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[Intervention Review]

Antifibrinolytic therapy to reduce haemoptysis from any cause

Gabriela Prutsky^{1,2}, Juan Pablo Domecq^{2,3}, Carlos A Salazar⁴, Roberto Accinelli⁵

¹Knowledge and Evaluation Research Unit, Mayo Clinic, Rochester, Minnesota, USA. ²CONEVID, Unidad de conocimiento y evidencia, Cayetano Heredia Peruvian University, Lima, Peru. ³Department of Internal Medicine, Henry Ford Health System, Detroit, Michigan, USA. ⁴Department of Medicine, Universidad Peruana Cayetano Heredia, Lima, Peru. ⁵Laboratorio de Respiración of the Instituto de Investigaciones de la Altura, Departamento de Medicina, Universidad Peruana Cayetano Heredia and Hospital Nacional Cayetano Heredia, Lima, Peru

Contact: Juan Pablo Domecq, CONEVID, Unidad de conocimiento y evidencia, Cayetano Heredia Peruvian University, Lima, Peru. jpdomecq@gmail.com.

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ABSTRACT

Background

Haemoptysis is a common pathology around the world, occurring with more frequency in low-income countries. It has different etiologies, many of which have infectious characteristics. Antifibrinolytic agents are commonly used to manage bleeding from different sources, but their usefulness in pulmonology is unclear.

Objectives

To evaluate the effectiveness and safety of antifibrinolytic agents in reducing the volume and duration of haemoptysis in adult and paediatric patients.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) and the Database of Abstracts of Reviews of Effects (DARE) in The Cochrane Library, EMBASE and LILACS for publications that describe randomized controlled trials (RCTs) of antifibrinolytic therapy in patients presenting with haemoptysis. We also performed an independent search in MEDLINE for relevant trials not yet included in CENTRAL or DARE. Searches are up to date to the 19th September 2016. We conducted electronic and manual searches of relevant national and international journals. We reviewed the reference lists of included studies to locate relevant randomized controlled trials (RCTs). An additional search was carried out to find unpublished RCTs.

Selection criteria

We included RCTs designed to evaluate the effectiveness and safety of antifibrinolytic agents in reducing haemoptysis in adult and paediatric patients of both genders presenting with haemoptysis of any etiology and severity. The intervention of interest was the administration of antifibrinolytic agents compared with placebo or no treatment.

Data collection and analysis

All reviewers independently assessed methodological quality and extracted data tables pre-designed for this review.

Main results

The electronic literature search identified 1 original study that met the eligibility criteria. One unpublished study was also identified through manual searches. Therefore two randomized controlled trials met the inclusion criteria: [Tscheikuna 2002](#) (via electronic searches) and [Ruiz 1994](#) (via manual searches).

Antifibrinolytic therapy to reduce haemoptysis from any cause (Review)

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[Tscheikuna 2002](#), a double-blind RCT performed in Thailand, evaluated the effectiveness of tranexamic acid (TXA, an antifibrinolytic agent) administered orally in 46 hospital in- and outpatients with haemoptysis of various etiologies. [Ruiz 1994](#), a double-blind RCT performed in Peru, evaluated the effectiveness of intravenous TXA in 24 hospitalised patients presenting with haemoptysis secondary to tuberculosis.

Pooled together, results demonstrated a significant reduction in bleeding time between patients receiving TXA and patients receiving placebo with a weighted mean difference (WMD) of -19.47 (95% CI -26.90 to -12.03 hours), but with high heterogeneity ($I^2 = 52\%$). TXA did not affect remission of haemoptysis evaluated at seven days after the start of treatment. Adverse effects caused by the drug's mechanism of action were not reported. There was no significant difference in the incidence of mild side effects between active and placebo groups (OR 3.13, 95% CI 0.80 to 12.24).

Authors' conclusions

There is insufficient evidence to judge whether antifibrinolytics should be used to treat haemoptysis from any cause, though limited evidence suggests they may reduce the duration of bleeding.

PLAIN LANGUAGE SUMMARY

Antifibrinolytic therapy to reduce haemoptysis

Haemoptysis is the coughing up of blood or of blood-stained sputum from the lower respiratory tract. It is a common pathology around the world and can be caused by a number of different diseases, including bronchitis, pneumonia, lung cancer, and tuberculosis.

