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Joseph J, Martinez-Devesa P, Bellorini J, Burton MJ

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Tranexamic acid for patients with nasal haemorrhage (epistaxis).
Cochrane Database of Systematic Reviews 2018, Issue 12. Art. No.: CD004328.
DOI: 10.1002/14651858.CD004328.pub3.

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[Intervention Review]

Tranexamic acid for patients with nasal haemorrhage (epistaxis)

Jonathan Joseph[1], Pablo Martinez-Devesa[2], Jenny Bellorini[3], Martin J Burton[4]

[1]Royal National Throat, Nose and Ear Hospital, London, UK. [2]ENT Department, John Radcliffe Hospital - West Wing, Oxford, UK. [3]Cochrane ENT, Nuffield Department of Surgical Sciences, University of Oxford, Oxford, UK. [4]Cochrane UK, Oxford, UK

Contact address: Jonathan Joseph, Royal National Throat, Nose and Ear Hospital, 330 Gray's Inn Road, London, WC1X 8DA, UK. jajoseph@doctors.org.uk.

Editorial group: Cochrane ENT Group.
Publication status and date: New, published in Issue 12, 2018.

Citation: Joseph J, Martinez-Devesa P, Bellorini J, Burton MJ. Tranexamic acid for patients with nasal haemorrhage (epistaxis). *Cochrane Database of Systematic Reviews* 2018, Issue 12. Art. No.: CD004328. DOI: 10.1002/14651858.CD004328.pub3.

ABSTRACT

Background

Epistaxis (nosebleed) most commonly affects children and the elderly. The majority of episodes are managed at home with simple measures. In more severe cases medical intervention is required to either cauterise the bleeding vessel, or to pack the nose with various materials. Tranexamic acid is used in a number of clinical settings to stop bleeding by preventing clot breakdown (fibrinolysis). It may have a role in the management of epistaxis as an adjunct to standard treatments, reducing the need for further intervention.

Objectives

To determine the effects of tranexamic acid (oral, intravenous or topical) compared with placebo, no additional intervention or any other haemostatic agent in the management of patients with epistaxis.

Search methods

The Cochrane ENT Information Specialist searched the Cochrane ENT Register (via CRS Web); Central Register of Controlled Trials (CENTRAL) (via CRS Web); PubMed; Ovid Embase; CINAHL; Web of Science; ClinicalTrials.gov; ICTRP and additional sources for published and unpublished trials. The date of the search was 29 October 2018.

Selection criteria

Randomised controlled trials (RCTs) of tranexamic acid (in addition to usual care) compared with usual care plus placebo, usual care alone or usual care plus any other haemostatic agent, to control epistaxis in adults or children.

Data collection and analysis

We used the standard methodological procedures expected by Cochrane. The primary outcomes were control of epistaxis: re-bleeding (as measured by the proportion of patients re-bleeding within a period of up to 10 days) and significant adverse effects (seizures, thromboembolic events). Secondary outcomes were control of epistaxis as measured by the time to stop initial bleeding (the proportion of patients whose bleeding is controlled within a period of up to 30 minutes); severity of re-bleeding (as measured by (a) the proportion of patients requiring any further intervention and (b) the proportion of patients requiring blood transfusion); length of hospital stay and other adverse effects. We used GRADE to assess the quality of the evidence for each outcome; this is indicated in *italics*.

Main results

We included six RCTs (692 participants). The overall risk of bias in the studies was low. Two studies assessed oral administration of tranexamic acid, given regularly over several days, and compared it to placebo. In the other four studies, a single application of topical tranexamic acid was compared with placebo (one study) and a combination of epinephrine and lidocaine or phenylephrine (three studies). All participants were adults.

Tranexamic acid versus placebo

For our primary outcome, control of epistaxis: re-bleeding (proportion re-bleeding within 10 days), we were able to pool data from three studies. The pooled result demonstrated a benefit of tranexamic acid compared to placebo, the risk of re-bleeding reducing from 67% to 47% (risk ratio (RR) 0.71, 95% confidence interval (CI) 0.56 to 0.90; three studies; 225 participants; *moderate-quality evidence*).

When we compared the effects of oral and topical tranexamic acid separately the risk of re-bleeding with **oral** tranexamic acid reduced from 69% to 49%, RR 0.73 (95% CI 0.55 to 0.96; two studies, 157 participants; *moderate-quality evidence*) and with **topical** tranexamic acid it reduced from 66% to 43%, RR 0.66 (95% CI 0.41 to 1.05; single study, 68 participants). We rated the quality of evidence provided by the single study as *low*, therefore it is uncertain whether topical tranexamic acid is effective in stopping bleeding in the 10-day period after a single application.

No study specifically sought to identify and report our primary outcome: significant adverse effects (i.e. seizures, thromboembolic events).

The secondary outcome time to stop initial bleeding (proportion with bleeding controlled within 30 minutes) was measured in one study using topical tranexamic acid and there was no evidence of a difference at 30 minutes (RR 0.79, 95% CI 0.56 to 1.11; 68 participants; *low-quality evidence*).

No studies reported the proportion of patients requiring any further intervention (e.g. repacking, surgery, embolisation).

One study of oral tranexamic acid reported the proportion of patients requiring blood transfusion and found no difference between groups: 5/45 (11%) versus 6/44 (14%) (RR 0.81, 95% CI 0.27 to 2.48; 89 participants; *low-quality evidence*).

Two studies reported hospital length of stay. One study reported a significantly shorter stay in the oral tranexamic acid group (mean difference (MD) -1.60 days, 95% CI -2.49 to -0.71; 68 participants). The other study found no evidence of a difference between the groups.

Tranexamic acid versus other haemostatic agents

When we pooled the data from three studies the proportion of patients whose bleeding stopped within 10 minutes was significantly higher in the topical tranexamic acid group compared to the group receiving another haemostatic agent (70% versus 30%: RR 2.35, 95% CI 1.90 to 2.92; 460 participants) (*moderate-quality evidence*).

Adverse effects across all studies

Five studies recorded 'adverse effects' in a general way. None found any difference between the groups in the occurrence of minor adverse effects (e.g. mild nausea and diarrhoea, 'bad taste' of gel). In one study a patient developed a superficial thrombophlebitis of both legs following discharge, however it is not reported in which group this occurred. No "other serious adverse effect" was reported in any study.

Authors' conclusions

We found *moderate-quality evidence* that there is probably a reduction in the risk of re-bleeding with the use of either oral or topical tranexamic acid in addition to usual care in adult patients with epistaxis, compared to placebo with usual care. However, the quality of evidence relating solely to *topical* tranexamic acid was low (one study only), so we are uncertain whether or not *topical* tranexamic acid is effective in stopping bleeding in the 10-day period after a single application. We found *moderate-quality evidence* that topical tranexamic acid is probably better than other topical agents in stopping bleeding in the first 10 minutes.

There have been only three RCTs on this subject since 1995. Since then there have been significant changes in nasal cauterisation and packing techniques (for example, techniques including nasal endoscopy and more invasive approaches such as endoscopic sphenopalatine artery ligation). New trials would inform us about the effectiveness of tranexamic acid in light of these developments.

PLAIN LANGUAGE SUMMARY

Tranexamic acid to help treat nosebleeds (epistaxis)

Background

Nosebleeds are a very common condition, with the majority of those affected either children or those over the age of 60. They usually stop on their own or by simply compressing the nose with fingers, although a small number require medical attention. This will involve either cauterising (sealing) the bleeding vessel, if it can be seen, or packing the inside of the nose with a material to cause pressure to build up and stop the bleeding ('usual care'). Occasionally bleeding continues despite these measures, or it restarts having initially been controlled. This can lead to a prolonged hospital stay and the possibility of further procedures such as repacking with a different type of nasal pack or an operation.

Tranexamic acid is a drug that is known to help promote blood clotting by preventing a natural process called fibrinolysis (dissolution of a clot). It is already used in a number of situations where bleeding is a significant worry, such as after heart surgery or major trauma. It can be given by mouth (orally), directly to the bleeding site (topically) or by injection into a vein (intravenously).

Study characteristics

We searched for randomised controlled trials in patients of any age with nosebleed requiring intervention. Patients were treated with tranexamic acid (in addition to usual care) compared to placebo, no treatment or any other agent used to stop bleeding. We found six studies that met our inclusion criteria, with a total of 692 participants. Two studies used oral administration of tranexamic acid and four used topical administration. All participants in the studies were adults. Three of the six studies were conducted over 20 years ago.

Key results

Three studies measured re-bleeding within 10 days. When we combined the results we found that fewer patients who were given either oral or topical tranexamic acid had further episodes of re-bleeding following an initial nosebleed compared to those treated with usual care.

The time to stop initial bleeding (control of bleeding within 30 minutes) was measured in four studies. In three studies the proportion of patients whose bleeding stopped within 10 minutes was significantly higher in the group receiving topical tranexamic acid compared to the group receiving a different drug (topical epinephrine and lidocaine or phenylephrine). In the other study there was no significant difference at 30 minutes when topical tranexamic acid was compared with placebo.

No studies reported the proportion of patients requiring any further intervention (e.g. repacking, surgery).

Only one study of oral tranexamic acid reported the proportion of patients requiring a blood transfusion and there was no evidence of a difference between the groups.

Length of hospital stay was reported in two studies. One study reported a significantly shorter stay in the oral tranexamic acid group, while the other found no evidence of a difference.

Five studies mention recording "adverse effects". None found any difference between the groups in the occurrence of minor adverse effects (e.g. mild nausea and diarrhoea, 'bad taste' of gel). In one study a patient did develop a superficial thrombophlebitis (inflammation and a blood clot in a vein near the surface of the skin) of both legs following discharge, but the study did not report in which treatment group this happened. No serious adverse event was seen in any of the studies.

Quality of the evidence and conclusions

Overall, the risk of bias in the six studies was low. We graded the quality of the evidence for the main outcome (control of epistaxis: re-bleeding within 10 days) as moderate, which means that further research is likely to have an important impact on our confidence in the estimate of the effect and is likely to change the estimate. In light of this and the fact that 'usual care' has changed, with the development of more modern nasal cauterisation and packing techniques, since three of the included studies were carried out, there remains uncertainty about the role of tranexamic acid in the treatment of patients with epistaxis. Newer research into the effect of tranexamic acid as a treatment for nosebleeds would inform future management decisions for this condition.

The evidence in this review is up to date to October 2018.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Tranexamic acid compared to placebo plus usual care or usual care alone for patients with nasal haemorrhage (epistaxis)

Patient or population: adults with nasal haemorrhage (epistaxis)
Setting: inpatients and outpatients
Intervention: tranexamic acid
Comparison: placebo plus usual care or usual care alone

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	What happens?
	Risk with placebo plus usual care or usual care alone	Risk with tranexamic acid				
Control of epistaxis: episodes of re-bleeding over 10 days All treatments (topical and oral)	Study population 672 per 1000	477 per 1000 (376 to 605)	RR 0.71 (0.56 to 0.90)	225 (3 RCTs)	⊕⊕⊕◯ MODERATE [1]	Tranexamic acid probably leads to fewer re-bleeding events compared to placebo at 10 days
Control of epistaxis: episodes of re-bleeding over 10 days Oral treatment only	Study population 679 per 1000	496 per 1000 (373 to 652)	RR 0.73 (0.55 to 0.96)	157 (2 RCTs)	⊕⊕⊕◯ MODERATE [1]	Oral tranexamic acid probably leads to fewer re-bleeding events compared to placebo at 10 days
Control of epistaxis: episodes of re-bleeding over 10 days Topical application (10% gel) only	Study population		RR 0.66 (0.41 to 1.05)	68 (1 RCT)	⊕⊕◯◯ LOW [1,2]	A single study found no evidence of a difference in the chance of re-bleeding in the 10 days after a single topical application of tranexamic acid

	658 per 1000	434 per 1000 (270 to 691)				
Control of epistaxis: time to stop initial bleeding (proportion of patients whose bleeding is controlled in ≤ 30 minutes)	Study population		RR 0.79 (0.56 to 1.11)	68 (1 RCT)	⊕⊕◯◯ LOW [1,2]	A single study found no evidence of a difference in the proportion of patients whose epistaxis was controlled in the first 30 minutes
	600 per 1000	474 per 1000 (336 to 666)				
Severity of re-bleeding: proportion of patients requiring blood transfusion within 10 days	Study population		RR 0.81 (0.27 to 2.48)	89 (1 RCT)	⊕⊕◯◯ LOW [1,2]	A single study found no evidence of a difference in the proportion of patients needing a blood transfusion
	136 per 1000	110 per 1000 (37 to 338)				
Length of hospital stay	One study reported a significantly shorter stay in the oral tranexamic acid group (MD -1.60 days, 95% CI -2.49 to -0.71; 68 participants). The other study found no evidence of a difference between the groups			157 (2 RCTs)	-	We did not pool the data due to heterogeneity
Adverse effects: serious or other	See comment	See comment	-	-	-	No study specifically sought to identify and report our primary outcome, the significant adverse effects of seizure and thromboembolism. All the studies recorded "adverse effects" in a general way and there were no significant differences between groups in the occurrence of the minor adverse effects noted (e.g. mild nausea and diarrhoea, 'bad taste' of gel)

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

__CI:__ confidence interval; __RCT:__ randomised controlled trial; __RR:__ risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1]Imprecision: downgraded by one level - small number of studies (or single study) and small number of participants (per study).
[2]Study limitations (risk of bias): downgraded by one level due to study risk of bias (differences in baseline severity of bleeding that could affect the result in Tibbelin 1995; selective reporting in White 1988).

BACKGROUND

Description of the condition

Epistaxis (nosebleed) is extremely common. It has a pronounced bimodal distribution, being common in childhood and then becoming less frequent before the incidence rises again in the sixth decade (McGarry 2008). Its prevalence in random samples of the population was found in one study to be 10% to 12% at any given time (Shaheen 1967). The cause of epistaxis is unknown in 70% to 80% of cases (idiopathic epistaxis) (Stell 1977). However, epistaxis may be secondary to a number of causes such as surgery, trauma, hypertension, coagulation abnormalities, hereditary haemorrhagic telangiectasia and the use of medications such as aspirin and warfarin (McGarry 2008).

