Does tranexamic acid stop haemoptysis?

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Received 24 April 2013; received in revised form 9 July 2013; accepted 30 July 2013

Abstract

A best evidence topic in thoracic surgery was written according to a structured protocol. The question addressed was ‘Does tranexamic acid stop haemoptysis?’. Altogether 49 papers were found using the reported search strategy, of which 13 represented the best evidence to answer the clinical question. The authors, journal, date and country of publication, patient group studied, study type, relevant outcomes and results of these papers are tabulated. This consisted of one systematic review including a meta-analysis of two double-blind randomized controlled trials (RCTs), the two RCTs, one cohort study, two case-series and seven case reports. Main outcomes included bleeding time, bleeding volume and occurrence of thromboembolic complications after start of treatment. Based on results from the meta-analysis, no difference in remission of bleeding within 1 week was found between tranexamic acid (TA) and placebo groups (odds ratio 1.56, 95% CI: 0.44–5.46). However, overall bleeding time was significantly shorter for the TA group (weighted mean difference -19.47, 95% CI: -26.90, -12.03 h). In one RCT, TA reduced both the duration and the volume of bleeding compared with patients receiving placebo (both P < 0.0005). However, the other RCT failed to find a difference in bleeding time (P = 0.2). In these studies, no patient suffered from thromboembolic complications. Two case reports, however, describe development of pulmonary embolism during TA treatment. Several case reports on the use of TA for treatment of haemoptysis secondary to cystic fibrosis were found. In general, they suggest that TA may be a useful and well-tolerated medication for the treatment of intractable haemoptysis in this patient group. We conclude that limited research on the use of TA for treatment of haemoptysis exists. As aetiology of haemoptysis as well as length of treatment, dosage and form of TA administration varied between the studies, strong recommendations are difficult to give. Current best evidence, however, indicates that TA may reduce both the duration and volume of bleeding, with low risk of short-term thromboembolic complications, in patients with haemoptysis.

Keywords: Review • Haemoptysis • Tranexamic acid • Anti fibrinolytic agents • Bleeding • Haemostasis

INTRODUCTION

A best evidence topic was constructed according to a structured protocol. This is fully described in the ICVTS [1].

THREE-PART QUESTION

In [patients with haemoptysis] does [administration of tranexamic acid] stop [bleeding]?

CLINICAL SCENARIO

While working in a cardiothoracic surgery unit, you receive a phone call from the emergency unit where they are updating local hospital guidelines on patient management. They are currently reviewing the section on management of haemoptysis and ask you whether you recommend administration of tranexamic acid (TA) as part of the treatment. You admit that you are unsure what to answer and decide to check the literature concerning TA as treatment for haemoptysis.

SEARCH STRATEGY

Medline was searched from 1946 to February week 11 2013 using the OVID interface.

[Haemoptysis.mp. OR Hemoptysis.mp. OR exp Hemoptysis/OR bloody sputum.mp. OR pulmonary bleeding.mp. OR bronch$.mp.] AND [Tranexamic acid.mp. OR exp Tranexamic acid/OR exp Anti fibrinolytic Agents/] AND [Bleeding.mp. OR exp Hemorrhage/OR exp Hemostasis/].

Studies were included if TA was used as part of treatment for haemoptysis in humans. The reference list of included articles was then scanned for additional articles of relevance not occurring in the primary search. Also, PubMed was searched using phrases from the primary search.

SEARCH OUTCOME

Forty-six papers were found using the reported search. From these, 10 papers were identified that provided the best evidence to answer the question. Three additional papers, one randomized controlled trial (RCT) and two case reports were found from the extended search. The 13 papers are presented in Table 1.