Antifibrinolytic agents (tranexamic acid, aminocaproic acid, nafamostat and aprotinin) are drugs that act by inhibiting the process that dissolves clots, thereby reducing bleeding.

We identified two trials up to the 19th September 2016. Both of them evaluated the use of tranexamic acid, one for haemoptysis caused by tuberculosis and the other for haemoptysis from a variety of causes.

Tranexamic acid significantly reduced the bleeding time, but it did not make any difference to the number of patients who were still suffering from haemoptysis when it was evaluated at seven days after the start of treatment. Severe adverse effects were not reported and mild side effects were not different between patients receiving tranexamic acid and those not receiving tranexamic acid.

There is too little evidence to judge whether any antifibrinolytics should be used to treat haemoptysis.

BACKGROUND

Description of the condition

Haemoptysis is the coughing up of blood originating in the respiratory tract and below the glottis. Based on the volume of bleeding in the hemorrhagic sputum, it is classified as mild, moderate, severe and massive (haemodynamic involvement and capable of causing asphyxia) (Bravo 2009; Gourini 1974; Pursel 1961; Sanchez 2002).

Haemoptysis is a common pathology around the world, and occurs with more frequency in low-income countries (Unsal 2006).

The main causes of haemoptysis are bronchiectasis, malignant pulmonary neoplasia, bronchitis and pneumonia (Haro 2001; Hirshberg 1997; Tsoumakidou 2006; Unsal 2006).

Description of the intervention

There are three types of antifibrinolytic agents: aprotinin, a natural inhibitor of the serine protease; nafamostat, a synthetic inhibitor of the serine protease; and synthetic lysine analogues, such as tranexamic acid (TXA) and aminocaproic acid (ACA).

TXA and ACA are the antifibrinolytic agents most commonly used to reduce blood loss. Evidence shows that TXA has greater strength (100 times more) and a longer mean life (two hours versus one hour) than other antifibrinolytics (Andersson 1965; Nilsson 1980; Okamoto 1959; Verstraete 1985). TXA and ACA reversibly bind to plasminogen, blocking its bonding to fibrin and the activation and transformation to plasmin (Hoylaerts 1981; Thorsen 1975). TXA and ACA are even effective in locations where there is no excessive fibrinolytic activity (Verstraete 1985).

How the intervention might work

Haemoptysis originates from the bronchial circulation in 90% of cases. The endothelium of the bronchial circulation has fibrinolytic activity at all levels. Since antifibrinolytics reduce fibrinolytic activity, they have been suggested as a means of reducing the occurrence of haemoptysis (Levin 1997).

TXA and ACA are synthetic lysine analogues (synthetic derivatives of the amino acid lysine) that act as effective inhibitors of fibrinolysis. TXA and ACA act principally by blocking the two lysine binding sites (strong site and weak site) on plasminogen molecules, inhibiting the formation of plasmin and therefore inhibiting fibrinolysis (Coleman 1994). These inhibitors of fibrinolysis bind to both sites of the plasminogen molecule, where TXA demonstrates more potency than ACA (Coleman 1994; Mannucci 1998).

Systematic reviews and meta-analyses of antifibrinolytics in different bleeding conditions have concluded that they can reduce blood loss. Among the conditions evaluated are menometrorrhagia (Lethaby 2000), perioperative bleeding in elective surgery (Henry 2011), paediatric orthopedic surgery (Tzortzopoulou 2007), and cardiac surgery (Brown 2007). However, the effect of antifibrinolytics in haemoptysis is uncertain.

Why it is important to do this review

The management of haemoptysis aims to stop bleeding, prevent aspiration, and treat the underlying cause (Bidwell 2005).

Although mortality from haemoptysis is low (5-10%), the risk of death varies according to the underlying diagnosis and the severity of the bleeding. This percentage is higher when the haemoptysis is secondary to pulmonary malignant neoplasia (21%) and hemorrhagic diathesis (38%). In mild and moderate haemoptysis, mortality is 2.5% and 6% respectively, while in massive haemoptysis it ranges from 38% to 80% (Crocco 1968; Hirshberg 1997; Garzon 1978; Sehhat 1978).