Most epistaxis is self-limiting or settles with simple measures such as compression (pinching the nose for example), and is ideally managed at home without further medical interference. Patients with more severe bleeding may require medical attention. Two basic methods are used: cauterisation to seal the bleeding vessel if it can be seen and, when this is not possible, various materials may be used to pack the nose to arrest the blood flow. In anterior epistaxis, which is the most common type, a bleeding point is often visible and can be cauterised under local anaesthetic by either a locally applied chemical such as silver nitrate or by electrocautery (hot wire). In some cases this is not sufficient and nasal packing is required with materials such as ribbon gauze, nasal tampons, balloons or inflatable packs. Posterior epistaxis is more common in older adults with hypertension and arteriosclerosis. In these cases a bleeding point is often not identified and nasal packing is necessary. This packing usually stays in for one to two days and applies pressure to the bleeding site thereby stopping the bleeding. Re-bleeding may occur after initial management, which often results in a longer hospital stay and further treatments including repeat nasal packing, surgery or embolisation.

If bleeding persists or recurs despite nasal packing then surgical intervention may be necessary and if the blood loss is great, transfusion may be necessary.

Patients admitted with a severe epistaxis, whether anterior or posterior, may face significant morbidity. Nasal packing is uncomfortable. There is also a very small risk of death from a number of causes including the epistaxis itself (when uncontrollable) and the effects of treatments. For example, nasal packing can lead to hypoxia and, if a general anaesthetic is required as part of the treatment, this also carries small but significant risks.

Description of the intervention

Tranexamic acid is an anti-fibrinolytic agent, used to prevent or treat bleeding in a wide variety of clinical situations. It can be administered orally or intravenously, or applied topically. It is contraindicated in patients with thromboembolic disease such as stroke and heart attack.

How the intervention might work

Tranexamic acid stabilises blood clots by competitively inhibiting the binding of plasminogen to fibrin preventing fibrinolysis. This antifibrinolytic effect means that it is routinely used to reduce excessive bleeding and to prevent re-bleeding in many clinical situations (Ker 2012; Roberts 2013). For example, it is used following cardiac surgery when cardiopulmonary bypass is used and in acute upper gastrointestinal bleeding (Dunn 1999).

Tranexamic acid may therefore have a role to play in the management of epistaxis as an adjunct to usual therapies. It may have roles in (a) stopping initial bleeding, and (b) preventing or reducing the frequency and/or severity of re-bleeding. This will reduce the need for further interventions with all their attendant risks.

Tranexamic acid to stop or minimise initial bleeding

In patients with epistaxis, tranexamic acid may help stop bleeding at the time of initial administration (or very shortly thereafter), preventing the need for more invasive treatments such as cautery and nasal packing. It is uncertain whether a single dose (or a very short period of treatment) might result in a more rapid resolution of the patient's condition with fewer re-bleeding episodes and the need for fewer interventions in a 'recovery' period lasting several days.

The initiation of a course of tranexamic acid treatment destined to last several days may have a similar effect.

Tranexamic acid to prevent re-bleeding

Tranexamic acid may be prescribed regularly, over a number of days after the initial epistaxis, in order to achieve similar ends: that is, more rapid resolution of the patient's condition with fewer re-bleeding episodes and the need for fewer interventions in that period.

Adverse effects

The most common adverse events are gastrointestinal (for example, nausea, diarrhoea and abdominal cramping), which are mild and uncommon (Robb 2014). However, thromboembolic events (Nishihara 2015) and seizures (Sharma 2014) have been reported (although these two studies do not evaluate patients with epistaxis or receiving tranexamic acid in doses similar to patients with epistaxis).

Why it is important to do this review

There is uncertainty about the role of tranexamic acid in the management of patients with epistaxis. A recent audit of epistaxis management in the UK analysed the data from 1122 patients and found that tranexamic acid was used in 8.2% of cases (UK Epistaxis Audit 2017). Time to haemostasis was longer and re-bleeding rates were higher in these patients; however, the number of patients was small and they had a "higher degree of illness". A consensus document on the hospital management of epistaxis (BRS 2017) highlighted the inconsistent findings from a systematic review (Williams 2017) and therefore did not recommend the use of either oral or topical tranexamic acid, except in relevant cases (i.e. following national guidelines on the use of tranexamic acid in major haemorrhage). Further studies are, however, ongoing and their findings may expand the evidence base (ISRCTN34153772; NCT02930941; NCT03360045).

An up-to-date Cochrane Review, which can be updated as further studies are completed, is warranted.

OBJECTIVES

To determine the effects of tranexamic acid (oral, intravenous or topical) compared with placebo, no additional intervention or any other haemostatic agent in the management of patients with epistaxis.

METHODS

Criteria for considering studies for this review

Types of studies

We included studies with the following design characteristics:

- Randomised controlled trials (RCTs) including cluster-randomised trials.
- Patients were followed up for at least seven days.

Types of participants

Patients of any age with epistaxis requiring intervention by a healthcare professional.

Exclusion criteria

- Patients with a clotting or bleeding disorder, sinonasal malignancy and chronic inflammatory nasal conditions.

Types of interventions

Tranexamic acid in any formulation, delivered orally, intravenously or topically.

If other interventions were used at the start of treatment, when tranexamic acid or placebo was given or first started, these should have been used in both treatment arms. Allowed co-interventions included cautery and nasal packing.

The comparators were:

- placebo;
- no treatment;
- any other haemostatic agent.

After the start of treatment, patients may require further interventions to control re-bleeding. These include: cauterisation, nasal packing, surgery and embolisation.

The main comparison pair was:

- tranexamic acid *versus* placebo or no treatment.

A second comparison pair was:

- tranexamic *versus* any other haemostatic agent.

For a more detailed description of how we planned to group the interventions together for analysis see Subgroup analysis and investigation of heterogeneity.

Types of outcome measures

We analysed the following outcomes in the review, but we did not use them as a basis for including or excluding studies.

Primary outcomes

- Control of epistaxis: re-bleeding, as measured by the proportion of patients re-bleeding within a period of up to 10 days (minimum five days).
- Significant adverse effects: seizures, thromboembolic events.

Secondary outcomes

- Control of epistaxis: time to stop initial bleeding (as measured by the proportion of patients whose bleeding is controlled within 30 minutes).
- Severity of re-bleeding, as measured by:
    - the proportion of patients requiring any further intervention (e.g. repacking, surgery, embolisation) within 10 days;
    - the proportion of patients requiring blood transfusion within 10 days.
- Length of hospital stay in days.
- Other adverse effects.

Search methods for identification of studies

The Cochrane ENT Information Specialist conducted systematic searches for randomised controlled trials and controlled clinical trials. There were no language, publication year or publication status restrictions. The date of the search was 29 October 2018.

Electronic searches

The Information Specialist searched:

- the Cochrane ENT Register (searched via CRS Web 29 October 2018);
- the Cochrane Central Register of Controlled Trials (CENTRAL) (searched via CRS Web 29 October 2018);
- PubMed (1946 to 29 October 2018);
- Ovid EMBASE (1974 to 29 October 2018);
- Ovid CAB Abstracts (1910 to 29 October 2018);
- EBSCO CINAHL (1982 to 29 October 2018);
- LILACS, lilacs.bvsalud.org (searched 29 October 2018);
- KoreaMed, www.koreamed.org (searched 29 October 2018);
- IndMed, www.indmed.nic.in (searched 29 October 2018);
- PakMediNet, www.pakmedinet.com (searched 29 October 2018);
- Web of Knowledge, Web of Science (1945 to 29 October 2018);
- CNKI, www.cnki.com.cn (searched via Google Scholar 29 October 2018);
- ClinicalTrials.gov, (searched via CRS Web 29 October 2018);
- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP), www.who.int/ictrp (searched 29 October 2018).

In searches prior to 2012, we also searched BIOSIS Previews 1926 to November 2012.

The Information Specialist modelled subject strategies for databases on the search strategy designed for CENTRAL. Where appropriate, they were combined with subject strategy adaptations of the highly sensitive search strategy designed by Cochrane for identifying randomised controlled trials and controlled clinical trials (as described in the *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0, Box 6.4.b. (Handbook 2011). Search strategies for major databases including CENTRAL are provided in Appendix 1.

Searching other resources

We scanned the reference lists of identified publications for additional trials and contacted trial authors where necessary. In addition, the Information Specialist searched PubMed to retrieve existing systematic reviews relevant to this systematic review, so that we could scan their reference lists for additional trials. The Information Specialist also ran non-systematic searches of Google Scholar to retrieve grey literature and other sources of potential trials.

Data collection and analysis

Selection of studies

Two authors (JJ and PMD or JB and MB) independently scanned the search results to identify studies that loosely met the inclusion criteria. We then independently reviewed the full texts of the retrieved trials and applied the inclusion criteria. We resolved any differences between the authors in study selection through discussion and reaching a consensus. We documented our search and study selection process and depicted this graphically in a PRIMSA flowchart.

Data extraction and management

We extracted data from the studies using standardised data forms, allowing for an intention-to-treat analysis. The main data items that we extracted were: date, duration and setting for the study, number of participants, participant (baseline) characteristics (age, gender, other), type of 'usual care' provided, method of delivery and dosage of tranexamic acid and type of outcome measures used (see Appendix 2). Where data were missing we attempted to contact the authors of the study to request the missing information.

Assessment of risk of bias in included studies

Two authors (JJ and PMD) undertook independent assessment of the risk of bias of the included studies. The following were taken into consideration, as guided by the *Cochrane Handbook for Systematic Reviews of Interventions* (Handbook 2011):

- sequence generation;
- allocation concealment;
- blinding;
- incomplete outcome data;
- selective outcome reporting; and
- other sources of bias.

We used the Cochrane 'Risk of bias' tool in RevMan 5 (RevMan 2014), which involves describing each of these domains as reported in the study and then assigning a judgement about the adequacy of each entry: low, high or unclear (or unknown) risk of bias.

Measures of treatment effect

We summarised the effects of dichotomous outcomes (e.g. proportion of patients with re-bleeding) as risk ratios (RR) with CIs. For the key outcomes that we presented in the 'Summary of findings' table, we also expressed the results as absolute numbers based on the pooled results and compared to the assumed risk. The assumed

baseline risk is typically either (a) the median of the risks of the control groups in the included studies, this being used to represent a 'medium-risk population' or, alternatively, (b) the average risk of the control groups in the included studies is used as the 'study population' (Handbook 2011). If a large number of studies were available, and where appropriate, we also planned to present additional data based on the assumed baseline risk in (c) a low-risk population and (d) a high-risk population.
For continuous outcomes, we expressed treatment effects as a mean difference (MD) with standard deviation (SD).

Unit of analysis issues

If we had found cluster-randomised trials, we would have analysed these according to the methods in section 16.3.3 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Handbook 2011).

Dealing with missing data

We planned to undertake an intention-to-treat analysis where possible.
We planned to contact study authors via email whenever the outcome of interest was not reported, if the methods of the study suggested that the outcome had been measured. We planned to do the same if not all data required for meta-analysis had been reported, unless the missing data were standard deviations. If standard deviation data were not available, we planned to approximate these using the standard estimation methods from P values, standard errors or 95% CIs if these were reported as detailed in the *Cochrane Handbook for Systematic Reviews of Interventions* (Handbook 2011). If it was impossible to estimate these, we would have contacted the study authors.
Apart from imputations for missing standard deviations, we did not plan to conduct any other imputations.

Assessment of heterogeneity

We assessed clinical heterogeneity (which may be present even in the absence of statistical heterogeneity) by examining the included studies for potential differences between them in the types of participants recruited, interventions or controls used or outcomes measured. In this review we anticipated that the intervention might have been used in two different ways: as a single treatment at the time of bleeding, or over a period following initial treatment to prevent re-bleeding, or a combination of both.
We assessed statistical heterogeneity using the Chi^2 test with $P < 0.05$ indicating significance. We also used the I^2 statistic with the following thresholds for assessing the impact of the heterogeneity the pooled analyses:

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity;
- 75% to 100%: considerable heterogeneity.

Assessment of reporting biases

We planned to assess reporting bias as between-study publication bias (using funnel plots if sufficient studies were available) and as within-study outcome reporting bias. There was sometimes insufficient information to judge the risk of selective reporting bias: we noted this as an 'unclear' risk of bias.

Data synthesis

We conducted all meta-analyses using Review Manager 5.3 (RevMan 2014). For dichotomous data, we analysed treatment differences as a risk ratio (RR) calculated using the Mantel-Haenszel method.
For continuous outcomes, we planned to pool mean values obtained at follow-up and report a mean difference (MD).
When statistical heterogeneity is low, random-effects versus fixed-effect methods yield trivial differences in treatment effects. However, when statistical heterogeneity is high, the random-effects method provides a more conservative estimate of the difference.

Subgroup analysis and investigation of heterogeneity

We planned to conduct the following subgroup analyses regardless of whether statistical heterogeneity was observed, as these may be effect modifiers:

- mode and timing of administration;
- patient age (children versus adults);
- setting (inpatient versus outpatient);
- site of nosebleed (anterior versus posterior).

The various modes of administration of tranexamic acid are likely to affect the primary outcome in different ways. Topical administration is likely to have a faster effect but with a shorter duration. Oral and intravenous delivery will have a delayed onset (greater with oral administration than intravenous) but if repeated doses are given, the duration of effect will last at least as long as therapeutic doses are being administered.

Sensitivity analysis

We planned to carry out sensitivity analyses to determine whether the findings were robust to the decisions made in the course of identifying, screening and analysing the trials. We planned to conduct sensitivity analysis for the following factors, whenever possible, and where applicable:

- impact of model chosen: fixed-effect versus random-effects model;
- risk of bias of included studies: excluding studies with high risk of bias (we defined these as studies that had a high risk of allocation concealment bias and a high risk of attrition bias

(overall loss to follow-up of 20%, differential follow-up observed).

