Tranexamic acid in epistaxis: a systematic review

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Background: The role of tranexamic acid in the management of epistaxis remains unclear. There is uncertainty about its safety and about the contraindications for its use. We performed a systematic review of the use of systemic and topical tranexamic acid in epistaxis and a comparative review of its use in other specialties.
Objective of review: This review assesses and summarises the existing evidence for the efficacy and safety of tranexamic acid in the management of epistaxis.
Type of review: Systematic review.
Search strategy: MEDLINE and EMBASE were searched for 'epistaxis' and equivalent MESH terms, combined with the Boolean operator 'OR' and 'tranexamic acid'. The Cochrane library and society guidelines were reviewed for evidence regarding the use of tranexamic acid in other specialties.
Evaluation method: All five relevant RCTs were included in the review and were evaluated according to the recommendations of the Cochrane Handbook for Systematic Reviews.
Results: Three RCTS pertained to spontaneous epistaxis; of these, one trial found no benefit of oral tranexamic acid in acute epistaxis, one trial found no significant benefit of topical tranexamic acid, but the largest of the trials showed significant benefit of topical tranexamic acid in acute epistaxis management. Two RCTs examined oral tranexamic acid for prophylaxis of recurrent epistaxes in patients with hereditary haemorrhagic telangiectasia; both showed significant reduction in severity and frequency.
Conclusions: Tranexamic acid, as a WHO 'essential medicine', is a powerful, readily available tool, the use of which in epistaxis has been limited by uncertainty over its efficacy and its safety profile. This systematic review summarises the existing evidence and extrapolates from the wealth of data for other specialties to address the clinical question – does TXA have a role in epistaxis management?

Background

Epistaxis is one of the most common emergency ENT presentations, with up to 6% of the UK population having sought medical care for it[1]. Severe cases, complicated by anticoagulant medication or patient comorbidities, can result in significant blood loss and rarely death. A potential adjunct to the management of epistaxis is tranexamic acid; however, it is used inconsistently amid uncertainty regarding its efficacy and safety.

First created in the 1960s, tranexamic acid (TXA) is an antifibrinolytic agent. A lysine analogue, it binds competitively to the lysine binding site on plasminogen, preventing fibrin binding and converting plasminogen to plasmin[2]. Intravenous TXA has a bioavailability nearing 100% and reaches peak plasma concentration immediately. Oral TXA has only 35–45% bioavailability, and plasma concentration peaks at 3 h[3]. Topical TXA was shown to have less than 30% systemic absorption in one study[4] (intra-articular use) and nil absorption in other studies (pericardial and oral use)[5,6].

TXA is a WHO essential medicine[7] and as such, cheap and readily available in most hospitals. Yet its use has been limited by uncertainty over its safety, for example in patients with previous thrombotic events.

Objective

This review assesses and summarises the existing evidence for the efficacy and safety of tranexamic acid (TXA) in the management of epistaxis.

Methods

Search strategy

A search was performed of the MEDLINE (1950 onwards) and EMBASE (1980 onwards) databases, for 'epistaxis' and MESH terms (nosebleed, nose bleeding, bleeding nose, nose haemorrhage, nasal bleeding, nasal haemorrhage, and

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epistaxis, combined with the Boolean operator 'OR') and 'tranexamic acid', limited to human subjects and English language.

The Cochrane database, specialty society guidelines, and literature from other specialties were also reviewed. All searches were conducted in the last week of October 2015.

Study selection

Included were all randomised controlled trials (RCTs) assessing tranexamic acid in epistaxis management published in peer-reviewed journals. Case reports, abstracts and retrospective studies were excluded.

Study evaluation

Each study was reviewed independently by both authors and assessed for risk of bias according to the Cochrane Handbook for Systematic Reviews of Interventions[8].

Results

Search results

Searches of the databases yielded 273 results (figure 1). These consisted of 21 duplicates, 79 case reports, 119 retrospective studies or reviews, 8 conference abstracts, 35 educational or pharmacological reviews, 3 miscellaneous and 4 RCTs on the use of tranexamic acid in endoscopic sinus surgery (FESS). Only 3 RCTs were found pertaining to the use of tranexamic acid in spontaneous epistaxis and 2 pertaining to epistaxis in hereditary haemorrhagic telangiectasia (HHT). All 5 RCTs were included.