Other than general principles, there are currently no clear recommendations for the management of mild and moderate haemoptysis (Bidwell 2005). For massive haemoptysis, experts suggest the use of bronchoscopic techniques to control bleeding (including balloon tamponade, iced saline lavage, topical medications, laser therapy, electrocautery, arterial embolization and surgery). The majority of these approaches require an experienced bronchoscopist or radiologist, resources that may not be readily available in resource poor settings (Jean-Baptiste 2000). The cost of these bronchoscopic techniques exceeds the cost of antifibrinolytic agents. A cost effectiveness analysis in the CRASH-2 trial found that early administration of TXA to bleeding trauma patients is likely to be cost effective in low, middle and high income settings (Guerreiro 2011). Additionally, antifibrinolytic agents could possibly be used as a temporary therapy for patients being prepared for embolization or surgery for massive haemoptysis until the procedures could find and treat the source of bleeding; antifibrinolytics have been shown to reduce mortality in bleeding trauma patients (Roberts 2011) and the rate of blood transfusion in surgery (Henry 2011). The use of antifibrinolytic therapy for these purposes could be of particular importance for patients in rural areas or in low-income countries where access to a full examination for definitive diagnoses and surgical strategies might be limited.

Despite the lack of definitive support for the use of antifibrinolytics in the management of haemoptysis, reports in the literature suggest that they are used for this purpose in practice, making it important to assess the efficacy and safety of this approach. (Chang 1996; Graff 2001; Kaufman 1993; Solomonov 2009; Wong 1996).

OBJECTIVES

To evaluate the effectiveness and safety of the use of antifibrinolytic agents to reduce the volume and duration of haemoptysis in adult and paediatric patients.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials (RCTs) designed to evaluate the effectiveness and safety of antifibrinolytic agents in reducing haemoptysis, where the active treatment is compared to placebo or no treatment.

Types of participants

Adult and paediatric patients of both genders presenting with haemoptysis of any etiology and severity.

Types of interventions

The intervention of interest will be the administration of antifibrinolytics (endovenous or orally) compared with placebo or no treatment.

Types of outcome measures

Primary outcomes

Efficacy

- Bleeding time: duration of the haemoptysis after start of treatment.
- Bleeding volume: amount of blood lost after start of treatment.
- Mortality due to haemoptysis.

Secondary outcomes

Efficacy

- Hospitalization time: days of hospitalisation due to haemoptysis.
- Requirement of invasive procedures and necessity of blood transfusion.
- Number of episodes of haemoptysis: any new bleeding episode.

Safety

Adverse effects attributable to the mechanism of action:

- Venous thromboembolism: clots that are able to cause an obstruction of the venous system, including pulmonary thromboembolism and deep vein thrombosis ([Mannucci 1998](#)).
- Acute myocardial infarction and coronary bypass occlusion.
- Stroke: sudden, non convulsive event, due to cerebral ischemia or intracranial haemorrhage ([Adams 1981](#)).
- Acute renal failure: increase of creatinine equal to or greater than 0.3mg/100mL, an increase of 50% or urinary flow lower than 0.5ml/kg/h during six hours or more that occurs during 48 hours or less ([Mehta 2007](#)).
- Mortality related to the treatment.

Adverse effects not attributable to the mechanism of action (these cannot be explained by the effect of the drug in the fibrinolytic process):

- Serious adverse effects (seizures, myopathy and muscular necrosis, [Furtmüller 2002](#); [Seymour 1997](#); [Winter 1995](#)).
- Mild adverse effects (nausea, dizziness, vomiting, abdominal pain and diarrhoea, [Brown 2007](#)).

Search methods for identification of studies

Electronic searches

With the support of the Cochrane Tobacco Addiction Group we originally searched the Cochrane Central Register of Controlled Trials (CENTRAL) and the Database of Review Abstracts on Effectivity (DARE) in The Cochrane Library, MEDLINE, EMBASE and LILACS (Latin American and Caribbean Health Sciences Literature) for publications indexed from inception to February 2012 that describe (or that may have described) randomized controlled trials of antifibrinolytic agents in patients who have presented with haemoptysis. These searches were updated in September 2016, to

search for studies indexed between the dates of the original search and the 19th September 2016.

Although CENTRAL and DARE contain MEDLINE and EMBASE databases, we also performed an independent search in MEDLINE for trials not yet included in CENTRAL or DARE.

For the search strategies used for electronic databases see [Appendix 1](#), [Appendix 2](#) and [Appendix 3](#).

Searching other resources

We conducted both electronic and manual searches of relevant national and international journals. For the manual search we also contacted local librarians to search for unpublished papers, theses or any other kind of study that had not been published and might be within their archives.