If any of these investigations found a difference in the size of the effect or heterogeneity, we had planned to mention this in the Effects of interventions section.

GRADE and 'Summary of findings' table

Two authors (MB, JB) independently used the GRADE approach to rate the overall quality of evidence. The quality of evidence reflects the extent to which we are confident that an estimate of effect is correct and we applied this in the interpretation of results. There are four possible ratings: high, moderate, low and very low. A rating of high quality of evidence implies that we are confident in our estimate of effect and that further research is very unlikely to change our confidence in the estimate of effect. A rating of very low quality implies that any estimate of effect obtained is very uncertain.

The GRADE approach rates evidence from RCTs which do not have serious limitations as high quality. However, several factors can lead to the downgrading of the evidence to moderate, low or very low. The degree of downgrading is determined by the seriousness of these factors:

- study limitations (risk of bias);
- inconsistency;
- indirectness of evidence;
- imprecision; and
- publication bias.

We included 'Summary of findings' tables for the comparisons of tranexamic acid *versus* placebo or no treatment and tranexamic acid *versus* other haemostatic agent, constructed according to the recommendations described in Chapter 10 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Handbook 2011).

We planned to include the following seven outcomes in the 'Summary of findings' table, but only those where data were available were actually included:

- Primary outcomes
    - Control of epistaxis: re-bleeding (the proportion of patients re-bleeding within a period of up to 10 days (minimum five days)).
    - Significant adverse effects (seizures, thromboembolic events).
- Secondary outcomes
    - Control of epistaxis: time to stop initial bleeding (the proportion of patients whose bleeding is controlled within 30 minutes).
    - Severity of re-bleeding, as measured by:
        - the proportion of patients requiring any further intervention (e.g. repacking, surgery, embolisation) within 10 days);
        - the proportion of patients requiring blood transfusion within 10 days).
    - Length of hospital stay in days.
    - Other adverse effects.

RESULTS

Description of studies

Results of the search

A total of 680 references were retrieved by the searches in October 2018. This reduced to 431 following de-duplication and removal of clearly irrelevant references. We discarded 401 records in first-level screening, leaving 30 references for further consideration.

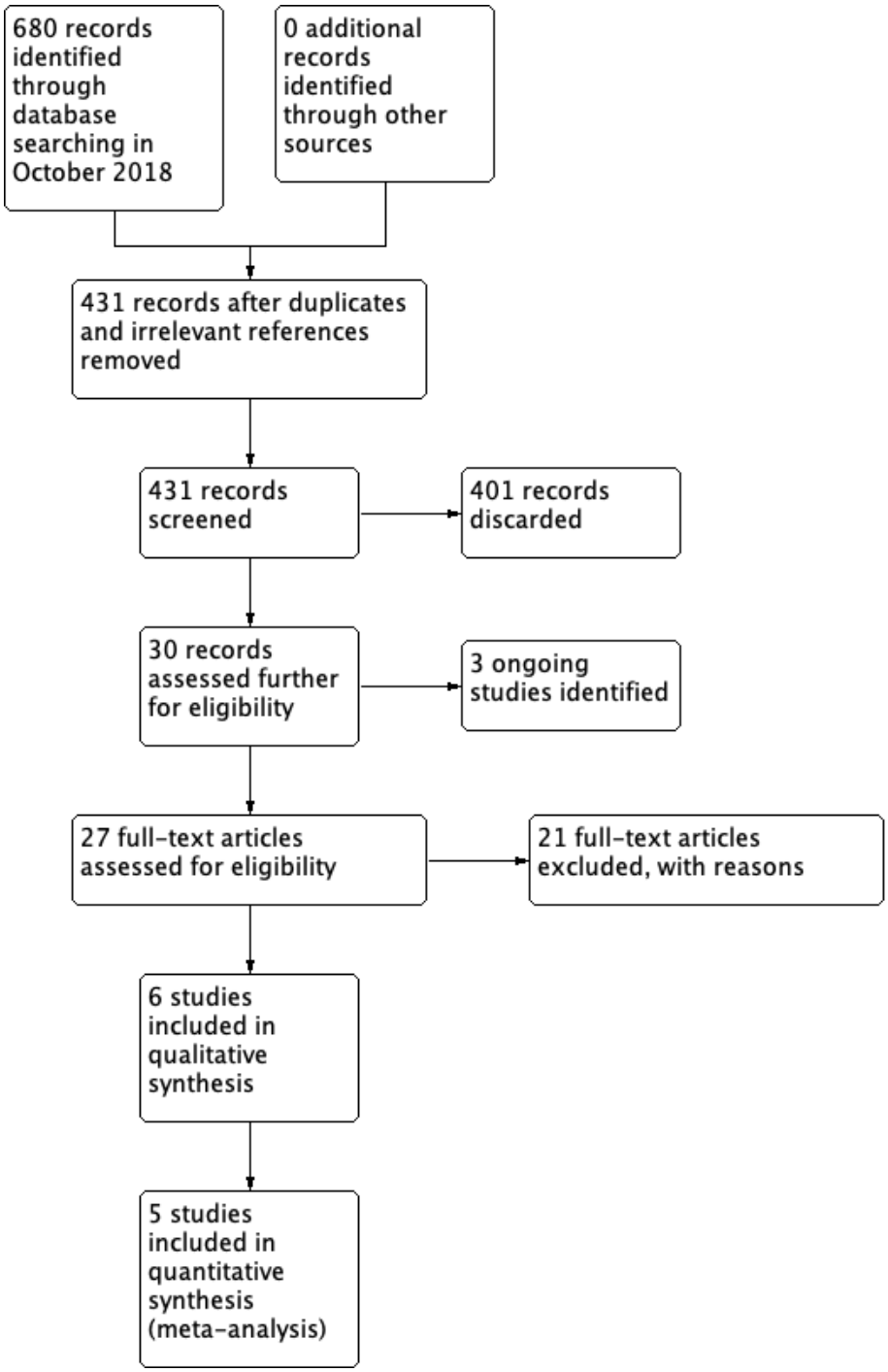
We excluded 21 studies (see Excluded studies below and Characteristics of excluded studies for the reasons for exclusion).

We identified three ongoing studies (see Characteristics of ongoing studies). No studies are awaiting assessment.

We selected six studies for inclusion in the review.

A PRISMA flow diagram depicting our search and selection process is shown in Figure 1.

Figure 1. Process for sifting search results and selecting studies for inclusion.



Included studies

We included six studies with a total of 692 participants (Petruson 1974; Tibbelin 1995; White 1988; Zahed 2013; Zahed 2018). Full details of the included studies are shown in the Characteristics of included studies table.

Design

Three of the included studies were randomised, placebo-controlled and double-blinded (Petruson 1974; Tibbelin 1995; White 1988). Two studies were randomised, non-placebo-controlled, single-blinded studies (Zahed 2013; Zahed 2018). Atabaki 2017 was a randomised, double-blind, non-placebo-controlled study.

Sample sizes

The number of participants in each study ranged from 68 to 216.

Setting and participants

Included in the review are two inpatient studies (Petruson 1974; White 1988) and four outpatient studies (Atabaki 2017; Tibbelin 1995; Zahed 2013; Zahed 2018). All participants were adults. Two studies were carried out in Sweden (Petruson 1974; Tibbelin 1995), one in the UK (White 1988), and three in Iran (Atabaki 2017; Zahed 2013; Zahed 2018).

None of the studies documented the aetiology of the bleeds. In most cases there was no known cause (idiopathic). Three studies differentiated between anterior and posterior bleeds and only included those with anterior bleeding (Atabaki 2017; Zahed 2013; Zahed 2018).

In Zahed 2018, all participants were currently taking antiplatelet drugs (aspirin, clopidogrel or both).

Interventions

Oral tranexamic acid for 10 days

Both the inpatient studies used the same intervention, 1 g tranexamic acid tablets, three times daily, to begin within one hour of admission and to continue for 10 days, or placebo. They differed in what was termed 'usual care':

Petruson 1974 used packing alone, comprising a posterior Foley catheter in all cases with the addition of an anterior gauze tampon if necessary. Twelve to 24 hours after bleeding was stopped, the balloon was deflated and the catheter removed three to six hours later. If there was no further bleeding the gauze was removed until fresh blood was seen on it. Every three to six hours the gauze was removed in a similar fashion until it was all out. If there was a new severe bleed, the patients were re-packed as above.

White 1988 treated the patients with a combination of nasal cautery and packing. Packing was removed 24 hours after bleeding had stopped and patients were discharged home a further 24 hours later if there was no further bleeding.

Topical tranexamic acid (gel or liquid)

Tibbelin 1995 treated the study participants with either 15 mL tranexamic acid gel (10%) or placebo gel applied locally to fill the nasal cavity. If bleeding was not arrested 30 minutes after gel application, traditional methods were used, which constituted 'usual care'.

In the intervention group in both Zahed 2013 and Zahed 2018 a 15 cm cotton pledget soaked in the injectable form of tranexamic acid (500 mg in 5 mL) was placed in the nostril of the bleeding side. It was removed after bleeding was arrested. If "rescue treatment" was needed (presumably meaning that if bleeding did not stop) "routine anterior nasal packing and cautery" was used. The study participants in the control groups of both studies were treated with a cotton pledget soaked in epinephrine (1:100,000) and lidocaine (2%) to "decongest" the nose for 10 minutes followed by packing with several cotton pledgets coated in tetracycline on the bleeding side for three days. "Rescue treatment" for the control group in both studies consisted of nasal cautery.

There are differences (or potential differences) between the intervention and control arms of the Zahed 2013 and Zahed 2018 studies *other than* the application of tranexamic acid after the first 10 minutes of treatment. In the first 10 minutes, the two groups in both studies had either tranexamic acid or epinephrine/lidocaine; thereafter, the control groups were all packed and the intervention groups may or may not have been. This means that from 10 minutes to three days, one comparator group - the control group - comprised participants all of whose noses were cauterised and packed, and the other group had an unknown proportion of participants (< 100%) who were cauterised and packed. For this reason, Zahed 2013 and Zahed 2018 therefore contributed data only to the comparison tranexamic versus any other haemostatic agent, and only to one epistaxis-related outcome (see below) and to adverse effects.

In Atabaki 2017, the intervention group received 1 cc tranexamic acid (injection solution, 500 mg/5 mL) poured onto a cotton ball and inserted into each nasal cavity. The control group received 1 cc phenylephrine (phenylephrine HCL, nasal drops, 0.5%) administered in the same way.

Outcomes

Control of epistaxis: re-bleeding, as measured by the proportion of patients re-bleeding within a period of up to 10 days (minimum five days)

Three studies recorded the number of patients with bleeding episodes over a 7- to 10-day period (Petruson 1974; Tibbelin 1995; White 1988).

Significant adverse effects: seizures, thromboembolic events

Five of the studies referred to recording "adverse effects" and in Tibbelin 1995, White 1988, Zahed 2013 and Zahed 2018 mention is made of looking for "severe" adverse effects but these were not pre-defined. Separate data relating to any adverse effects in the first 10 minutes of the Zahed 2013 and Zahed 2018 studies were not available. Atabaki 2017 did not report these.

Control of epistaxis: time to stop initial bleeding (as measured by the proportion of patients whose bleeding is controlled within 30 minutes)

This outcome was evaluated in four studies: Tibbelin 1995 (30 minutes) and Atabaki 2017, Zahed 2013 and Zahed 2018 (10 minutes).

Severity of re-bleeding: as measured by a) the proportion of patients requiring any further intervention (e.g. repacking, surgery, embolisation) within 10 days and b) the proportion of patients requiring blood transfusion within 10 days

None of the studies reported the proportion of patients requiring any further intervention. The proportion of patients requiring blood transfusion within 10 days was reported only in White 1988.

Length of hospital stay in days

Hospital stay was reported in Petruson 1974 and White 1988.

Other adverse effects

As mentioned above, five studies mention recording "adverse effects".

Excluded studies

We excluded 21 studies. The reasons for exclusion are detailed in the Characteristics of excluded studies table. Several studies specifically studied tranexamic acid in participants with bleeding abnormalities such as hereditary haemorrhagic telangiectasia or in patients undergoing surgery (such as functional endoscopic sinus surgery or rhinoplasty).

Ongoing studies

We identified three ongoing placebo-controlled randomised controlled trials of tranexamic acid in adults with epistaxis (ISRCTN34153772; NCT02930941; NCT03360045). One has an estimated completion date of August 2018 and two are due to complete during 2019. (See Characteristics of ongoing studies for details).

Risk of bias in included studies

Please see the 'Risk of bias' table for each of the included studies (Characteristics of included studies), Figure 2 for a 'Risk of bias' graph (our judgements about each risk of bias item presented as percentages across all included studies) and Figure 3 for a 'Risk of bias' summary (our judgements about each risk of bias item for each included study).