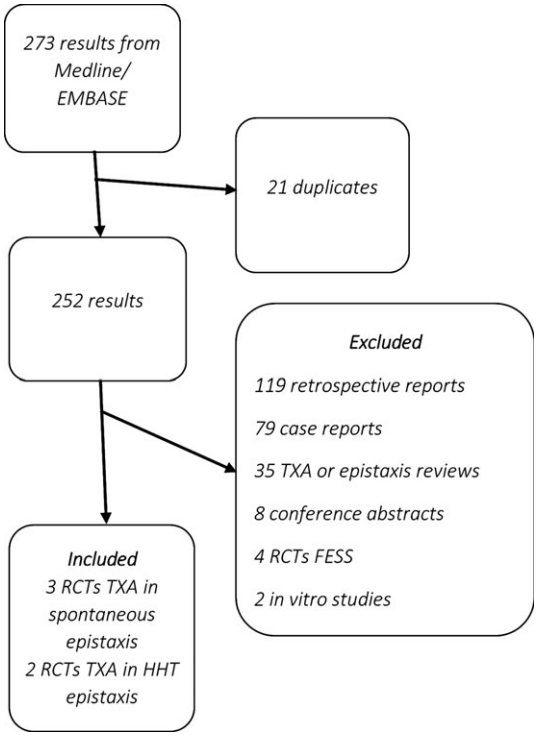

Fig. 1. Search results.

Study settings and participants

Included studies are summarised in Tables 1 and 2 below. They were set in Iran, Sweden, Britain, Germany and France. White *et al.*[9] excluded children and patients with renal insufficiency, haematuria, anticoagulant or antiplatelet medication, oral contraception or a history of a thrombotic event within 2 years. Tibbelin *et al.*[10] excluded children and patients with impaired haemostasis, fractured skull or nose, or perforated septum. Zahed *et al.*[11] did not specify inclusion age (median age of participants was 50 – 54 years). They excluded patients with trauma, posterior epistaxis, bleeding disorders, shock, INR > 1.5 or a visible vessel. In all 3 studies, the treatment and control groups were similar for age and sex. Severity of the bleed at presentation was recorded by Tibbelin *et al.* as mild, moderate or severe, and patients allocated to the TXA group had a significantly higher rate of moderate or severe bleeds. White *et al.* approximated the severity of initial bleed by the haemoglobin level at admission and found no difference between groups. Zahed *et al.* did not assess severity of initial bleed.

The two HHT trials recruited adult HHT patients with recurrent epistaxis. Geisthoff *et al.*[12] excluded patients who were pregnant or had cardiac arrhythmias, renal insufficiency, haematuria, colour-blindness, raised coagulation markers or a history of thromboses. Gaillard *et al.*[13] excluded patients with prior thrombosis, a history of convulsions, DVT on preliminary screening leg Doppler and patients unlikely to comply with treatment. Both HHT trials differed from the acute epistaxis trials in that they assessed the prophylactic role of TXA for reducing recurrent epistaxes.

Study design and intervention

The authors' judgements on the risk of bias for each study is shown in Table 3. In the study of White *et al.*, the trial was double-blinded. Patients received epistaxis management according to their presentation (cautery or anterior or posterior packing) and were then commenced on either 1 g TDS of TXA orally for 1 week, or a placebo tablet of the same appearance. Tibbelin *et al.* conducted a single-blind trial in which patients had the nasal cavity filled with either TXA gel (10% or 100 mg/mL) or placebo gel, for 30 min. Zahed

Table 1. Summary of included RCTs for spontaneous epistaxis

Study	*N*	Design	Dose	Effect	Safety
White *et al.* (1987)	89	RCT Double blind	1 g TXA TDS PO 10 days	No significant overall effect	1 superficial thrombophlebitis, group not specified
Tibbelin *et al.* (1995)	68	RCT Single blind	1.5 g TXA in gel, no packing	Trend to reduce re-bleed after TXA but not significant	Nil adverse 'Bad taste' both groups
Zahed *et al.* (2013)	216	RCT Single blind	500 mg TXA on pledgets	Significantly reduced duration of bleed and re-bleed rate	Nil adverse Nausea/vomiting both groups

Table 2. Summary of included RCTs for recurrent epistaxis in HHT

Study	N	Design	Dose	Effect	Safety
Geisthoff *et al.* (2014)	20 (40)	Crossover Double blind	1 g TXA TDS PO	No effect on Hb Significant reduction in frequency, duration and severity of bleeds	Nil adverse
Gaillard *et al.* (2014)	118 (236)	Crossover Double blind	1.5 g TXA BD PO	No effect on Hb Significant reduction in frequency and duration of bleeds	More diarrhoea and vertigo reported in TXA groups

N, number of participants. Numbers in parentheses represent the effective N., considering the crossover design of the trials. Hb, haemoglobin.