We reviewed reference lists of identified studies to locate any other relevant RCTs. In addition, a search was carried out to find unpublished RCTs through personal communication with colleagues, experts, authors of published studies, and representatives of pharmaceutical companies.

Data collection and analysis

Selection of studies

All review authors independently evaluated the titles and abstracts of the reports of trials identified by electronic searches. Copies of the full text were obtained for trials meeting the selection criteria.

Data extraction and management

All authors independently extracted data using data extraction sheets pre-designed for this review and verified the data. We did not find any studies that had been published in more than one source.

Assessment of risk of bias in included studies

All authors independently evaluated the quality of the studies according to the Cochrane risk of bias approach. The review authors avoided bias with regard to journal, institution, or study results by erasing this information prior to inclusion or exclusion.

Regarding the analysis of studies according to methodological quality, the following features were considered: generation of the randomization sequence and allocation concealment (Yes, Unclear, No), blinding (partially open, double-blind, triple-blind), incomplete outcome data (including whether an intention to treat analysis or per protocol analysis was reported) and duration of follow-up (optimum = until the haemoptysis is stopped; adequate = until the haemoptysis turns into hemorrhagic sputum; inadequate or not defined = arbitrarily determined). We also used a table comparing the methodologies of the included studies which evaluated the number of initially randomized patients versus the numbers that were used in the actual analysis.

Measures of treatment effect

We summarized the dichotomous results for each study using the odds ratio (OR). For the continuous results we used weighted mean differences (WMD). We used the Mantel-Haenszel fixed effect method for pooling dichotomous outcomes, and the generic inverse variance for continuous outcomes.

Dealing with missing data

We included the events reported in the study and follow-up period in the data analysis. Studies without complete information were re-evaluated if the additional information from the authors became available after contacting them. Differences of opinion were solved by consensus.

Assessment of heterogeneity

We used the I^2 test instead of the χ^2 test to ascertain homogeneity among the studies as it is a more useful method with which to analyse heterogeneity when only a few studies exist.

The I^2 is expressed as a percentage and describes the proportion of variability caused by heterogeneity rather than sampling error. Based on [Higgins 2003](#), we have defined low heterogeneity as I^2 values less than 25%, moderate heterogeneity as I^2 values greater than or equal to 25% and less than 50% and high heterogeneity as I^2 values greater than or equal to 50%.

Assessment of reporting biases

We had intended to use a funnel plot to help identify possible publication bias but did not identify a sufficient number of studies to warrant this approach.

Other bias could have arisen in the form of selection bias (location, citation, language, multiple publications), poor methodological quality, inadequate analysis, or inconsistency between studies.

For further information regarding this see [Other potential sources of bias](#).

Data synthesis

We performed a meta analysis for two outcomes where the heterogeneity between the studies was low ($I < 25\%$): remission of haemoptysis in seven days ([Analysis 1.1](#)) and mild adverse effects ([Analysis 1.3](#)). The heterogeneity was high ($I^2 \geq 50\%$) for duration of bleeding ([Analysis 1.2](#)) and therefore we did not pool the results for this outcome.

Subgroup analysis and investigation of heterogeneity

We identified four subgroup analyses relevant to this review: duration of treatment; method of administration; dose; and type of antifibrinolytic agent. However, as this review only includes two studies we were unable to perform subgroup analysis. We analysed the methodological quality of included studies.

We explored the reasons for heterogeneity among the studies. Conclusions were obtained from observations, and the heterogeneity among studies was also evaluated subjectively by means of clinical judgement, based on the differences in patient population, interventions and measurement of the results.

Bearing in mind that the measurement of adverse events was a secondary outcome, results here were interpreted with caution.

Sensitivity analysis

In our protocol, we planned to investigate the impact of excluding trials of questionable design, methodology or outcome measures from the meta-analysis, to test the effect this would have on the overall summary statistics for the estimated treatment effects. As

we only included two studies, sensitivity analysis was not relevant in writing the full review.

RESULTS

Description of studies

Details of the individual studies are given in the [Characteristics of included studies](#) tables. Our searches did not find any studies which subsequently required exclusion from the review.

Results of the search

The original electronic and manual searches (to February 2012) retrieved one randomized control trial (RCT) each. We did not find titles, abstracts or articles in languages other than English or Spanish. When the searches were updated in September 2016 we found no further studies meeting our inclusion criteria.