Figure 2. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

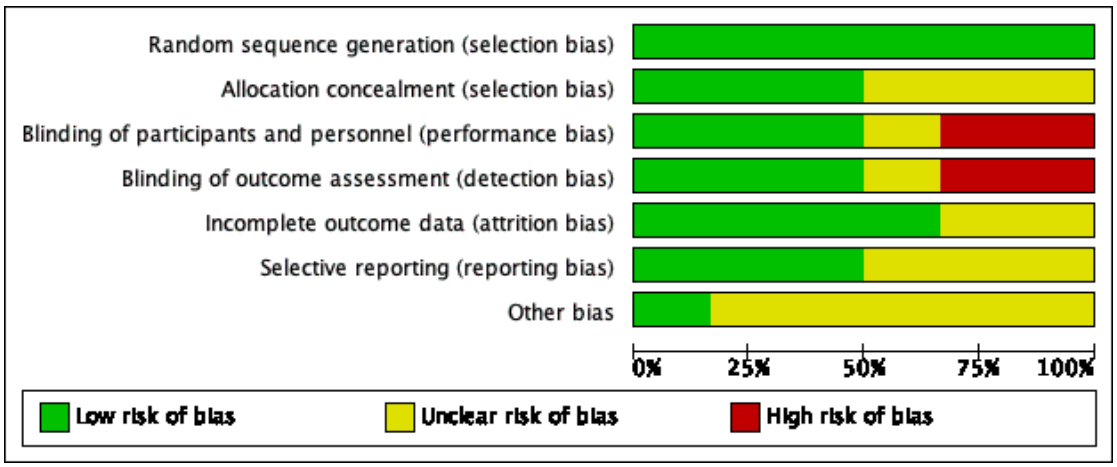
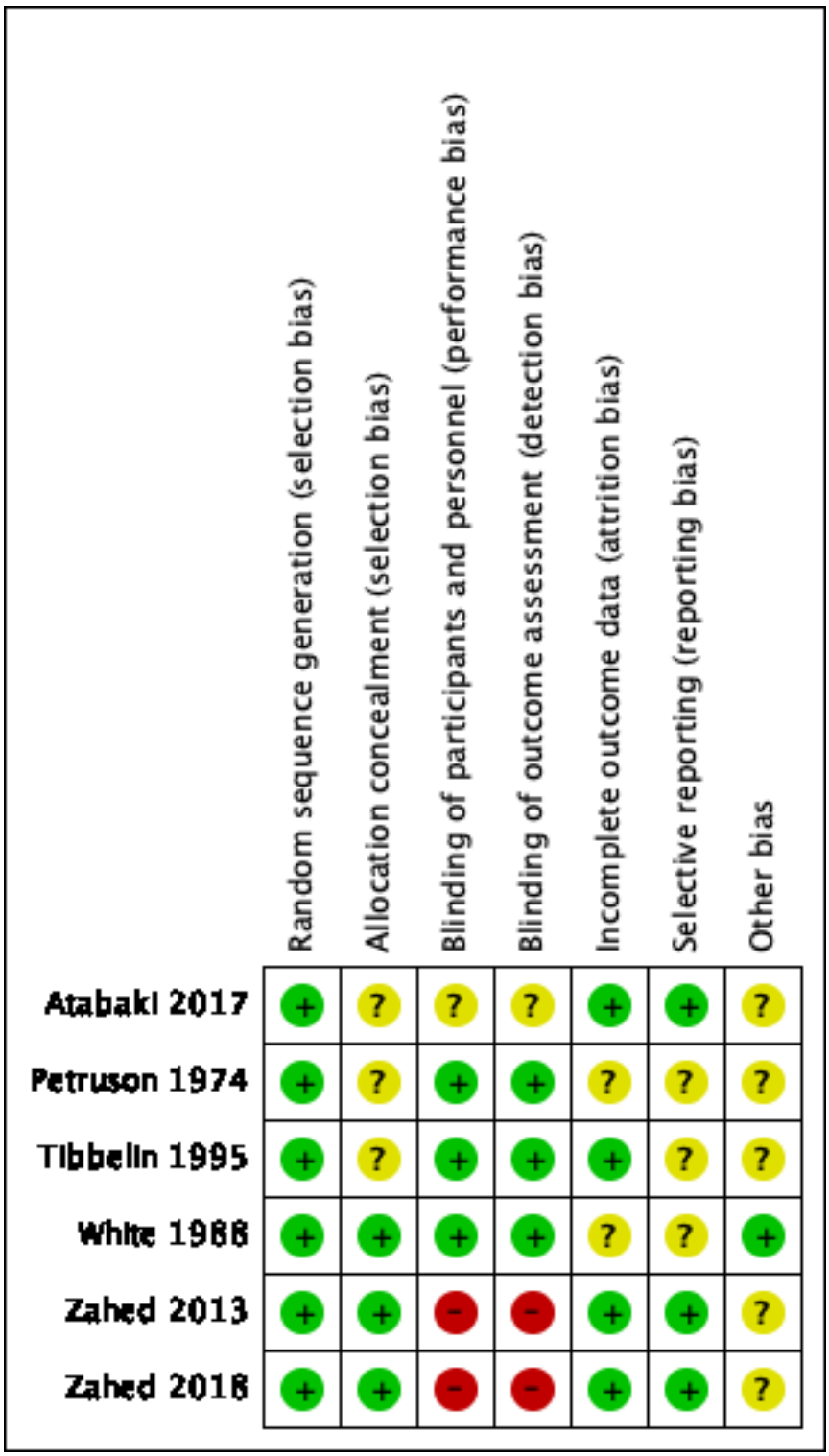


Figure 3. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.



As the Figures show, the overall risk of bias in the included studies is low. We found White 1988, Petruson 1974 and Tibbelin 1995 to have a low risk of bias overall while Zahed 2013 and Zahed 2018 at high risk due to the absence of blinding. In White 1988, the risk of attrition bias was unclear, but the number of participants lost to follow-up was small. Atabaki 2017 had an unclear risk of bias in several domains.

Allocation

Sequence generation

We assessed all studies to be at low risk of selection bias with regard to sequence generation: all used randomisation, although two studies did not fully define how this was done (Petruson 1974; Tibbelin 1995).

Allocation concealment

For allocation concealment the risk of bias was low in three studies (White 1988; Zahed 2013; Zahed 2018) and unclear in three studies (Atabaki 2017; Petruson 1974; Tibbelin 1995).

Blinding

Three studies are described as 'double-blind' and were at low risk of bias (Petruson 1974; Tibbelin 1995; White 1988); however, only White 1988 fully defined how this was achieved. Atabaki 2017 is described as a "double-blind" study but no further details are provided (unclear risk of bias).

It was not possible to blind the participants and those administering treatment in Zahed 2013 and Zahed 2018 due to clear differences in the methods of administration in the two groups (high risk of bias). Those analysing the data were blinded making these single-blinded studies, however as only data from the first 10 minutes are used in this review, this is the only relevant time period for outcome assessment and evaluators at this point were not blind to the intervention.

Incomplete outcome data

The risk of attrition bias in four studies was low (Atabaki 2017; Tibbelin 1995; Zahed 2013; Zahed 2018). There is an unclear risk of bias due to a lack of data in one study (Petruson 1974). In the other included study seven of 96 patients (7%) did not complete the course of treatment with no explanation given or comment on the distribution between groups (White 1988). The data for these patients were removed from the analysis, which leads to an unclear risk of bias in this study.

Selective reporting

All planned outcomes from the methods section in each study were reported on in Atabaki 2017, Petruson 1974, Tibbelin 1995, Zahed 2013 and Zahed 2018. Zahed 2013 and Zahed 2018 had low risk of bias due to robust outcome reporting strategies. There was some lack of clarity in the other three studies due to unclear methods of reporting of efficacy variables in one (Tibbelin 1995), failure to report the number of units required for blood transfusion in another (Petruson 1974), and general poor reporting of patient allocation in the last (White 1988). In addition, several outcomes were not presented in the methods section of White 1988, but are reported in the outcomes section (length of stay, number of blood transfusions and amount of blood transfused).

Other potential sources of bias

There is an unclear risk of other bias. Petruson 1974 noted bleeding resulting from the removal of nasal tampons but did not record these bleeds in their results. The overall effect of this is unknown. Tibbelin 1995 noted that the baseline bleeding intensity was not equal between the treatment and control groups. They had applied a linear logistic model to data affected by this. Both Zahed 2013 and Zahed 2018 noted a difference between the treatment and control groups in the history of epistaxis. There were no concerns in the other study and therefore the risk of other bias is low (White 1988). We detected no other sources of bias in Atabaki 2017, but our assessments are based on information extracted by a translator of this study, which is published in Farsi, so the judgement is unclear.

None of the studies gave details of study funding. Only one study provided a statement about conflicts of interest and declared that there were none (Zahed 2013).

Effects of interventions

See: **Summary of findings for the main comparison** Tranexamic acid compared to placebo plus usual care or usual care alone for patients with nasal haemorrhage (epistaxis); **Summary of findings 2** Tranexamic acid compared to other haemostatic agent for patients with nasal haemorrhage (epistaxis)

Tranexamic acid versus placebo or usual care alone

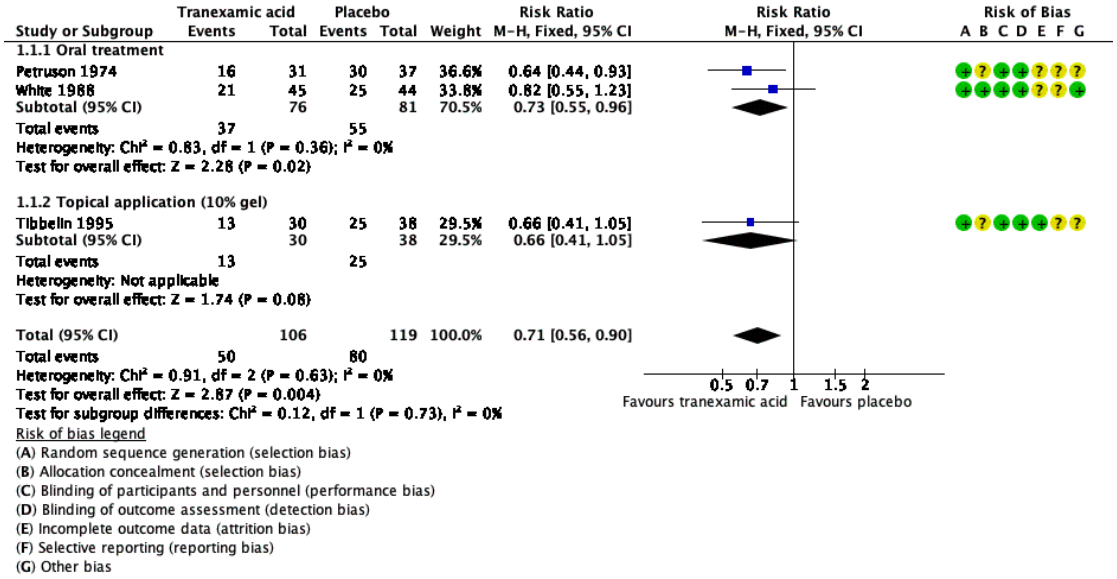
Primary outcomes

Control of epistaxis: re-bleeding (proportion of patients re-bleeding within a period of up to 10 days)

See Summary of findings for the main comparison.

The primary outcome measure for this review was the effectiveness of tranexamic acid in the control of epistaxis. We measured this primarily as the proportion of patients who had an episode of re-bleeding *within the first 10 days of treatment*. Combining the results of three studies with a total of 225 participants, we found moderate-quality evidence that tranexamic acid probably reduces the risk of re-bleeding (risk ratio (RR) 0.71, 95% confidence interval (CI) 0.56 to 0.90, I^2 = 0%) (Analysis 1.1; Figure 4). In the three studies tranexamic acid was used in two very different ways: as an oral treatment, given regularly over several days (Petruson 1974; White 1988) and as a 'one-off' topical intervention at the patients' initial presentation (Tibbelin 1995). Whilst the intervention may be very similar in terms of its composition and cellular mechanism of action, it is reasonable to assume that, overall, the way in which it is working as an agent to reduce bleeding is different. Therefore the subgroup analysis is especially pertinent.

Figure 4. Forest plot of comparison: 1 Tranexamic acid versus placebo plus usual care or usual care alone, outcome: 1.1 Control of epistaxis: episodes of re-bleeding over 10 days.



When we compared the effects of **oral** tranexamic acid (RR 0.73, 95% CI 0.55 to 0.96; two studies, 157 participants, Analysis 1.1.1) (Petruson 1974; White 1988) and the effects of **topical** tranexamic acid (RR 0.66, 95% CI 0.41 to 1.05; single study, 68 participants, Analysis 1.1.2) (Tibbelin 1995), both showed an effect similar to the overall result, although for the topical tranexamic acid group the 95% confidence interval included unity. We rated the quality of the evidence provided by this single study as *low*, and it is therefore uncertain whether or not topical tranexamic acid is effective in stopping bleeding in the period 10 days after a single application. A formal test of subgroup differences did not indicate any difference between the treatment effects of the two different methods of administration.

We were unable to carry out any of our other planned subgroup analyses: patient age (children versus adults), setting (inpatient versus outpatient) or site of nosebleed (anterior versus posterior).

Significant adverse effects: seizures, thromboembolic events

No study specifically sought to identify and report these particular adverse events, although all recorded 'adverse effects' in a general way. No significant adverse effects were reported in any study.

Secondary outcomes

Control of epistaxis: time to stop initial bleeding (as measured by the proportion of patients whose bleeding is controlled within 30 minutes)

We also measured control of epistaxis in terms of the proportion of participants who had stopped bleeding within a specified period of up to 30 minutes of treatment. Only Tibbelin 1995 provided data for this comparison. The study found no evidence of a difference between the topical tranexamic acid and control groups at 30 minutes (RR 0.79, 95% CI 0.56 to 1.11; single study; 68 participants) (Analysis 1.2). The quality of this evidence was *low*.

Severity of re-bleeding: as measured by a) the proportion of patients requiring any further intervention (e.g. repacking, surgery, embolisation) within 10 days and b) the proportion of patients requiring blood transfusion within 10 days

No studies reported the proportion of patients requiring any further intervention.

When comparing oral tranexamic acid with placebo White 1988 found no evidence of a difference in the proportion of patients requiring blood transfusion: 5/45 versus 6/44 (RR 0.81, 95% CI 0.27 to 2.48; 89 participants) (Analysis 1.3) (*low-quality evidence*).

Length of hospital stay in days

Petruson 1974 reported a significantly shorter stay in the oral tranexamic acid group (mean difference (MD) -1.60 days, 95% CI -2.49 to -0.71; 68 participants). White 1988 found no difference (MD 0.40 days, 95% CI -0.84 to 1.64; 89 participants) (Analysis 1.4). When we attempted to combine the data from these studies, the heterogeneity was high (I^2= 85%).