Table 3. The authors' judgement of the risk of bias for each of the included trials, in key domains as set out in the Cochrane Handbook for Systematic Reviews

	White *et al.* (1987)	Tibbelin *et al.* (1995)	Zahed *et al.* (2013)	Geisthoff *et al.* (2014)	Gaillard *et al.* (2014)
Random sequence generation	Low risk	High risk (strategy not described)	Low risk	Low risk	Low risk
Allocation concealment	Low risk	High risk (strategy not described)	Low risk	Low risk	Low risk
Blinding of participants and personnel	Low risk	High risk (single blind only)	High risk (single blind only)	Low risk	Low risk
Blinding of outcome assessment	Low risk	High risk (single blind only)	High risk (single blind only)	Low risk	Low risk
Incomplete outcome data	Possible risk (7 patients lost to follow-up)	Low risk	Low risk	Low risk	Possible risk (5 lost to follow-up, 4 stopped medication)
Selective reporting	Low risk	Low risk	Low risk	Low risk	Low risk
Other sources of bias	Low risk	Low risk	Low risk	No break period between the crossover	

et al., also single-blinded, used injectable TXA (100 mg/mL) on a 15-cm pledget as an anterior pack vs. a control of pledgets soaked in 1 : 100 000 adrenaline.

Geisthoff *et al.* randomised patients to either receive TXA (1 g TDS PO) for 3 months followed by placebo for 3 months, or vice versa. The outcomes were haemoglobin levels during the trial, and patient-recorded severity, duration and frequency of bleeds. Gaillard *et al.* had the same crossover design but a much larger number (n = 118), with TXA 1.5 g BD, and had similar findings. Both were double-blind trials.

Outcome 1: efficacy

The study of oral TXA following epistaxis (White *et al.*, n = 89, low risk of bias) assessed the rate and severity of re-bleeding following treatment and found no significant difference overall. It reported significantly fewer mild

re-bleeds per patient on TXA. Allowing 24 h for oral TXA to take effect, there was a non-significant reduction in frequency of re-bleeding (31% TXA group vs. 45% placebo). This trial was, however, underpowered by approximately half.

The smaller of the two RCTs of topical TXA (Tibbelin *et al.*, $n = 68$, high risk of bias) assessed per cent bleeding stopped within 30 min and per cent re-bleed within 8 h and within 10 days. No results achieved significance; in the TXA group, slightly more bleeds exceeded 30 min. Importantly, the TXA group had significantly more moderate or severe epistaxes at presentation than the control group; after linear regression analysis was used to compensate for this, no treatment effect was seen. This trial was underpowered by approximately a third. The largest RCT (Zahed *et al.*, $n = 216$, moderate risk of bias) found that 71% of the TXA group stopped bleeding within 10 min, compared with 31% of the controls ($P < 0.001$). There were significantly fewer re-bleeds within 24 h and 7 days. This trial achieved over 85% power for its primary endpoint.

In both HHT trials ($n = 40$ moderate risk of bias, $n = 236$ low risk of bias), TXA had no effect on the mean haemoglobin levels of participants over a 3-month period. However, it did significantly reduce the duration, severity and frequency of epistaxis, according to patient-recorded data (diaries and a visual analogue scale in Geisthoff *et al.*, and the French HHT Association epistaxis grid in Gaillard *et al.)*

Outcome 2: safety

There were no significant adverse safety events across the groups. In the study of White *et al.*, one patient developed superficial thrombophlebitis after discharge. Of note, Gaillard *et al.* conducted regular screening leg Doppler scans and found no DVTs during the trial.

Diarrhoea and vertigo were significantly greater in the TXA group in the study of Gaillard *et al.* Nausea was reported equally in both groups in the studies of White and in Zahed.

Discussion

Summary of main results

Of the trials in spontaneous epistaxis, one well-designed trial assessed oral TXA and found no significant benefit. A possible explanation is the limited absorption of oral TXA (45%); a further consideration is that the trial was underpowered by half; thus, the conclusions could represent a type II error. To date, no studies have assessed intravenous TXA.

Of the two RCTs of topical TXA, one showed significant benefit (Zahed *et al.*) and one showed no effect (Tibbelin *et al.*). The study of Zahed *et al.* was larger and powered at over 85%. It also tested TXA against current therapy (adrenaline-soaked pledgets) rather than simple placebo. Importantly, it excluded patients with a visible bleeding vessel because these were treated with cautery and patients with posterior bleeds. TXA was used as an adjunct to anterior packing with pledgets, not as a complete therapy. In the study of Tibbelin *et al.*, in contrast, both groups received gel alone without any mechanical pressure, and patients with a clear bleeding point were not excluded. This could have contributed to the reported higher overall re-bleed rate in study participants than in that institution's usual practice.

Both preventative RCTs in HHT showed significant improvement in self-reported severity of epistaxis over three months, but no improvement in the objective outcome, patient haemoglobin levels. One potential confounding factor in these trials was the lack of a 'washout' period between crossover, but given the rapid excretion of TXA, it would seem unlikely to have a big effect.

Quality, completeness and applicability of evidence

The 5 RCTs found in this systematic search were, broadly, well designed and constitute level IB evidence. The larger trial in HHT achieved high numbers for this uncommon condition. However, in spontaneous epistaxis, only one of the three RCTs was large enough to achieve power. The small number of RCTs and the conflicting results do not allow for any firm conclusions to be drawn.