Overall, two RCTs met the inclusion criteria and were included: [Tscheikuna 2002](#) (electronic search) and [Ruiz 1994](#) (manual search).

We found no studies in children nor any studies in which a type of control other than placebo was used. We did not find any relevant studies of antifibrinolytic agents other than tranexamic acid (TXA).

Included studies

Two RCTs complied with the inclusion criteria. [Ruiz 1994](#) is a double-blind RCT performed at the Hipolito Unanue Hospital (Lima, Peru) in which the intravenous effectiveness of TXA (1g three times a day) administered over three days in 24 hospitalised patients presenting with haemoptysis secondary to tuberculosis was compared with placebo. It measures the duration and volume of bleeding and the number of recurrences of haemoptysis. Adverse events were also reported. Unpublished data from this study were obtained from direct communication with the author in order to clarify funding and the allocation of the participants.

[Tscheikuna 2002](#) is a double-blind RCT performed in Thailand, in which the effectiveness of TXA administered orally (500mg three times a day for up to seven days, stopping when the haemoptysis resolved) in 46 hospital in- and outpatients with haemoptysis of various etiologies was compared with placebo. The duration of the bleeding and adverse effects were reported in the study.

Excluded studies

No potentially relevant studies were excluded.

Risk of bias in included studies

Allocation

In [Ruiz 1994](#) patients were assigned to the respective groups using randomized number tables. Allocation was unknown to all researchers and patients and there was no possibility that the allocation was revealed at any time throughout the study.

In [Tscheikuna 2002](#) the randomization method is not clear; the authors state only that subjects were assigned randomly, without providing information on how randomization was performed.

Blinding

In [Ruiz 1994](#), both groups received intravenous treatment with ampoules of the same characteristics, which prevented

differentiation by patients and personnel administering treatment. The caregivers and outcome assessors were blind to allocation throughout the study. In [Tscheikuna 2002](#), both groups received packs of capsules with the same characteristics and quantities, but it is not clear whether personnel in charge of providing the medicines were blinded.

Incomplete outcome data

Both studies report the number of patients who were initially enrolled but removed from the study before completion (6/30 in [Ruiz 1994](#) and 18/64 in [Tscheikuna 2002](#)). Intention to treat analysis was not carried out and the data obtained from these patients were not reported, indicating a high risk of attrition bias.

Selective reporting

The objectives of both studies were answered clearly, but their protocols could not be obtained making the risk of reporting bias unclear.

Other potential sources of bias

In [Ruiz 1994](#) the number of included patients was fewer than the calculated sampling size and the study was underpowered. Additionally, measuring biases are suggested in the volume of bleeding.

[Tscheikuna 2002](#) is also underpowered as the number of included patients is small and no calculation of the sampling size was included.

As there are only two included studies, we were not able to include a funnel plot to assess publication bias. However, there is a substantial probability that this type of bias exists as there are many more publications about the use of antifibrinolytic agents in other areas ([Brown 2007](#); [Henry 2011](#); [Henry 2011](#); [Tzortzopoulou 2007](#)) and as both of the included studies had small sample sizes.

Effects of interventions

Efficacy

Remission of haemoptysis in seven days or less

No differences in remission rates were found between the patients receiving antifibrinolytics and the patients receiving placebo (OR 1.56, 95% CI 0.44 to 5.46, $I^2=0\%$, [Analysis 1.1](#)). The absolute rate of remission (in patients in both arms of the study) was higher in [Ruiz 1994](#) than in [Tscheikuna 2002](#).

Duration of bleeding

When pooled, the duration of bleeding was significantly shorter in TXA groups when compared with placebo (WMD -19.47, 95% CI -26.90 to -12.03 hours, [Analysis 1.2](#)) with high heterogeneity ($I^2=52\%$).

[Ruiz 1994](#) found a significant difference in the duration of bleeding between groups (54%, treatment group: 23.538+/-13.519 hours vs. placebo group: 50.272+/-17.872, $p<0.0005$), while in [Tscheikuna 2002](#) the difference in the duration of bleeding between the two groups was not statistically significant (treatment group: 54.96+/-41.42 vs placebo group: 70.56+/-41.42, $p=0.2$).