Other adverse effects

All five studies recorded 'adverse effects' in a general way. Petruson 1974 identified no "symptoms which might be taken for general side effects". Two patients (one in each group) experienced small synechiae, likely to be related to the nasal packing rather than the intervention. Three patients in each group in the Tibbelin 1995 study reported that the gel had a 'bad taste' but no serious adverse event was recorded. White 1988 reported some complaints of mild nausea and diarrhoea, but these were experienced equally each group. One patient did develop a "a superficial thrombophlebitis of both legs following discharge from hospital", however it is not reported in which group this occurred.

Tranexamic acid versus other haemostatic agents

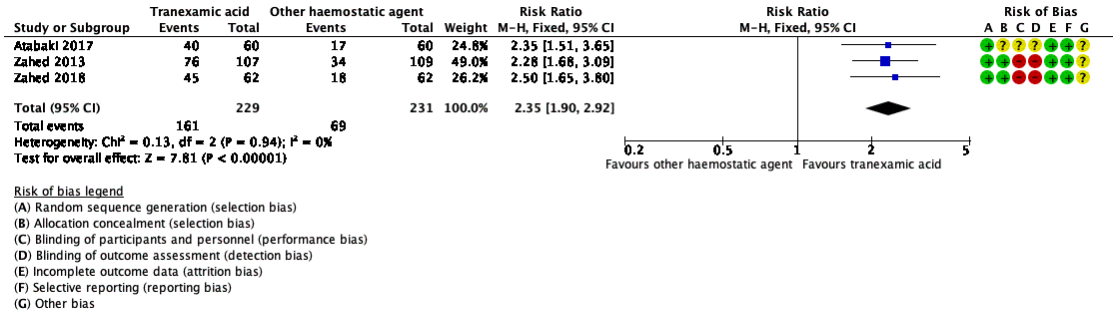
See Summary of findings 2.

Atabaki 2017, Zahed 2013 and Zahed 2018 evaluated this comparison and data were only available for two outcomes.

Control of epistaxis: time to stop initial bleeding (as measured by the proportion of patients whose bleeding is controlled within 30 minutes)

When we pooled the data from the three studies the proportion of patients whose bleeding stopped within 10 minutes was significantly higher in the topical tranexamic acid group (70% versus 30%; RR 2.35, 95% CI 1.90 to 2.92, three studies, 460 participants) (Analysis 2.1; Figure 5). There was no heterogeneity in the pooled analysis (I^2 = 0%).

Figure 5. Forest plot of comparison: 2 Tranexamic acid versus other haemostatic agent, outcome: 2.1 Control of epistaxis: time to stop initial bleeding (proportion with bleeding controlled within 10 minutes).



Adverse events

There was no difference between the groups in complications (nausea/vomiting and intolerance) and no serious adverse event was observed (Zahed 2013; Zahed 2018). Atabaki 2017 did not report adverse events.

No data were available for any of our other outcomes.

ADDITIONAL SUMMARY OF FINDINGS *[Explanation]*

Tranexamic acid compared to other haemostatic agent for patients with nasal haemorrhage (epistaxis)

Patient or population: adults with nasal haemorrhage (epistaxis)
Setting: outpatients
Intervention: tranexamic acid
Comparison: other haemostatic agent

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with other haemostatic agent	Risk with tranexamic acid				
Control of epistaxis: episodes of re-bleeding over 10 days	We could not assess this outcome due to differences between the intervention and control arms (other than the application of tranexamic acid) after the first 10 minutes of treatment in Zahed 2013 and Zahed 2018 (see Included studies).					
Control of epistaxis: time to stop initial bleeding (proportion with bleeding controlled within 10 minutes)	Study population		RR 2.35 (1.90 to 2.92)	460 (3 RCTs)	⊕⊕⊕◯ MODERATE [1,2,3]	Tranexamic acid probably leads to a higher proportion of participants with bleeding controlled within 10 minutes
	299 per 1000	702 per 1000 (568 to 872)				
Severity of re-bleeding: proportion of patients requiring blood transfusion within 10 days	Outcome not assessed.					
Length of hospital stay	We could not assess this outcome due to differences between the intervention and control arms (other than the application of tranexamic acid) after the first 10 minutes of treatment (see Included studies).					

Adverse effects: serious or other	See comment	See comment	-	-	-	No study specifically sought to identify and report our primary outcome, the significant adverse effects of seizure and thromboembolism. Five of the studies recorded "adverse effects" in a general way and there were no significant differences between groups in the occurrence of the minor adverse effects noted (e.g. mild nausea and diarrhoea, 'bad taste' of gel)

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; **RCT:** randomised controlled trial; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1]Downgraded by one level due to study limitations (risk of bias - no blinding) (Zahed 2013; Zahed 2018).
[2]Downgraded by one level for imprecision (wide confidence interval).
[3]Upgraded by one level - large effect size (RR 2.35).

DISCUSSION

Summary of main results

See Summary of findings for the main comparison.

The primary outcome measure for this review was the effectiveness of tranexamic acid in the control of epistaxis as measured by the proportion of patients who had an episode of re-bleeding *within the first 10 days of treatment*.

We found moderate-quality evidence that tranexamic acid probably reduces the risk of re-bleeding when compared to placebo or no treatment. Tranexamic acid was used in two very different ways in the three studies on which this finding is based: as an oral treatment, given regularly over several days (Petruson 1974; White 1988) and as a 'one-off' topical intervention at the patients' initial presentation (Tibbelin 1995). Subgroup analysis to compare the effects of oral and topical tranexamic acid showed a similar effect to the overall result, although for the topical tranexamic acid group the 95% confidence interval included unity. The quality of evidence provided by this single study is low therefore it is uncertain whether or not topical tranexamic acid is effective in stopping bleeding in the period 10 days after a single application.

We also measured control of epistaxis in terms of the proportion of participants who had stopped bleeding within 30 minutes of treatment. For the comparison of tranexamic acid versus placebo we found low-quality evidence from a single study and determined that tranexamic acid may lead to little or no difference (Tibbelin 1995). This outcome was also addressed in three studies comparing tranexamic acid versus another haemostatic agent (epinephrine/lidocaine combination or phenylephrine) and moderate-quality evidence indicates that tranexamic acid probably increases the chance of bleeding stopping in the first 10 minutes after application (Atabaki 2017; Zahed 2013; Zahed 2018).

No study specifically sought to identify and report seizures or thromboembolic events (significant adverse effects).

No studies reported the proportion of patients requiring any further intervention (e.g. repacking, surgery, embolisation) within 10 days.

Blood transfusion requirements were only recorded in one study with no significant differences between the oral tranexamic acid and control groups (White 1988).

One study reported a significantly shorter length of hospital stay in the oral tranexamic acid group (Petruson 1974), while another found no difference (White 1988).

Five included studies mentioned recording adverse effects but none identified any significant differences between groups.

Overall completeness and applicability of evidence

Whilst the limited amount of evidence identified in this review is applicable to the review question, the paucity of it means that the evidence is far from complete. The identified studies also highlight a clear difference between the two ways in which tranexamic acid has been used: as a short-term topical treatment and a longer-term oral one. In neither case is there a clear and unequivocal answer about the merits of tranexamic acid.

The adult participants recruited to the studies are representative of those seen in day-to-day practice.

The definition of 'usual care' encompasses most of the standard treatments used, but such 'usual care' varies around the world and is in a continuous state of evolution as new types of packs and packing materials are introduced.

Quality of the evidence

The body of evidence included in this review (six studies with a total of 692 participants) is insufficient to allow robust conclusions to be drawn. The quality of evidence for the outcomes assessed was moderate or low; we downgraded the evidence because of imprecision and study limitations (risk of bias).

Potential biases in the review process

Three of the most recent included studies took place in Iran (Atabaki 2017; Zahed 2013; Zahed 2018). Two were conducted by the same research group (Zahed 2013; Zahed 2018); however, patient numbers, characteristics and recruitment periods in the three studies were clearly different.

The search for relevant studies for this review encompassed all the main databases as outlined in the Search methods for identification of studies section. The search terms used should have identified all randomised controlled trials comparing the use of tranexamic acid in epistaxis to either placebo or 'usual care'. We do not believe that the methodology of the review is likely to have introduced any bias into the review process.

Agreements and disagreements with other studies or reviews

A number of systematic reviews have evaluated the use of tranexamic acid in patients undergoing nasal surgery but we are only aware of two other systematic reviews of its use in patients with epistaxis (Kamhieh 2016; Williams 2017). Kamhieh 2016 does not appear to have pre-specified the outcome measures of interest, does not include the studies Atabaki 2017, Petruson 1974 and Zahed 2018, and provides a narrative description of the studies and the results. The authors do not seem to have noted the additional differences (other than the topical treatment applied at the outset) between the two arms of the Zahed 2013 study, and the implications of this. Williams 2017 identified four of the same randomised controlled trials that are included in our review and

drew comparable conclusions, noting the small numbers of participants and study limitations and proposing the need for further studies. A recent UK consensus document reflects these findings and does not recommend the use of tranexamic acid in the management of epistaxis, beyond its use as defined in national guidelines for major haemorrhage (BRS 2017).

AUTHORS' CONCLUSIONS

Implications for practice

Tranexamic acid probably reduces the risk of patients with epistaxis having further bleeding episodes. We found moderate-quality evidence that there may be a reduction in the risk of re-bleeding from 67% to 47% with the use oral or topical tranexamic acid in addition to usual care in adult patients with epistaxis, compared to placebo with usual care. Low-quality evidence suggests that topical tranexamic acid may make little or no difference to the control of bleeding in the first 30 minutes after its application. In three studies, the proportion of patients whose bleeding stopped within 10 minutes was significantly higher in the topical tranexamic acid group compared with other haemostatic agents (topical epinephrine/lidocaine combination or phenylephrine) (moderate-quality evidence). No significant adverse effects of treatment were reported in the included studies.

Implications for research

This review has found evidence to suggest that there is probably a reduction in re-bleeding episodes when using oral or topical tranexamic acid in addition to 'usual care'. However, although the latest randomised controlled trials were published between 2013 and 2018, all the other trials were conducted before 1995. Further randomised controlled trials, on similar cohorts of patients, attending hospital with epistaxis, using modern nasal cauterisation and packing techniques (for example, techniques including nasal endoscopy and more invasive approaches such as endoscopic sphenopalatine artery ligation), and investigating the use of tranexamic acid in light of these advances, compared to 'usual care' alone, would be informative and improve our certainty about any treatment effect. Trials may specifically look at the effectiveness and safety of topical tranexamic acid. It has been suggested that the use of this formulation may be associated with fewer adverse events (due to an absence of systemic absorption).

ACKNOWLEDGEMENTS

We would like to thank Dr Ali Yadollahpour for translating a study from Farsi for this review.

This project was supported by the National Institute for Health Research, via Cochrane Infrastructure, Cochrane Programme Grant or Cochrane Incentive funding to Cochrane ENT. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, NHS or the Department of Health.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Atabaki 2017

Methods	**Allocation:** double-blind, parallel-group randomised controlled trial with a single treatment and follow-up at 10 minutes
Participants	**Setting:** Imam Khomeini Hospital, Urmia, Iran; April to September 2016 **Sample size:** 120 • **Number randomised:** 60 in intervention group, 60 in control group • **Number completed:** 60 in intervention group, 60 in control group **Participant (baseline) characteristics:** • Age: range 20 to 90 years (mean: 48.88 ± 18.64 years; intervention group 48.85 ± 19.34 years; control group: 48.91 ± 18.08 years) • Gender: 40 male/80 female (intervention group 22 male/38 female; control group: 18 male/42 female) **Inclusion criteria:** anterior nasal haemorrhage; aged over 14 years **Exclusion criteria:** posterior nasal haemorrhage; hypertension above 140/90 mmHg; known sensitivity to phenylalanine and/or tranexamic acid; history of coagulation disorders such as haemophilia, embolism and venous thrombosis; stroke; use of warfarin
Interventions	**Intervention group:** 1 cc tranexamic acid, injection solution, 500 mg/5 mL) was poured onto cotton and the cotton ball inserted into each nasal cavity. The patients were asked to press the soft part of the nose continuously for 10 minutes and then the pressure was removed **Comparator group:** 1 cc phenylephrine (phenylephrine HCL, nasal drops, 0.5%) with the same administration method
Outcomes	**Outcomes of interest in the review** *Secondary outcome* Control of epistaxis: time to stop initial bleeding (as measured by the proportion of patients whose bleeding is controlled within 10 minutes) **Other outcomes reported by the study** Not applicable
Declarations of interest	None reported
Funding	None reported
Notes	The study was approved by a local ethics committee

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Allocation was performed using a random number table generator, although the authors did not report the process in detail

Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Study is described as "double-blind", but no details are reported as to how this was done
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Study is described as "double-blind", but no details are reported as to how this was done
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients completed the study
Selective reporting (reporting bias)	Low risk	There was only one planned outcome (cessation of bleeding at 10 minutes) and this was reported. We did not locate a trial registration
Other bias	Unclear risk	No other sources of bias were detected, but our assessments are based on information extracted by a translator of this study, which is published in Farsi

Petruson 1974

Methods	**Allocation:** double-blind, parallel-group, placebo-controlled randomised trial with 10 days of treatment and 10 days of follow-up
Participants	**Setting:** inpatients, Sweden **Sample size:** 68 • **Number randomised:** 31 in intervention group, 37 in placebo group • **Number completed:** not reported **Participant (baseline) characteristics:** • **Age:** intervention group mean 56 years; control group mean 56 years • **Gender:** not recorded • **Risk factors:** 69% of participants were taking acetylsalicylic acid and 26% had hypertension **Inclusion criteria:** all hospitalised patients with epistaxis **Exclusion criteria:** none mentioned
Interventions	**Intervention group:** Cyklokapron (tranexamic acid) 1 g, 3 times daily, started 1 hour after hospitalisation, for 10 days **Comparator group:** placebo 1 tablet, 3 times daily, started 1 hour after hospitalisation, for 10 days **Use of additional interventions:** all but 3 of the participants were treated with anterior and/or posterior nasal packing at presentation