Patients on warfarin, or with a history of thromboses, were excluded from these RCTs, yet they represent a significant proportion of epistaxes encountered clinically. Assessments of severity of bleeding varied widely in the spontaneous epistaxis trials, as there is no accepted validated tool to allow standardised reporting.

Potential biases in review

Strategies to reduce the risk of review bias included independent author analyses of the 5 RCTs against the criteria in the Cochrane Handbook. A thorough search strategy was devised, appraised by a librarian trained in literature search and run twice to ensure reproducible results. However, the search was limited to English language sources and extended back only to 1950 (MEDLINE).

Comparisons with other applications

Extrapolating from other clinical applications, two RCTs[14,15] showed that topical TXA in FESS significantly improved

visual field and reduced blood loss; however, the trials were small and one had a high risk of bias. A large (n = 400) well-designed trial found that topical TXA applied post-adenoidectomy in children reduced blood loss and primary haemorrhage rate[16]. In oral surgery, irrigation with topical TXA[17] or postoperative TXA mouthwash[18] has been shown to reduce blood loss. Surgical site irrigation with topical TXA is also used in intra-articular orthopaedic surgery and coronary artery bypass surgery. A 2013 Cochrane review found topical TXA reduced surgical bleeding by up to a third[19] across different specialties.

Intravenous TXA use is increasing in cardiothoracic surgery[20] after the withdrawal of aprotinin. In orthopaedic surgery, several studies have shown benefit from peri-operative IV TXA in arthroplasties[21,22]. Most notable is a 2014 review[23] of 872,416 patients undergoing either a total hip or total knee replacement, which found that IV TXA significantly reduced the need for blood transfusion and intensive care admissions. Three RCTs showed benefit in endoscopic sinus surgery[24–26] and one in adenotonsillectomy[27]. A smaller trial (n = 28) found no benefit in FESS[28], and a trial in head and neck surgery (n = 35) found no benefit[29] in reducing postoperative drain output. A 2013 Cochrane review found that IV TXA reduced the need for transfusion in emergency or urgent surgery[30]. In the CRASH-2 multicentre trial[31] involving 20211 trauma patients, 1 g IV TXA given within 3 h resulted in a significant reduction in all-cause mortality.

The safety of TXA remains a question, considering that many severe epistaxes occur in patients anticoagulated due to previous thromboses. No adverse events occurred in any of the epistaxis trials; however, patients with previous thromboses were excluded in all. The CRASH-2 trial included patients with a history of thromboses and found no increase in thrombotic events in patients treated with TXA. The Cochrane reviews on topical and IV TXA found that the reporting of safety outcomes was too inconsistent to allow conclusions to be drawn. A trial in cardiac surgery involving patients with previous thrombotic events showed no increase in adverse events with high-dose TXA[20]. The large (n = 872,416) review of IV TXA in orthopaedic surgery found no increase in thromboembolic events following IV TXA[23]. A meta-analysis of adverse events due to IV TXA[32] found the overall rates of limb ischaemia, myocardial infarction and venous thromboembolism to be too low to allow meaningful comparison between events on TXA vs. spontaneous events.

Implications for research

Further well-designed, powered RCTs are needed to assess each of topical, oral and intravenous TXA in spontaneous epistaxis. Moreover, across surgical specialties a trial assessing the safety of each of IV and topical TXA is needed, particularly with regard to patients with recent thromboses.

Implications for clinical practice

Currently, one large RCT suggests that topical TXA has benefit in spontaneous epistaxis, but the data is insufficient to draw firm conclusions regarding either efficacy or safety.

Conclusion

Tranexamic acid (TXA) is a cheap, readily available WHO essential medicine with proven efficacy in reducing blood loss, in its topical and intravenous forms, across different applications. However, there is insufficient evidence for its use in epistaxis as yet; the larger of 2 trials on topical TXA suggest a benefit, but no trials on intravenous TXA have been conducted. Large meta-analyses and a large multicentre trial have found no increase in thrombotic events in patients treated with TXA, but the evidence base is incomplete. Extrapolating from the evidence, it is the authors' opinion that both IV and topical TXA may prove to be a powerful adjunct to the management of severe epistaxis; powered, well-designed trials are required to test this hypothesis.

Keypoints

- There is clinical uncertainty about the efficacy and safety of tranexamic acid in epistaxis.
- The largest RCT assessing topical tranexamic acid in epistaxis shows significant benefit.
- Two RCTs assessing oral tranexamic acid in hereditary haemorrhagic telangiectasia showed benefit.
- There is evidence for the efficacy of tranexamic acid in multiple other applications.
- The evidence for the safety of tranexamic acid is increasing but not yet sufficient.

Conflicts of interests

None to declare.

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