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<table>
<thead>
<tr>
<th>Author, date, journal, country</th>
<th>Study type</th>
<th>Patient group</th>
<th>Outcomes</th>
<th>Key results</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prutsky et al. (2012), Cochrane Database Syst Rev, USA and Peru [2]</td>
<td>Systematic review with meta-analysis of RCTs (level 1a)</td>
<td>Meta-analysis of two RCTs. A total of 70 patients with haemoptysis were randomized to receive TA or placebo. In one study, only patients with tuberculosis were investigated (n = 24) while the other study included various underlying aetiologies (n = 46)</td>
<td>Remission of haemoptysis in 7 days or less</td>
<td>No difference in remission rates between the TA and the placebo groups (odds ratio 1.56, 95% CI: 0.44–5.46)</td>
<td>The study concluded that there was insufficient evidence to determine whether TA should be used in treatment of haemoptysis</td>
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<tr>
<td>Ruiz (1994), PhD thesis, Peru [3]</td>
<td>Double-blind RCT (level 1b)</td>
<td>24 patients with haemoptysis secondary to tuberculosis were randomized to receive TA or placebo intravenously for 3 days</td>
<td>Bleeding time</td>
<td>TA: 23.5 ± 13.5 h Placebo: 50.3 ± 17.9 h (P = 0.0005)</td>
<td>TA significantly reduced both duration and volume of bleeding</td>
</tr>
<tr>
<td>Tscheikuna et al. (2002), J Med Assoc Thai, Thailand [4]</td>
<td>Double-blind RCT (level 1b)</td>
<td>46 patients with haemoptysis of various underlying aetiologies were randomized to receive TA or placebo orally for 7 days or until haemoptysis resolved</td>
<td>Bleeding time</td>
<td>TA: 55 ± 41 h Placebo: 71 ± 41 h (P = 0.2)</td>
<td>TA did not significantly shorten bleeding time</td>
</tr>
<tr>
<td>Márquez-Martín et al. (2010), J Bronchol Intervent Pulmonol, Spain [5]</td>
<td>Single centre prospective non-randomized observational trial (level 2b)</td>
<td>48 consecutive patients with non-life-threatening haemoptysis. All patients underwent bronchoscopy with endobronchial administration of a TA solution directly onto the bleeding lesion or selectively in the bleeding bronchus</td>
<td>Cessation of bleeding as judged by visual inspection through the bronchoscope</td>
<td>Bleeding successfully stopped in 31 of 48 patients (65%)</td>
<td>Patients with acute pulmonary bleeding may benefit from endobronchial instillation of TA</td>
</tr>
<tr>
<td>Solomonov et al. (2009), Respir Med, Israel [6]</td>
<td>Case-series (level 4)</td>
<td>6 patients with haemoptysis of various aetiologies treated with TA instilled through the bronchoscope (n = 2) or inhaled (n = 4)</td>
<td>Thrombotic effects</td>
<td>None observed</td>
<td>Number of cases small</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cessation of bleeding</td>
<td>In all the 6 patients bleeding stopped within minutes to hours of starting with TA</td>
<td>Different types of patients</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td>Length of treatment</td>
<td>Single dose to 3 months</td>
<td>Different doses, forms of administration and duration of treatment with TA</td>
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<tr>
<td>Zamani (2011), Blood Coagul Fibrinolysis, Turkey [7]</td>
<td>Case-series (level 5)</td>
<td>2 patients undergoing bronchoscopy were treated with intratumoral injection of TA for control of biopsy-induced bleeding</td>
<td>Cessation of bleeding</td>
<td>For both patients bleeding stopped within minutes of intratumoral injection of TA</td>
<td>No adverse effects of TA reported</td>
</tr>
<tr>
<td>Devine and Radford (2013), Cardiol Young, Australia [8]</td>
<td>Case report (level 5)</td>
<td>25-year old woman with pulmonary atresia and haemoptysis. BAE or surgery was considered too risky. Treatment with TA alone resolved the haemoptysis</td>
<td>Cessation of bleeding</td>
<td>Immediately after start of treatment</td>
<td>Case report</td>
</tr>
<tr>
<td>Wong et al. (1996), Pediatr Pulmonol, Canada [9]</td>
<td>Case report (level 5)</td>
<td>8-year old girl with CF and recurrent episodes of haemoptysis. TA was started after bleeding was not fully controlled by BAE</td>
<td>Cessation of bleeding</td>
<td>Within 1 day. Two subsequent attempts to stop or reduce the dose resulted in recurrence of haemoptysis</td>
<td>Case report</td>
</tr>
<tr>
<td>Chang et al. (1996), Pediatr Pulmonol, Australia [10]</td>
<td>Case report (level 5)</td>
<td>13-year old boy with CF presenting with major haemoptysis. TA was started after bleeding was not fully controlled by BAE and surgery</td>
<td>Cessation of bleeding</td>
<td>Stopped after 2 days and did not reoccur for 5 months when a lobectomy was performed</td>
<td>It is concluded that TA should be considered when BAE is unsuccessful, prior to pulmonary resection</td>
</tr>
<tr>
<td>Graff (2001), Respiration, USA [11]</td>
<td>Case report (level 5)</td>
<td>24-year old female with CF who had previously undergone two lobectomies and 12 BAE procedures. With known bronchial artery to spinal artery anastomoses, she did not wish to undergo a repeat BAE. TA was therefore initiated when haemoptysis recurred</td>
<td>Cessation of bleeding</td>
<td>Within 2 weeks. Two subsequent attempts to stop or reduce the dose resulted in recurrence of haemoptysis</td>
<td>Case report</td>
</tr>
<tr>
<td>Hurley et al. (2011), J R Soc Med, UK [12]</td>
<td>Case report (level 5)</td>
<td>Young man with CF presenting with massive haemoptysis. TA was started although the artery responsible for haemoptysis was amenable to BAE</td>
<td>Cessation of bleeding</td>
<td>Yes, but time from start of treatment until haemoptysis stopped was not reported</td>
<td>Case report</td>
</tr>
<tr>
<td>Flight et al. (2012), Thorax, UK [13]</td>
<td>Case report (level 5)</td>
<td>72-year old man with CF presenting with recurrent haemoptysis. TA initiated in hospital and continued after discharge</td>
<td>Cessation of bleeding</td>
<td>Within 2 weeks, although streaks of blood was seen in the sputum on a daily basis</td>
<td>It is possible that the use of TA contributed to the development of venous thrombosis</td>
</tr>
<tr>
<td>Krivokuca and Lammers (2011), Clin Appl Thromb Hemost, Netherlands [14]</td>
<td>Case report (level 5)</td>
<td>59-year old woman with a history of PE who used TA for chronic haemoptysis due to bronchiectasis</td>
<td>Cessation of bleeding</td>
<td>Yes, but time from start of treatment until haemoptysis stopped was not reported</td>
<td>Case report</td>
</tr>
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Table 1: (Continued)
RESULTS