Outcomes	**Outcomes of interest in the review** *Primary outcomes* • Control of epistaxis: re-bleeding - proportion of patients with re-bleeding in a period of up to 10 days post-intervention. This was calculable from the data presented. • "Adverse effects" (severity not defined) *Secondary outcomes* • Length of hospital stay (days) **Other outcomes reported by the study** • Number of episodes of re-bleeding (not patients) requiring further intervention • Frequency and severity of re-bleeding episodes using a point scale (0 points = no bleeding to 6 points = large amount of bleeding requiring packing) measured in 12-hour periods over 10 days. Minimum number = 0 (no bleeding at any point); maximum number (theoretical) = 6 x 10 x 2 = 120). The authors felt that measurement of blood loss was not possible due to the patients swallowing a considerable volume. At the end of the 10-day study period the participants were brought back to the hospital and questioned about whether any further bleeding had occurred after discharge
Declarations of interest	None stated
Funding	None declared
Notes	**Participants lost to follow-up:** not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Assignment ... by random numbers" Comment: this was probably done
Allocation concealment (selection bias)	Unclear risk	Comment: no information was provided about allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Double blind", "The labels of the bottles bore only the patients' serial number" Comment: this was probably done. The bottles did not reveal whether they contained the treatment or placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "Double blind" Comment: this was probably done
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Quote: "One to three days after the drug treatment was finished the patients visited

Petruson 1974 (*Continued*)

		the hospital again“ Comment: it is not stated whether all patients returned or not
Selective reporting (reporting bias)	Unclear risk	A standard bleeding score was used for all patients Hospitalisation time was recorded from patient records Adherence to these protocols would prevent selective reporting Number of units required for blood transfusion was not recorded
Other bias	Unclear risk	Quote: ”The tampons must be regarded as errors in the evaluation of the therapy effect. When the tampons were taken away or moved small bleeding sometimes started. These small bleedings were not recorded.“ Comment: this will have had an unknown effect on the overall outcome

Tibbelin 1995

Methods	**Allocation:** double-blind, parallel-group randomised controlled trial with a single treatment and 10 days of follow-up
Participants	**Setting:** outpatients, Sweden (multicentre) **Sample size:** 68 • **Number randomised:** 30 in intervention group, 38 in placebo group • **Number completed:** 30 in intervention group, 38 in placebo group **Participant (baseline) characteristics:** • **Age:** intervention group mean 50 years; control group mean 65 years • **Gender:** 49 males (21 in the tranexamic acid group, 28 in the control group); 24 females (14 in the tranexamic acid group, 10 in the control group) • **Risk factors:** 51% of participants were taking acetylsalicylic acid within 2 weeks. ”There was significantly higher relative frequency of moderate and severe bleeding in the tranexamic acid group“ **Inclusion criteria:** adult patients with ongoing nosebleeds **Exclusion criteria:** impaired haemostasis, skull or nasal fracture, septal perforation
Interventions	**Intervention group:** local application of tranexamic acid (10%) gel - 1 application with 10-day follow-up **Comparator group:** local application of glycine (placebo) gel - 1 application with 10-day follow-up In both cases the entire nasal cavity was filled with gel **Use of additional interventions:** all patients still bleeding after 30 minutes were treated with ’usual care’ but no further detail is provided about this

Outcomes	**Outcomes of interest in the review** *Primary outcomes* • Control of epistaxis: re-bleeding - proportion of patients with re-bleeding in a period of up to 10 days post-intervention • "Serious adverse effects" (not defined) *Secondary outcomes* • Control of epistaxis: time to stop bleeding (as measured by the proportion of patients whose bleeding is controlled within 30 minutes) **Other outcomes reported by the study** • "The patient's acceptance of treatment" Participants were followed up for 10 days
Declarations of interest	None stated
Funding	None declared
Notes	**Participants lost to follow-up:** 0

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "patients were randomised" Comment: no statement as to how this was done although it probably was carried out
Allocation concealment (selection bias)	Unclear risk	Comment: no information on allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "the study was double blind" Comment: placebo and treatment gel looked identical and were administered in the same way
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "the study was double blind"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients completed the full follow-up
Selective reporting (reporting bias)	Unclear risk	The authors planned to record 3 different "efficacy variables" Comment: it is unclear exactly how this was carried out
Other bias	Unclear risk	The baseline bleeding intensity was not equal between the 2 groups, the severity of bleeding being higher in the tranexamic

Tibbelin 1995 (*Continued*)

		acid group. The population in the tranexamic acid group was older and had a significantly higher frequency of moderate and severe bleeding. Although this could have occurred by chance it could also have occurred through the allocation of more serious cases to the active treatment group. The study report states that adjustment was made but it is not clear whether the numbers presented are unadjusted or adjusted

White 1988

Methods	**Allocation:** double-blind, parallel-group, placebo-controlled randomised trial with 10 days of treatment and 3 weeks of follow-up
Participants	**Setting:** inpatients, UK **Sample size:** 96 • **Number randomised:** 96 (distribution not stated) • **Number completed:** 45 in intervention group, 44 in placebo group **Participant (baseline) characteristics:** • **Age:** intervention group mean 64.8 years; control group mean 63.5 years • **Gender:** 48 males (25 in the tranexamic acid group, 23 in the control group), 41 females (20 in the tranexamic acid group, 21 in the control group) (7 participants unaccounted for) • **Risk factors:** 4% to 6% of participants had a recent upper respiratory infection and 29% to 36% had hypertension **Inclusion criteria:** all adults admitted with epistaxis **Exclusion criteria:** history of thrombosis or embolus, anticoagulation, renal insufficiency, taking oral contraceptive
Interventions	**Intervention group:** oral tranexamic acid 1 g (2 tablets) 3 times daily for 10 days **Comparator group:** placebo 2 tablets 3 times daily for 10 days **Use of additional interventions:** all but 2 of the participants were treated with cautery or anterior or posterior nasal packing at presentation
Outcomes	**Outcomes of interest in the review** *Primary outcomes* • Control of epistaxis: re-bleeding - proportion of patients with re-bleeding in a period of up to 10 days post-intervention • Significant adverse effects: seizures, thromboembolic events *Secondary outcomes* • Severity of re-bleeding: proportion of patients requiring blood transfusion within 10 days • Length of hospital stay in days • Other adverse effects **Other outcomes reported by the study** • Severity of re-bleeding events

	• Number of re-bleeding events • Amount of blood transfused All participants were reviewed daily during the 10-day course of treatment and then again after 3 weeks to record any late complications or side effects
Declarations of interest	None stated
Funding	None declared
Notes	**Participants lost to follow-up:** 7 (distribution not stated)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Treatment allocation... according to a previously determined randomisation code." Comment: this was probably done adequately
Allocation concealment (selection bias)	Low risk	Quote: "Treatment allocation was in a double blind manner according to a previously determined randomisation code" Comment: the people allocating to treatment group were unaware of the treatment group
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Treatment allocation was in a double blind manner." "Tablets which were identified only by a trial number" Comment: this was probably done well; the participants would not have known which group they were in
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: the double-blind nature of this study would have made this low risk
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: 7 participants did not complete the course of treatment; no comment is made regarding the reasons for discontinuation or the distribution of these participants
Selective reporting (reporting bias)	Unclear risk	Comment: there was poor reporting of patient allocation (how many were allocated to each group, how many dropped out of each group and why, how many adverse

White 1988 (*Continued*)

		events were there and in which group the thrombophlebitis event occurred). In addition, several outcomes were not presented in the methods section but are reported in the outcomes section (length of stay, number of blood transfusions and amount of blood transfused)
Other bias	Low risk	No other potential sources of bias identified

Zahed 2013

Methods	Single-blinded, parallel-group randomised controlled trial with a single treatment and 7 days of follow-up
Participants	**Setting:** patients attending the emergency department, Iran **Sample size:** 216 (see Notes) • **Number randomised:** 107 in intervention group, 109 in control group • **Number completed:** 107 in intervention group, 109 in control group **Participant (baseline) characteristics:** • **Age:** intervention group 50.4 (± 19) years; control group 54 (± 15.5) years • **Gender:** intervention group (%) (male/female) 62.6/37.4; control group (%) (male/female) 52.3/47.7 • **Risk factors:** 58.1% in the intervention group had a history of epistaxis; 13.6% in the control group had a history of epistaxis **Inclusion criteria:** adults presenting with ongoing epistaxis that was idiopathic and anterior **Exclusion criteria:** major trauma, posterior epistaxis, history of bleeding disorder, international normalised ratio (INR) > 1.5, shock, visible bleeding vessel
Interventions	**Intervention group:** a 15 cm piece of cotton pledget soaked in the injectable form of tranexamic acid (500 mg in 5 mL) was inserted in the nostril of the bleeding side, then "rescue treatment" (in the form of anterior nasal packing and cautery) was provided if required **Comparator group:** usual nasal decongestion with a cotton pledget **soaked in epinephrine (1:100000) + lidocaine (2%)** for 10 minutes, then anterior packing with cotton pledgets covered with tetracycline for 3 days **Use of additional interventions:** see above
Outcomes	**Outcomes of interest in the review** *Primary outcome* • Significant adverse effects: seizures, thromboembolic events (**but see NOTE below**) *Secondary outcomes* • Control of epistaxis: time to stop initial bleeding (as measured by the proportion of patients whose bleeding is controlled within 10 minutes). **Other outcomes reported by the study** • Not applicable Participants were assessed every 5 minutes while they were in the emergency department

	and then for the next 7 days either by telephone or return to the department **NOTE: Only data derived from the first 10 minutes of this study are useable in this review. After that period, the groups were not treated similarly in all respects other than the application of the intervention under evaluation or the comparator.**
Declarations of interest	"The authors declare that there is no conflict of interest with this manuscript."
Funding	None declared
Notes	**Participants lost to follow-up:** 0. The methods section states that 224 patients were randomised but only 216 participants are mentioned thereafter. Following contact with the author 224 has been confirmed as a misprint Baseline imbalance: by chance, the proportion of patients with a history of epistaxis is higher in the tranexamic acid group than the epinephrine/lidocaine group

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Treatment allocation was according to a previously determined randomization code by SPSS software as simple randomization." Comment: this was done well
Allocation concealment (selection bias)	Low risk	Quote: "The nurse randomized and blinded the boxes filled by medication and cotton pledgets required for management in a location removed from the ED and inaccessible to the ED personnel." Comment: this was done well
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "Because of the nature of the study, using different medications differing in consistency, color, and smell for soaking or coating the pledgets and discrepancy in the number of pledgets used, our physicians and patients were not blinded truly."
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "Data sets analyzed while analysts were blinded. The investigators doing the analysis were not the same as those performing the nasal packing." Comment: as only data from the first 10 minutes are used in this review, this is the only relevant time period for outcome assessment and evaluators at this point were not blind to the intervention

Zahed 2013 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	No patients were lost to follow-up. There is a misprint in the methods section stating that 224 patients were included. The correct number is 216
Selective reporting (reporting bias)	Low risk	Quote: "The taken time to arrest bleeding was evaluated and recorded in every 5-minute intervals and before leaving the ED ... Emergency medicine residents did the follow-up for rebleeding occurrence and possible complications by telephone call or revisiting schedule." Comment: robust procedures were in place to ensure a low risk of selective reporting
Other bias	Unclear risk	The study authors noted a difference between the treatment and control groups in the history of epistaxis

Zahed 2018

Methods	Randomised, 2-arm, parallel-group controlled trial with a single treatment and 7 days of follow-up
Participants	**Setting:** emergency departments of 2 large general teaching hospitals in Tehran, Iran from October 2015 to April 2016 **Sample size:** • Number randomised: 124 • Number completed: 124 **Participant (baseline) characteristics:** • **Age:** anterior nasal packing group 60.7 ± 12.2 years; tranexamic acid group 58.5 ± 16.1 years • **Gender (% male):** anterior nasal packing group 52%; tranexamic acid group 60% • **History of epistaxis (% yes):** anterior nasal packing group 21%; tranexamic acid group 53% • **History of drugs (acetylsalicylic acid/others):** anterior nasal packing group 82%/18%; tranexamic acid group 81%/19% **Inclusion criteria:** "Subjects were eligible for inclusion if they presented to the ED with an acute, new or recurrent, ongoing anterior epistaxis and were currently taking antiplatelet drugs (aspirin, clopidogrel, or both) ... we included patients with persistent bleeding requiring further treatment after 20 minutes of compression of both nostrils with the patient's thumb and index finger." **Exclusion criteria:** "We excluded those with traumatic epistaxis, current anticoagulant drug use, inherited bleeding disorders (including hemophilia), inherited platelet disorders, international normalize ratio > 1.5, shock, a visible bleeding vessel, a history of renal disease, and lack of consent."

Interventions	**Intervention group:** received a 15 cm piece of cotton pledget that had been soaked in the injectable form of tranexamic acid (500 mg in 5 mL) and inserted into the affected nostril. It was removed after the attending physician or a chief resident examined the oropharynx and blood-soaked pledgets to confirm that the bleeding had stopped **Comparator group:** anterior nasal packing. The anterior nasal packing group received a cotton pledget that had been soaked in epinephrine (1:100,000) + lidocaine (2%) inserted into the affected nostril and left in place for 10 minutes. anterior nasal packing was subsequently performed with several cotton pledgets covered with tetracycline ointment. The packs were left in situ for 3 days before removal **Use of additional interventions:** if the allocated treatment failed, the investigators considered anterior nasal packing and cautery (if indicated) for the tranexamic acid group and cautery alone for the anterior nasal packing group
Outcomes	**Outcomes of interest in the review:** *Primary outcome:* • Re-bleeding: "frequency of epistaxis recurrence at 24 hours and 7 days after treatment" • Serious adverse events *Secondary outcomes:* • Proportion of patients in each group whose bleeding had stopped at 10 minutes • Length of stay in the emergency department • Adverse effects **Other outcomes reported by study:** • Patient satisfaction (numerical rating scale of 0 to 10)
Declarations of interest	Not reported in paper. Tehran University of Medical Sciences, Faculty of Medicine in trials register
Funding	Not reported
Notes	The proportion of participants with a prior epistaxis history was significantly higher in the tranexamic acid group. The other baseline variables were comparable between the 2 groups

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised study Quote: "Eligible patients were randomly allocated to either the TXA group or the ANP group. Our research nurse used IBM SPSS Statistics for Windows, version 24 (IBM Corp) to generate the random allocation sequence, which was stratified by center. Randomization was done in blocks of two, four, and six."