Other measures of efficacy

Only [Ruiz 1994](#) reported volume of bleeding (treatment group: 203.07ml vs. placebo group: 528.18ml, $p<0.0005$), recurrence of bleeding and mortality. It reported two cases of recurrence that led to death: one patient from the TXA group died two weeks after the study was concluded (from asphyxia due to recurrence of bleeding) and one patient in the placebo group experienced massive haemoptysis that resulted in death. No other deaths were reported. Neither trial reported the requirement of invasive procedures, blood transfusions or hospitalisation days.

Safety

Neither of the included studies reported any severe adverse effects attributable to the drug mechanism (venous thromboembolism, acute myocardial infarction, coronary bypass occlusion, stroke, acute renal failure or mortality related to the treatment). No serious adverse effects attributable to the drug (seizures, myopathy and muscular necrosis) were reported in either of the trials.

No significant difference was apparent when we compared reports of mild side effects attributable to TXA (nausea, dizziness, vomiting, abdominal pain or diarrhoea) in the patients receiving active treatment versus patients receiving placebo (OR 3.13, 95% CI 0.8 to 12.24, [Analysis 1.3](#)).

Sensitivity analysis and analysis of the subgroups

Since there were only two included studies it was not appropriate to do additional sensitivity or subgroup analyses.

DISCUSSION

It is important to try to stop bleeding during episodes of haemoptysis. Antifibrinolytic agents are used to decrease bleeding, but there is insufficient evidence regarding their use for haemoptysis ([Martínez 2004](#)).

Summary of main results

[Ruiz 1994](#) found a significant difference between the duration and volume of the bleeding in treatment and control groups, while [Tscheikuna 2002](#) found no difference in duration of bleeding (the volume of the bleeding was not measured).

Despite the use of the same antifibrinolytic agent, the differences in outcomes between the studies may be attributed to:

1. Different doses and forms of administration ([Ruiz 1994](#): 3g per day, intravenous; [Tscheikuna 2002](#): 1.5g per day, orally);
2. Different duration of treatment (three days in [Ruiz 1994](#) vs. up to seven days in [Tscheikuna 2002](#));
3. Different types of patients ([Ruiz 1994](#) recruited only inpatients with haemoptysis secondary to tuberculosis whereas [Tscheikuna 2002](#) recruited in- and outpatients with haemoptysis of different etiologies).

These differences are likely responsible for the high heterogeneity observed when analysing efficacy.

Efficacy was measured with the two variables common to both included studies: remission of haemoptysis in seven days or less (dichotomous variable, [Analysis 1.1](#)) and duration of bleeding (continuous variable, [Analysis 1.2](#)).

In both studies, the groups receiving tranexamic acid (TXA) had a reduced duration of bleeding (WMD -19.47, 95% CI -26.90 to -12.03 hours) when compared to the placebo groups. The wide confidence interval can be attributed to the small sample size in the combined result of the meta-analysis. The substantial reduction in duration of bleeding found in [Ruiz 1994](#) is responsible for the odds ratio of the meta-analysis favouring TXA, even though [Tscheikuna 2002](#) showed no benefit.

TXA was not found to decrease bleeding after up to seven days of treatment when compared with placebo. This is likely due to the short half-life of TXA; its effect after stopping treatment would be brief and would allow recurrence of the bleeding if the fundamental cause had not been resolved. A solution could be the continuous infusion of antifibrinolytics ([CRASH-2 2010](#)).

No adverse effects attributable to the mechanism of action of antifibrinolytic agents were reported. However, these are infrequent and may appear in the long term, and the RCTs included in this review had short follow-up periods. The minor adverse effects reported did not differ between groups, which is consistent with literature on treatment regimes with much higher doses than those used in the included RCTs ([Brown 2007](#); [Henry 2011](#)), which also does not report any adverse effects. Moreover, the known major adverse effects of antifibrinolytics are more frequently caused by aminocaproic acid; as the two included trials used TXA only, it was to be expected that major adverse effects attributable to the drug mechanism would not be reported.

Overall completeness and applicability of evidence

Both included articles correspond to the same medical/clinical (PICO) questions set out in the review (**PICO**: **P**atients and problems, **I**ntervention, **C**omparison and **O**utcomes of relevance for the systematic review). [Ruiz 1994](#) presents enough information to be judged relevant for external applicability, whereas the external validity of [Tscheikuna 2002](#) is limited by insufficient information on study criteria and the power bias shown in the review.