Prutsky et al. [2] performed a meta-analysis (n = 70) of two double-blind RCTs studying the effect of TA in reducing haemoptysis from any cause. The main findings were that remission of haemoptysis within a week did not differ between the patients receiving TA and the patients receiving placebo (odds ratio 1.56, 95% CI: 0.44-5.46). However, overall bleeding time was significantly shorter for the TA group (weighted mean difference -19.47, 95% CI: -26.90, -12.03 h). No patient suffered from thromboembolic complications.

One of the two RCTs included in the review by Prutsky et al. [2] was a study by Ruiz [3] where 24 patients with haemoptysis secondary to tuberculosis were randomized to receive TA or placebo intravenously for 3 days. According to this study, TA reduced both the duration and the volume of bleeding compared with patients receiving placebo (both P < 0.0005). The other RCT was performed by Tscheikuna et al. [4] where 46 patients with haemoptysis of various underlying aetiologies were randomized to receive TA or placebo orally for 7 days or until haemoptysis resolved. Data from this study alone did, however, not find a difference in bleeding time between the TA and the placebo group (P = 0.2). Bleeding volume was not assessed in this study.

Márquez-Martín et al. [5] studied the effect of endobronchial administration of a TA solution during bronchoscopy in 48 consecutive patients with non-life-threatening haemoptysis. The TA solution was applied directly onto the bleeding lesion or selectively in the bleeding bronchus. Patients were divided into an iatrogenic group (bleeding due to diagnostic bronchoscopy, n = 20) or a non-iatrogenic group (spontaneous bronchial bleeding, n = 28). In the iatrogenic group, bleeding successfully stopped in all patients after endobronchial administration of TA. In the non-iatrogenic group, however, only 11 patients (39.2%) were successfully treated. It was found that non-responders more frequently had bronchiectasis (58.3 vs 18.8%, P = 0.039) and less frequently had malignancies (16.7 vs 56.3%, P = 0.040) when compared with responders. The study did not evaluate total blood loss and follow-up time was limited to 3 months. Of 66 patients originally included in the study, 11 (16.6%) had recurrent haemoptysis after 3 months. Recurrence rate did not differ between patients treated with endobronchial TA or not. No patient suffered from thrombotic events.

Solomonov et al. [6] presents a case-series of 6 patients treated with TA for haemoptysis of various aetiologies. TA was instilled through the bronchoscope as a single dose (n = 2) or inhaled up to four times a day lasting days to months (n = 4). In all the 6 patients, haemoptysis resolved within minutes to hours of starting with TA. This study concludes that TA administered via the bronchoscope or through inhalation seems effective in treating haemoptysis from both identifiable and unidentifiable bleeding sites.

Zamani [7] presents a case-series where patients undergoing bronchoscopy were treated with intratracheal injection of TA for control of biopsy-induced bleeding. For both patients, bleeding stopped within minutes of starting treatment, suggesting that this procedure could be performed as a prebiopsy measure to prevent biopsy-induced bleeding.

Devine and Radford [8] present a case report on the successful treatment of haemoptysis in pulmonary atresia with TA.

Several case reports on the use of TA for treatment of haemoptysis secondary to cystic fibrosis (CF) were found [9-13]. In these reports, TA was given alone, prior to, or in conjunction with bronchial artery embolization (BAE) or pulmonary resection. One study reports the occurrence of acute pulmonary embolism (PE) [13]. The other reports conclude that TA may be a useful and well-tolerated medication for the treatment of intractable haemoptysis in patients with CF.

Krivokuca and Lammers [14] presents a case report where a woman, with a history of PE, used TA as treatment for chronic haemoptysis secondary to bronchiectasis. After 6 months she was diagnosed with a new PE. It was concluded that care should be taken when prescribing TA to patients with a history of PE.

CLINICAL BOTTOM LINE

Limited research on the use of TA for treatment of haemoptysis exists. As the aetiology of haemoptysis as well as length of treatment, dosage and form of TA administration varied between the studies, strong recommendations are difficult to give. Current best evidence, however, indicates that TA may reduce both the duration and volume of bleeding, with low risk of short-term thromboembolic complications, in patients with haemoptysis.

FUNDING

This work was supported by the Bergen University Heart Fund.

Conflict of interest: none declared.

REFERENCES