Zahed 2018 (*Continued*)

Allocation concealment (selection bias)	Low risk	Allocation concealed from study personnel and participants Quote: "To implement the random allocation process, the research nurse randomized the consecutively numbered boxes filled with medication and cotton pledgets in a location removed from the ED and inaccessible to the ED personnel. Each box was identical in size, shape, and weight. The numbered boxes were held in the ED pharmacy and delivered sequentially to resident physicians treating patients with epistaxis who were enrolled in the study."
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants and personnel were not blinded Quote: "Due to differences in the numbers of pledgets required for ANP compared with topical TXA and in the consistency, color, and smell of the medications used for soaking and impregnating the pledgets, our patients and physicians were not blinded."
Blinding of outcome assessment (detection bias) All outcomes	High risk	Comment: although the authors state that those who analysed the data set were blinded to group assignment, those assessing this outcome (whether or not the patient re-bled in the first 10 minutes) were not blinded (see above)
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts from the study were reported
Selective reporting (reporting bias)	Low risk	Trials register: IRCT201509088872N9. All planned outcomes are reported All outcomes planned in the methods section are reported in the results section
Other bias	Unclear risk	The proportion of participants with a prior epistaxis history was significantly higher in the tranexamic acid group

ANP: anterior nasal packing
TXA: tranexamic acid

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Alimian 2011	ALLOCATION: Randomised, double-blind trial PARTICIPANTS: Intraoperative bleeding in endoscopic sinus surgery
ATERO 2014	ALLOCATION: Randomised trial PARTICIPANTS: Chronic epistaxis in patients with hereditary haemorrhagic telangiectasia
Athanasiadis 2007	ALLOCATION: Randomised, double-blind trial PARTICIPANTS: Intraoperative bleeding in endoscopic sinus surgery
Baradaranfar 2017	ALLOCATION: Randomised, double-blind trial PARTICIPANTS: Intraoperative bleeding in endoscopic sinus surgery
Beikaei 2015	ALLOCATION: Randomised, double-blind trial PARTICIPANTS: Intraoperative bleeding in rhinoplasty surgery
Chhapola 2011	ALLOCATION: Non-randomised study
Eftekharian 2016	ALLOCATION: Randomised, double-blind trial PARTICIPANTS: Intraoperative bleeding in rhinoplasty surgery
Fernandez-L 2007	ALLOCATION: In-vitro, non-randomised study
Geisthoff 2014	ALLOCATION: Randomised, double-blind trial PARTICIPANTS: Chronic epistaxis in patients with hereditary haemorrhagic telangiectasia
Ghavimi 2017	ALLOCATION: Randomised, double-blind trial PARTICIPANTS: Intraoperative bleeding in rhinoplasty surgery

(*Continued*)

Gossage 2015	ALLOCATION: Randomised, double-blind trial PARTICIPANTS: Chronic epistaxis in patients with hereditary haemorrhagic telangiectasia
IRCT2014122520434N1	ALLOCATION: Randomised, double-blind trial PARTICIPANTS: Intraoperative bleeding in rhinoplasty surgery
IRCT201509088872N9	ALLOCATION: Randomised, single-blind trial PARTICIPANTS: Patients on anticoagulation therapy with epistaxis
Jabalameli 2006	ALLOCATION: Non-randomised study of intraoperative bleeding
Keiani Motlagh 2003	ALLOCATION: Non-randomised, prospective, clinical study of the use of tranexamic mouthwash in minor oral surgery
Kulkarni 2018	ALLOCATION: Randomised trial PARTICIPANTS: Intraoperative bleeding in endoscopic sinus surgery
Mehdizadeh 2018	ALLOCATION: Randomised, triple-blind trial PARTICIPANTS: Intraoperative bleeding in rhinoplasty surgery
NOSE 2012	ALLOCATION: Randomised, double-blind trial PARTICIPANTS: Chronic epistaxis in patients with hereditary haemorrhagic telangiectasia
Sabba 2001	ALLOCATION: Non-randomised series of 3 case reports of successful use of tranexamic acid in epistaxis
Whitehead 2016	ALLOCATION: Randomised, double-blind trial PARTICIPANTS: Chronic epistaxis in patients with hereditary haemorrhagic telangiectasia
Yaniv 2006	ALLOCATION: Non-randomised study of intraoperative bleeding

Characteristics of ongoing studies *[ordered by study ID]*

ISRCTN34153772

Trial name or title	'Novel use of TXA to reduce the need for nasal packing in epistaxis'
Methods	Randomised, double-blind, placebo-controlled trial
Participants	Adults (> 18) presenting to the ED with spontaneous, atraumatic epistaxis, unresolved with simple first aid and standard initial therapy
Interventions	Intervention group: intranasal tranexamic acid 2 mL (200 mg) soaked on a dental roll and inserted into the bleeding nostril for 10 minutes; if bleeding not controlled, then a second dose of 2 mL over 10 minutes (400 mg in total) Comparator group: placebo (intranasal water for injection 2 mL)
Outcomes	**Primary outcome measure:** Use of anterior nasal packing (of any type) for treatment of epistaxis at any time during the ED attendance, as obtained from ED notes **Secondary outcome measures:** The following outcomes will be obtained from the ED records, hospital records and at the 7-day follow-up phone call to the participant: 1. Hospital admission 2. Need for blood transfusion 3. Any further treatment for epistaxis during the index ED attendance 4. Recurrent epistaxis requiring hospital treatment, following trial intervention and within 7 days of the index ED attendance 5. Any thrombotic event requiring any hospital re-attendance within 7 days of the index ED attendance 6. Any further hospital treatments required for epistaxis within 7 days of the index ED attendance, including details of the type of hospital episode 7. Number and nature of any adverse events
Starting date	August 2016
Contact information	Principal investigator: Dr Wendy Ingram, Peninsula Clinical Trials Unit, Plymouth (wendy.ingram@plymouth.ac.uk)
Notes	Royal Devon & Exeter Hospital (lead centre) and 13 other NHS hospitals in England and Scotland (UK) Estimated study completion date: January 2019

NCT02930941

Trial name or title	Topical intranasal tranexamic acid for epistaxis in the emergency department
Methods	Randomised, double-blind, single-centre, placebo-controlled trial
Participants	Adults (> 18) with anterior epistaxis

NCT02930941 (*Continued*)

Interventions	Intervention group: tranexamic acid (100 mg/1 mL) sprayed in to the affected nostril(s) via intranasal atomisation device; may repeat 2 doses in each affected nostril(s) Comparator group: 0.9% sodium chloride (1 mL)
Outcomes	**Primary outcome measure:** Time to control of bleeding (7 days) **Secondary outcome measures:** Length of stay in the emergency department Re-bleeding within the first 24 hours Re-bleeding within the first week Incidence of thromboembolic events (7 days) Incidence of drug-related events (7 days)
Starting date	February 2016
Contact information	Principal investigator: Aimee Moulin MD, University of California, Davis (akmoulin@ucdavis.edu)
Notes	Estimated study completion date: December 2019

NCT03360045

Trial name or title	The evaluation of effectiveness of nasal compression with tranexamic acid compared to simple nasal compression and Merocel packing
Methods	3-arm, double-blind, parallel-group randomised controlled trial
Participants	Patients over 18 years with anterior epistaxis (n = 135)
Interventions	Intervention group 1: 500 mg tranexamic acid delivered by atomiser spray, with manual nasal compression Comparator group (placebo): 5 mL normal saline delivered by atomiser spray, with manual nasal compression Comparator group (active): Merocel packing
Outcomes	**Primary outcomes:** Percentage of patients who have stopped bleeding within first 15 minutes after nasal compression or Merocel packing Number of patients who need rescue treatment (patients who have unstoppable epistaxis after 15 minutes, with Merocel packing applied as a rescue treatment) **Secondary outcome:** Re-bleeding: frequency of re-bleeding within the first 24 hours
Starting date	1 May 2018
Contact information	Associate Professor ş eref Kerem Çorbac oğ lu Kecioren Education and Training Hospital, Ankara, Turkey
Notes	Estimated study completion date: August 2018

ED: emergency department

DATA AND ANALYSES

Comparison 1. Tranexamic acid versus placebo plus usual care or usual care alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Control of epistaxis: episodes of re-bleeding over 10 days	3	225	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.56, 0.90]
1.1 Oral treatment	2	157	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.55, 0.96]
1.2 Topical application (10% gel)	1	68	Risk Ratio (M-H, Fixed, 95% CI)	0.66 [0.41, 1.05]
2 Control of epistaxis: time to stop initial bleeding (proportion with bleeding controlled within 30 minutes)	1	68	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.56, 1.11]
3 Severity of re-bleeding: proportion of patients requiring blood transfusion within 10 days	1	89	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.27, 2.48]
4 Length of hospital stay	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only

Comparison 2. Tranexamic acid versus other haemostatic agent

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Control of epistaxis: time to stop initial bleeding (proportion with bleeding controlled within 10 minutes)	3	460	Risk Ratio (M-H, Fixed, 95% CI)	2.35 [1.90, 2.92]

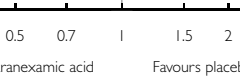
Analysis 1.1. Comparison 1 Tranexamic acid versus placebo plus usual care or usual care alone, Outcome 1 Control of epistaxis: episodes of re-bleeding over 10 days.

Review: Tranexamic acid for patients with nasal haemorrhage (epistaxis)

Comparison: 1 Tranexamic acid versus placebo plus usual care or usual care alone

Outcome: 1 Control of epistaxis: episodes of re-bleeding over 10 days

Study or subgroup	Tranexamic acid n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Oral treatment					
Petruson 1974	16/31	30/37		36.6 %	0.64 [0.44, 0.93]
White 1988	21/45	25/44		33.8 %	0.82 [0.55, 1.23]
Subtotal (95% CI)	**76**	**81**		**70.5 %**	**0.73 [0.55, 0.96]**
Total events: 37 (Tranexamic acid), 55 (Placebo)					
Heterogeneity: Chi^2 = 0.83, df = 1 (P = 0.36); I^2 =0.0%					
Test for overall effect: Z = 2.28 (P = 0.023)					
2 Topical application (10% gel)					
Tibbelin 1995	13/30	25/38		29.5 %	0.66 [0.41, 1.05]
Subtotal (95% CI)	**30**	**38**		**29.5 %**	**0.66 [0.41, 1.05]**
Total events: 13 (Tranexamic acid), 25 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.74 (P = 0.081)					
Total (95% CI)	**106**	**119**		**100.0 %**	**0.71 [0.56, 0.90]**
Total events: 50 (Tranexamic acid), 80 (Placebo)					
Heterogeneity: Chi^2 = 0.91, df = 2 (P = 0.63); I^2 =0.0%					
Test for overall effect: Z = 2.87 (P = 0.0041)					
Test for subgroup differences: Chi^2 = 0.12, df = 1 (P = 0.73), I^2 =0.0%					



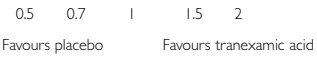
Analysis 1.2. Comparison 1 Tranexamic acid versus placebo plus usual care or usual care alone, Outcome 2 Control of epistaxis: time to stop initial bleeding (proportion with bleeding controlled within 30 minutes).

Review: Tranexamic acid for patients with nasal haemorrhage (epistaxis)

Comparison: 1 Tranexamic acid versus placebo plus usual care or usual care alone

Outcome: 2 Control of epistaxis: time to stop initial bleeding (proportion with bleeding controlled within 30 minutes)

Study or subgroup	Tranexamic acid n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Tibbelin 1995	18/30	29/38		100.0 %	0.79 [0.56, 1.11]
Total (95% CI)	**30**	**38**		**100.0 %**	**0.79 [0.56, 1.11]**
Total events: 18 (Tranexamic acid), 29 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.38 (P = 0.17)					
Test for subgroup differences: Not applicable					



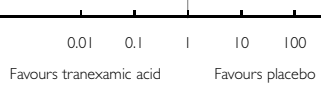
Analysis 1.3. Comparison 1 Tranexamic acid versus placebo plus usual care or usual care alone, Outcome 3 Severity of re-bleeding: proportion of patients requiring blood transfusion within 10 days.

Review: Tranexamic acid for patients with nasal haemorrhage (epistaxis)

Comparison: 1 Tranexamic acid versus placebo plus usual care or usual care alone

Outcome: 3 Severity of re-bleeding: proportion of patients requiring blood transfusion within 10 days

Study or subgroup	Tranexamic acid n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
White 1988	5/45	6/44		100.0 %	0.81 [0.27, 2.48]
Total (95% CI)	**45**	**44**		**100.0 %**	**0.81 [0.27, 2.48]**
Total events: 5 (Tranexamic acid), 6 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.36 (P = 0.72)					
Test for subgroup differences: Not applicable					

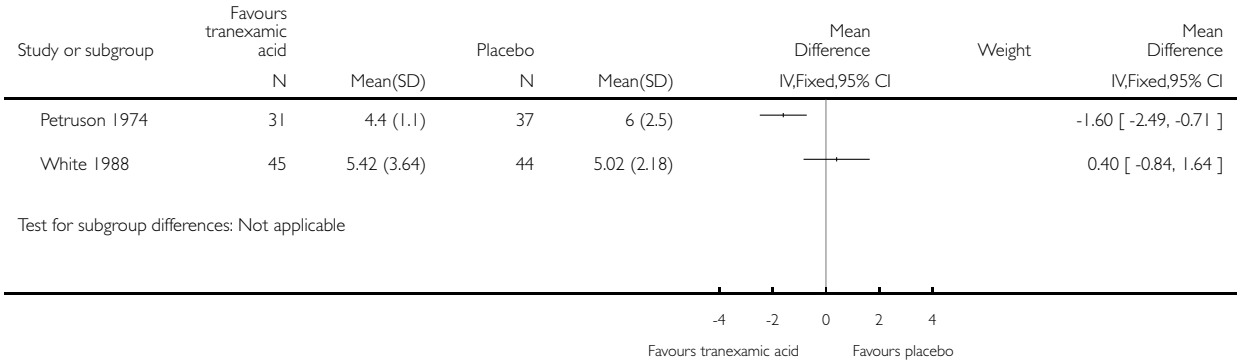


Analysis 1.4. Comparison 1 Tranexamic acid versus placebo plus usual care or usual care alone, Outcome 4 Length of hospital stay.