A small percentage of the possible operational variables of interest were found in the included studies; included studies only involved adults with a small group of etiologies. Based on this, the results are not widely applicable.

Quality of the evidence

No categorical conclusions can be made regarding the proposed objectives in the review because only two RCTs were included and both of them have serious methodological limitations, for example, the loss of data on patients without intention to treat analysis, small sample sizes (underpowered studies), short periods of follow-up, heterogeneity in the included studies, no evaluation of long-term adverse effects and the impossibility of inferring recurrent bleeding and mortality. Although the I^2 value permits a meta-analysis of the outcomes, we must take into account the differences between studies when considering the results.

The fact that only one antifibrinolytic agent and two administration modalities (only oral and intravenous by bolus, with no evaluation of continuous infusion, inhalation or nebulization, etc.) were analysed in an adult population with a short length of treatment should also be considered when looking at the results.

Potential biases in the review process

The main potential bias in this review was publication bias. It could not be assessed due to the small number of studies included but, considering the amount of studies published evaluating antifibrinolytics in other areas, the lack of published research on antifibrinolytics in haemoptysis raises concerns.

Agreements and disagreements with other studies or reviews

There is no literature evaluating the handling of haemoptysis at this level. In other pathologies and medical scenarios, antifibrinolytic therapy has proven to be safe. There were no disagreements among the reviewers.

AUTHORS' CONCLUSIONS

Implications for practice

There is insufficient evidence to determine if antifibrinolytic agents of any kind should be used in the treatment of haemoptysis. However, limited evidence suggests that antifibrinolytic agents may reduce the duration of bleeding in haemoptysis when compared with placebo and that their use is not related to short-term adverse effects. More evidence is necessary to draw conclusions about the role of this treatment for haemoptysis.

Implications for research

Further RCTs are needed to investigate the efficacy of antifibrinolytic agents in reducing haemoptysis when compared with conventional therapy and to investigate the comparative efficacy of different types of antifibrinolytic agents. Additional RCTs are also needed to evaluate the use of antifibrinolytics as reinforcement drugs in the surgical handling of haemoptysis. Reported results should include the volume and duration of bleeding, mortality attributed to haemoptysis, number of relapses, need for blood transfusions, need for invasive procedures, and data for a cost-effectiveness ratio.

Future research should aim to define which antifibrinolytic agent, administration method (oral vs. intravenous), regimen (basal bolus, continuous infusion or charge and maintenance), duration and treatment doses are the most efficacious in treating haemoptysis depending on its severity and etiology.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Ruiz 1994

Methods	Double blind randomized clinical trial performed at the Hipolito Unanue Hospital (Lima, Peru). Unpublished data from this study were obtained from direct conversation with the author in order to clarify the allocation of the participants and financing.
Participants	30 inpatients from the emergency room of the Hipolito Unanue Hospital, Lima, Peru presenting with haemoptysis secondary to tuberculosis. 24 participants included in final data.
Interventions	1. Intravenous TXA 1g tid over 3 days 2. Placebo
Outcomes	The duration and volume of the bleeding and the number of recurrences. The incidence of adverse effects was also reported.
Notes	6/30 patients were removed from the study.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The patients were assigned to the respective groups using randomized number tables.
Allocation concealment (selection bias)	Low risk	The allocation was unknown to all researchers (caregivers, data collectors and outcome assessors) and patients and there was no possibility that the allocation was revealed at any time throughout the study.
Blinding (performance bias and detection bias) All outcomes	Low risk	It is clearly explained that both groups were receiving intravenous treatment with ampoules of the same characteristics which prevented differentiation by the patients and administering personnel. The blinding of the outcome assessors was maintained throughout the study.
Incomplete outcome data (attrition bias) All outcomes	High risk	6/30 patients lost to follow-up. No intention to treat analysis was carried out and the data obtained from these patients were not reported.
Selective reporting (reporting bias)	Unclear risk	The objectives of the study were answered clearly, but its protocol could not be obtained.
Other bias	High risk	Measuring biases are mentioned in the volume of bleeding.

