examination was <50 ml in the majority of patients, except in patients 1, 6, and 10 in whom bronchial bleeding was quantified as 150–200 ml.

Cytological and bacteriological study of the bronchial washings provided specific diagnosis in three patients: squamous carcinoma (patient 4), pulmonary tuberculosis (patient 11) and Pseudomonas aeruginosa infection (>10⁶ cfu/ml) in a patient with diffuse bronchiectasis (patient 1).

Discussion

In our study the use of FT permitted immediate control of severe hemoptysis in all cases, as well as short-term control in 82% and long-term control in 70%.

Different types of substances have been used in the topical treatment of severe hemoptysis, such as irrigation with ice saline solution⁵,⁶,¹¹ and combination of saline solution and epinephrine,³⁰,³¹ which are effective in controlling minor bleedings and those occurring after transbronchial lung biopsy, but are not usually a satisfactory treatment of more extensive larger bleedings. Substances that favor or reproduce physiological hemostatic mechanisms such as Bosmin®, thrombin,²³,²⁴ FT²³,²⁴ and Reptilase®,³³ have been also used, with acceptable success rates, but a greater number of cases is lacking. Recently, n-butyl cyanoacrylate³⁴ a biocompatible glue that solidifies quickly, has been used in six patients with prolonged hemoptysis (200–1000 ml/7–45 days), not always >150 ml/12 h, with only one recurrence during the follow-
up period. Unlike the substances mentioned above, cyanoacrylate produces post-procedure cough and is expectorated gradually in the days after instillation.

FT has been widely and successfully used in surgery with multiple bleeding points or when the use of electrical cauterization, sutures or staples was not advisable. After including the patients of the present study (Table 2), the local application via FOB of FT in the treatment of massive hemoptysis has been described in 23 patients. Immediate control of the hemoptysis was achieved in 22 of these 23 cases (95%) and 16 of the 23 (69%) patients did not present relapses during the follow-up period, which varied between 6 h and 74 months (mean ± SD, 39.47 ± 27.37 months).

In the initial study by Tsukamoto et al., the instillation of FT was performed at different times using a thrombin solution of 1000 IU/ml which favors the rapid formation of the fibrin clot. Immediate control of hemoptysis was achieved with this technique in all cases; however, 3 of the 9 patients presented recurrences between the following 24 h and 14 days. Modifications in the administration technique were introduced in the present study and in that conducted by Bense such as simultaneous instillation at the bleeding point of equal volumes of fibrinogen and thrombin using the Duploject system; use of a thrombin solution that delays fibrin clot formation for up to 10 s, giving time for the mixture of fibrinogen and thrombin to penetrate distally towards the bleeding source from the point they were released; and addition to the solution of Factor XIII and aprotinin, whose actions consist of stabilizing the fibrin clot formed and delaying the fibrinolytic action of plasma for up to 10 days, respectively.

Although the fibrin glue instillation technique is simple, it may not prove effective when the patient bleeds copiously. In these cases, previous local hemostatic techniques are required: ice saline solution, combination of saline solution and epinephrine and airway collapse, which permit sufficient momentary bleeding control to ensure instillation of the fibrin glue in the correct site. Furthermore, airway drying with direct oxygen administration through the FOB channel permitted better adhesion of the fibrin glue to the bleeding bronchial wall. The fact that fibrinogen is a plasma derivate obtained from blood donors is the main drawback to its use; however, the control and manufacturing processes involved in its supply ensure viral inactivation; no cases of disease transmission have been described despite its extensive use in surgery.

In conclusion, the present study suggests that local instillation of FT in the bronchial tree is a simple, economical and efficacious technique as a palliative procedure in the immediate and short-term control of severe hemoptysis. Its routine use during FOB evaluation of patients with severe hemoptysis and in whom active bleeding is demonstrated could be considered prior to BAE. It could help to ensure better hemoptysis control during BAE and, particularly, when the latter proves ineffective or must be postponed. Although the results of this study also show acceptable mid- and long-term hemoptysis control, the scant number of patients and study design do not support its routine use in treatment for severe hemoptysis as an alternative to BAE. However, FT instillation could be considered when this technique is unavailable, fails or is counter-indicated.

**Acknowledgements**

To Cristina Mayordomo M.D. for her collaboration in data collection and Christine O’Hara for help with the English version of the manuscript.

**Table 2.** Efficacy of FT endobronchial infusion therapy in severe hemoptysis.

<table>
<thead>
<tr>
<th>Author</th>
<th>Patients (no.)</th>
<th>Agent</th>
<th>Efficacy</th>
<th>Follow-up months (mean)</th>
<th>Recurrent hemoptysis¹</th>
<th>²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tsukamoto (1989)</td>
<td>9</td>
<td>FT</td>
<td>9</td>
<td>11–60</td>
<td>3¹</td>
<td>1</td>
</tr>
<tr>
<td>Bense (1990)</td>
<td>3</td>
<td>FT (Tissucol®, 1 ml)</td>
<td>3</td>
<td>2–36(16)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>De Gratia (2003)</td>
<td>11</td>
<td>FT (Tissucol®, 2 ml)</td>
<td>11</td>
<td>0.23–72 (39.4)</td>
<td>2¹</td>
<td>1</td>
</tr>
</tbody>
</table>

*Immediate control of active bronchial bleeding. ¹Short-term recurrent hemoptysis (<14 days post-FT treatment). ²Long-term recurrent hemoptysis (> 6 months post-FT treatment).
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References