Review: Tranexamic acid for patients with nasal haemorrhage (epistaxis)

Comparison: 1 Tranexamic acid versus placebo plus usual care or usual care alone

Outcome: 4 Length of hospital stay

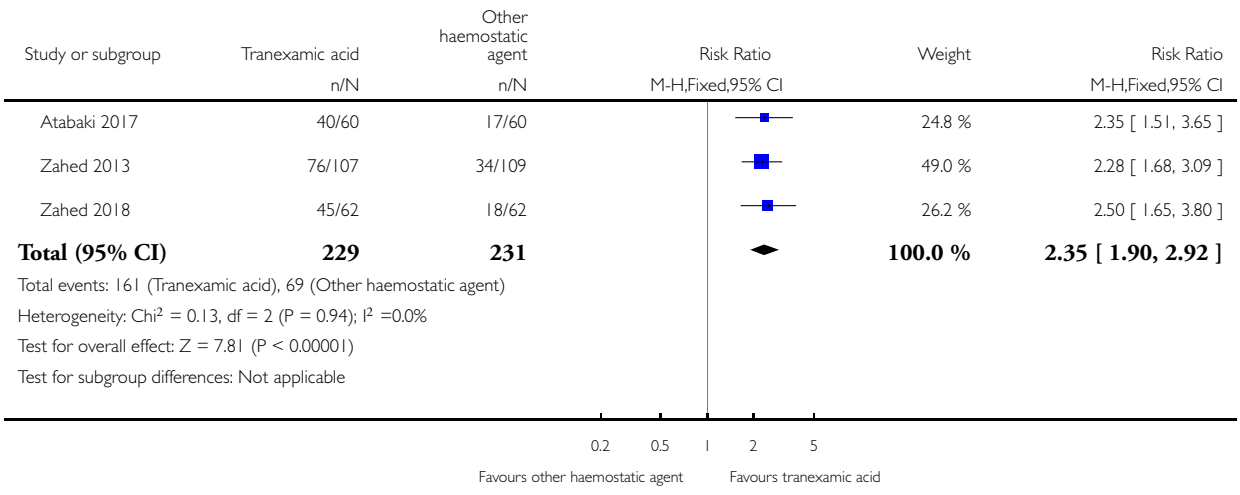


Analysis 2.1. Comparison 2 Tranexamic acid versus other haemostatic agent, Outcome 1 Control of epistaxis: time to stop initial bleeding (proportion with bleeding controlled within 10 minutes).

Review: Tranexamic acid for patients with nasal haemorrhage (epistaxis)

Comparison: 2 Tranexamic acid versus other haemostatic agent

Outcome: 1 Control of epistaxis: time to stop initial bleeding (proportion with bleeding controlled within 10 minutes)



APPENDICES

Appendix 1. Search strategies

CENTRAL	PubMed	EMBASE (Ovid)
1 MESH DESCRIPTOR Epistaxis EXPLODE ALL AND CENTRAL:TARGET 2 (epistax* OR nosebleed* OR rhinorrhag* OR rhinorrhaeg*):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET 3 #1 OR #2 AND CENTRAL:TARGET 4 MESH DESCRIPTOR Nose EXPLODE ALL AND CENTRAL:TARGET 5 (nose OR nasal):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET 6 #4 OR #5 AND CENTRAL:TARGET 7 MESH DESCRIPTOR Hemorrhage EXPLODE ALL AND CENTRAL:TARGET 8 (hemorrhag* OR haemorrhag* OR bleed* OR bloodloss*):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET 9 (blood NEAR loss*):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET 10 #7 OR #8 OR #9 AND CENTRAL:TARGET 11 #6 AND #10 AND CENTRAL:TARGET 12 #3 OR #11 AND CENTRAL:TARGET 13 MESH DESCRIPTOR Tranexamic Acid EXPLODE ALL AND CENTRAL:TARGET 14 MESH DESCRIPTOR Antifibrinolytic Agents AND CENTRAL:TARGET	#7 #3 AND #6 #6 #5 OR #4 #5 tranex* [tiab] OR amca [tiab] OR AMCHA [tiab] OR amchafibrin [tiab] OR amikapron [tiab] OR aminomethyl [tiab] OR (methylcyclohexane [tiab] AND carboxylate [tiab]) OR amstat [tiab] OR anvitoff [tiab] OR (cl [tiab] AND 65336 [tiab]) OR cl65336 [tiab] OR cyclocapron [tiab] OR [tiab] cyclokapron [tiab] OR cyklocapron [tiab] OR cyklokapron [tiab] OR exacyl [tiab] OR frenolyse [tiab] OR hexacapron [tiab] OR hexakapron [tiab] OR (trans [tiab] AND achma [tiab]) OR transamin* [tiab] OR ugurol [tiab]) #4 "Tranexamic Acid"[Mesh] #3 #1 OR #2 #2 ("nose" [Mesh] OR nose [ti] OR nasal [ti]) AND ("hemorrhag* [Mesh] OR haemorrhag* [tiab] OR bleed* [ti] OR bloodloss* [ti] OR (blood [ti] AND loss [ti])) #1 "Epistaxis" [Mesh] OR epistax* [tiab] OR nosebleed* [tiab] OR rhinorrhag* [tiab] OR rhinorrhaeg* [tiab]	1 *EPISTAXIS/ 2 (epistax* or nosebleed* or rhinorrhag* or rhinorrhaeg*).tw. 3 exp *NOSE/ 4 (nose or nasal).ti. 5 exp bleeding/ 6 (haemorrhag* or hemorrhag* or bleed* or bloodloss* or (blood and loss)).ti. 7 5 or 6 8 3 or 4 9 7 and 8 10 tranexamic acid/ 11 (tranex* or amca or AMCHA or amchafibrin or amikapron or aminomethyl or anvitofor or amstat or cl65336 or cyclocapron or cyclokapron or cyklocapron or cyklokapron or exacyl or frenolyse or hexacapron or hexakapron or transamin or ugurol).tw. 12 ((methylcyclohexane and carboxylate) or (cl and "65336") or (trans and achma)).tw. 13 10 or 11 or 12 14 1 or 2 or 9 15 13 and 14

(*Continued*)

15 (tranexamic OR amca OR AMCHA OR amchafibrin OR amikapron OR aminomethylcyclohexanecarbonic OR aminomethylcyclohexane carbonic OR aminomethylcyclohexanocarbonic):AB, EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET 16 (methylcyclohexane carboxylate OR aminomethylcyclohexanecarboxylicOR aminomethyl cyclohexane carboxylic OR aminomethyl cyclohexanecarboxylic OR aminomethylcyclohexane carboxylic OR aminomethylcyclohexanecarboxylic OR aminomethylcyclohexanocarboxylic OR aminomethylcyclohexanoic OR amstat OR anvitoff):AB, EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET 17 (cyclocapron OR cyclokapron OR cyklocapron OR cyklokapron OR exacyl OR frenolyse OR hexacapron OR hexakapron OR tranex OR tranexanic OR trans achma OR transamin OR transaminomethylcyclohexane carboxylic OR transexamic OR ugurol):AB,EH,KW,KY,MC,MH,TI,TO AND CENTRAL:TARGET 18 #13 OR #14 OR #15 OR #16 OR #17 AND CENTRAL:TARGET 19 #12 AND #18 AND CENTRAL:TARGET		
CINAHL (EBSCO)	**Web of Science (Web of Knowledge**	**Trial registries**
S12 S8 and S11 S11 S9 or S10 S10 TX ((methylcyclohexane and carboxylate) or (cl and "65336") or (trans and achma)) S9 TX tranex* or amca or AMCHA or amchafibrin or amikapron or aminomethyl or anvitofor or amstat or cl65336 or cyclocapron or cyclokapron or cyklocapron or cyklokapron or exacyl or frenolyse or hexacapron or hexakapron or transamin or ugurol S8 S1 or S2 or S7 S7 (S3 or S4) and (S5 or S6) S6 TI (haemorrhag* or hemorrhag* or bleed* or bloodloss* or (blood and loss))	#9 #8 AND #5 #8 #7 OR #6 #7 TS=((methylcyclohexane and carboxylate) or (cl and "65336") or (trans and achma)) #6 TS=(tranex* or amca or AMCHA or amchafibrin or amikapron or aminomethyl or anvitofor or amstat or cl65336 or cyclocapron or cyclokapron or cyklocapron or cyklokapron or exacyl or frenolyse or hexacapron or hexakapron or transamin or ugurol) #5 #4 OR #1 #4 #3 AND #2 #3 TI=(haemorrhag* or hemorrhag* or bleed* or bloodloss* or (blood and loss))	**ICTRP** epistaxis OR nosebleed* OR nose AND bleed* OR nose AND haemorr* OR nose AND hemorr* OR nose AND bloodloss **ClinicalTrials.gov (via CRS Web)** (epistaxis OR nosebleed) AND (tranexamic OR amca OR amcha OR amchafibrin OR amikapron OR aminomethyl OR anvitoff OR amstat OR cyclocapron OR cyclokapron OR cyklocapron OR cyklokapron OR exacyl OR frenolyse OR hexacapron OR hexakapron OR transamin) AND Study design: interventional

(*Continued*)

S5 (MH "Hemorrhage") S4 TI (nose OR nasal) S3 (MH "Nose") S2 TX (epistax* or nosebleed* or rhinorrhag* or rhinorrhaeg*) S1 (MH "Epistaxis")	#2 TI=(nose OR nasal) #1 TS=(epistax* or nosebleed* or rhinorrhag* or rhinorrhaeg*)	

Appendix 2. Data extraction

Methods

- (Double-/single-/non-) blinded, (cluster-/cross-over/ parallel -group/within-patient/quasi-/non-) randomised controlled trial with x duration of treatment and y duration of follow-up

Participants

- Setting
- Sample size:
  - Number randomised:
  - Number completed:
- Participant (baseline) characteristics:
  - Age
  - Gender
  - Other characteristics (risk factors)
- Inclusion criteria
- Exclusion criteria

Interventions

- Intervention group (method of delivery and dosage of tranexamic acid)
- Comparator group (placebo; type of 'usual care' provided)
- Use of additional interventions

Outcomes

- Primary and secondary outcomes and time points

Funding sources
Declarations of interest
Notes

HISTORY

Protocol first published: Issue 3, 2003

Review first published: Issue 12, 2018

Date	Event	Description
10 November 2010	New citation required and major changes	New authors took over the review and redrafted the protocol.

CONTRIBUTIONS OF AUTHORS

Jonathan Joseph: screened search results and selected studies, carried out 'Risk of bias' assessment and statistical analysis, wrote the text of the review.

Pablo Martinez-Devesa: screened search results and selected studies, carried out 'Risk of bias' assessment and statistical analysis, wrote the text of the review.

Jenny Bellorini: screened search results and selected studies (October 2018), carried out 'Risk of bias' assessment and statistical analysis, carried out GRADE assessment and edited the text of the review.

Martin J Burton: screened search results and selected studies (October 2018), carried out 'Risk of bias' assessment and statistical analysis, carried out GRADE assessment and wrote/edited the text of the review.

DECLARATIONS OF INTEREST

Jonathan Joseph: none known.

Pablo Martinez-Devesa: none known.

Jenny Bellorini: Jenny Bellorini is Managing Editor of Cochrane ENT, but had no role in the editorial sign-off process for this review.

Martin J Burton: Professor Martin Burton is joint Co-ordinating Editor of Cochrane ENT, but had no role in the editorial sign-off process for this review.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- National Institute for Health Research, UK.

Infrastructure funding for Cochrane ENT

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

- The title has been changed from 'Antifibrinolytic agent tranexamic acid for nasal haemorrhage (epistaxis)' to 'Tranexamic acid for patients with nasal haemorrhage (epistaxis)' in line with another Cochrane ENT protocol on this drug (Ravesloot 2017).
- The Background has been redrafted and updated.
- We have reworded the Objectives to show the review comparisons clearly.
- We have defined Types of studies more fully, including the minimum follow-up period.
- Types of participants has been set out more concisely and brought into line with the other Cochrane ENT tranexamic acid protocol (Ravesloot 2017).
- Types of interventions has been amended to define the review comparisons more clearly, in line with other recent ENT reviews.
- In Types of outcome measures, the primary outcome 'Effectiveness in control of epistaxis. Frequency and/or severity of rebleeds with a measure of blood loss' has been split into two separate outcomes: 'Control of epistaxis: re-bleeding, as measured by the proportion of patients re-bleeding within a period of up to 10 days (primary outcome)' and 'Control of epistaxis: time to stop initial bleeding (as measured by the proportion of patients whose bleeding is controlled within 30 minutes)' (secondary outcome). 'Adverse and/or side effects' has been similarly split into two outcomes: 'Significant adverse effects (seizures, thromboembolic events)' (primary) and 'Other adverse effects', to bring the review in line with other recent ENT reviews and the related tranexamic acid protocol (Ravesloot 2017). We have clarified the wording of other outcomes.
- We have added the following additional subheadings to the Methods section and expanded our descriptions, again to bring these into line with current MECIR standards and the methods used by Cochrane ENT: Measures of treatment effect; Unit of analysis issues; Dealing with missing data; Assessment of heterogeneity; Assessment of reporting biases; Subgroup analysis and investigation of heterogeneity; Sensitivity analysis; GRADE and 'Summary of findings' table.