Tscheikuna 2002

Methods	Double blind RCT performed in Thailand
Participants	64 in- and outpatients presenting with haemoptysis of varying etiologies who were treated in the department of Internal Medicine, Siriraj Hospital, Thailand. 46 participants were included in the final analysis.
Interventions	1. TXA 500mg orally tid for seven days or until haemoptysis was resolved 2. Placebo
Outcomes	The duration of the bleeding and adverse effects were evaluated in the study.
Notes	18/64 missing final outcome data.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The randomization method is not clear. The authors indicate that patients were assigned randomly but did not explain how randomization was performed.
Allocation concealment (selection bias)	Unclear risk	There is no information as to whether the assignment was kept concealed.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Both groups received packs of capsules of the same characteristics and quantities. It is unclear whether the personnel in charge of providing the medicines or the outcome assessors were blinded.
Incomplete outcome data (attrition bias) All outcomes	High risk	18/64 lost to follow-up. No intention to treat analysis was carried out and the data obtained from these patients were not reported.
Selective reporting (reporting bias)	Unclear risk	The objectives of the study were answered clearly, but its protocol could not be obtained.

tid = three times a day; TXA = tranexamic acid

DATA AND ANALYSES

Comparison 1. Tranexamic acid versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Remission of haemoptysis in 7 days or less	2	70	Odds Ratio (M-H, Fixed, 95% CI)	1.56 [0.44, 5.46]
2 Duration of bleeding (hours)	2	70	Mean Difference (IV, Fixed, 95% CI)	-24.61 [-35.95, -13.26]
3 Minor adverse effects	2	70	Odds Ratio (M-H, Fixed, 95% CI)	3.13 [0.80, 12.24]

Analysis 1.1. Comparison 1 Tranexamic acid versus placebo, Outcome 1 Remission of haemoptysis in 7 days or less.

Analysis 1.2. Comparison 1 Tranexamic acid versus placebo, Outcome 2 Duration of bleeding (hours).

Analysis 1.3. Comparison 1 Tranexamic acid versus placebo, Outcome 3 Minor adverse effects.

APPENDICES

Appendix 1. MEDLINE search strategy

#1	Search "Hemoptysis"[Mesh]
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(Continued)

#2	Search randomized controlled trial or randomized controlled trials or randomized trial or randomized trials or randomized clinical trial or randomized clinical trials or randomized double blind or double blind placebo or double blind or double blind randomized or clinical trial or clinical trials or controlled study or double-blind placebo-controlled or controlled trials or controlled trial.
#3	"Antifibrinolytic Agents"[Mesh]
#4	Search aprotinin or nafamostat or tranexamic acid or epsilon aminocaproic acid
#5	Search #1 and #2 and #3 and #4

Appendix 2. LILACS search strategy

We searched on the web page: <http://regional.bvsalud.org>, using the DeCS/MeSH descriptors:

#1	[MH] "hemoptysis" OR "haemoptysis"
#2	[MH] "antifibrinolytic" [Words]
#3	aprotinin or nafamostat or tranexamic acid or epsilon aminocaproic acid
#4	randomized controlled trial or randomized controlled trials or randomized trial or randomized trials or randomized clinical trial or randomized clinical trials or randomized double blind or double blind placebo or double blind or double blind randomized or clinical trial or clinical trials or controlled study or double-blind placebo-controlled or controlled trials or controlled.
#5	Search #1 and #2 and #3 and #4

Appendix 3. CENTRAL search strategy

#1	Hemoptysis OR haemoptysis
#2	antifibrinolytic agents
#3	aprotinin OR nafamostat OR tranexamic acid OR epsilon aminocaproic acid
#4	Search #1 and #2 and #3

WHAT'S NEW

Date	Event	Description
22 September 2016	New search has been performed	Searches updated, no new included, ongoing or excluded studies identified.
22 September 2016	New citation required but conclusions have not changed	Search dates changed, no other changes

CONTRIBUTIONS OF AUTHORS

All four authors participated in all the review processes.

DECLARATIONS OF INTEREST

None known.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In the protocol we planned to perform sensitivity and subgroup analysis, but we were unable to do so in the final review due to the fact that there were only two included studies.

INDEX TERMS

Medical Subject Headings (MeSH)

Administration, Oral; Antifibrinolytic Agents [administration & dosage] [*therapeutic use]; Hemoptysis [*drug therapy] [etiology] [mortality]; Injections, Intravenous; Peru; Randomized Controlled Trials as Topic; Thailand; Tranexamic Acid [administration & dosage] [*therapeutic use]; Tuberculosis, Pulmonary [complications]

MeSH check words

Adult; Humans