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REVIEW ARTICLE

Haematological factors in the management of adult epistaxis: systematic review

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Abstract

Background: The management of epistaxis requires an understanding of haematological factors that may complicate its treatment. This systematic review includes six distinct reviews examining the evidence supporting epistaxis-specific management strategies relating to warfarin, direct oral anticoagulants, heparin, antiplatelet agents, tranexamic acid and transfusion.

Method: A systematic review of the literature was performed using a standardised methodology and search strategy.

Results: Limited numbers of articles were identified in each systematic review, with level 1 evidence only regarding the use of tranexamic acid. No studies met the inclusion criteria within the heparin, direct oral anticoagulants or transfusion systematic reviews. Many studies were limited by small sample sizes and significant risk of bias.

Conclusion: The management of major bleeding and transfusion practice is well documented in national guidance from multiple sources. The guidelines include advice on anticoagulants, antiplatelet agents and tranexamic acid. In the absence of more specific evidence, these guidelines should be applied in the management of epistaxis.

Key words: Epistaxis; Therapy; Coumarins; Heparin; Blood

Introduction

The management of haemorrhage is becoming increasingly complex, with the availability of novel anticoagulant agents and polypharmacy increasing in prevalence in an ageing population. As a result, care practitioners involved in the management of epistaxis require a specific understanding of the management of the haematological factors that may complicate treatment. For example, there is an association between patients taking antiplatelet or anticoagulant medication and epistaxis in terms of both frequency and severity.[1,2] The risk of receiving a blood transfusion when presenting with epistaxis varies from 3.7 to 23 per cent.[3,4] The use of antifibrinolytics is commonplace in major haemorrhage due to trauma, to minimise blood loss and transfusion requirements, which could be relevant to epistaxis.

This systematic review aimed to explore the literature to establish the evidence base for haematological management specific to epistaxis and, where lacking, to suggest generic published guidance. The systematic review has been split into six distinct reviews of: warfarin, direct oral anticoagulants, heparin, antiplatelet agents, transfusion practice and tranexamic acid. Given the potential for overlap between this systematic review and another that covers initial assessment,[5] this document focuses solely on management strategies rather than identifying haematological risk factors and prognostic associations.

Aims

This systematic review aimed to address the following key clinical questions that were identified, which relate to haematology in the management of epistaxis: (1) how should warfarin be managed during treatment for epistaxis?; (2) how should novel oral anticoagulants be managed?; (3) how should heparin-based anticoagulation be managed?; (4) how should antiplatelet therapy be managed?; (5) when should patients be transfused blood products?; and (6) when and how should tranexamic acid be used in epistaxis management?.

Materials and methods

This work forms part of a set of systematic reviews designed to summarise the literature prior to the

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generation of a UK national management guideline for epistaxis. This review addresses two of the originally identified research domains: the management of anticoagulation, and other haematological factors affecting outcome. A common methodology has been used in all reviews and is described in the first of the publications.[5] Studies were only included if they primarily involved patients aged 16 years and above who were treated for epistaxis within a hospital environment. Search strategies for the two domains were kept separate, but the evidence was assessed together given the significant overlap. The search strategy can be found in the online supplementary material that accompanies this issue. The findings for the six distinct reviews are presented separately.

Warfarin

Warfarin is a commonly used coumarin derivative that antagonises the production of vitamin K dependent clotting factors (II, VII, IX, X). It is used in the treatment and prevention of venous and arterial thromboembolic events, including atrial fibrillation, deep vein thrombosis, pulmonary embolism and following metallic valve insertion. It has a half-life of 36–42 hours, which means that therapeutic anticoagulation takes several days of treatment to establish, and several days off treatment to subside.[6] Prothrombin complex concentrate is recommended if urgent reversal is required, or fresh frozen plasma if this is not available.[7]

Observational studies have identified a correlation between warfarin use and epistaxis severity, such as a longer in-patient stay and re-admission for bleeding. In two studies, which included control groups, the increased severity reported may have been largely associated with patients who were over anticoagulated, with international normalised ratio (INR) results above the therapeutic range.[8,9]

The generic management of patients anticoagulated with warfarin and presenting with bleeding episodes is well established.[7]

Results

Only one study was included for analysis in the warfarin review (Appendix I). Figure 1 illustrates the search and article selection process.

Summary of evidence

There were no randomised control studies identified that met the inclusion criteria. There was one interventional study, which aimed to identify if continuing warfarin influenced outcome.[10] Twenty consecutively admitted patients with epistaxis who were on warfarin continued their anticoagulant if the INR was within the therapeutic range. If the INR was high, warfarin was temporarily discontinued and fresh frozen plasma given. Warfarin was recommenced once the INR returned to within the therapeutic range. This group was matched for age and sex with 20 patients from a pool of 95 consecutively admitted epistaxis patients not on anticoagulation therapy. Patients were transfused blood if their haemoglobin dropped below 10 g/dl in both groups.

There was no significant difference in mean length of stay between the warfarin group (mean of 2.8 days, standard deviation (SD) = 1.5) and the control group (mean of 2.75 days, SD = 1.25) ($p = 0.93$). Only 15 per cent of patients on warfarin had an INR above the therapeutic range.

Limitations

The above study was small, with only 20 patients in each arm. Baseline characteristics of the control group compared to those on warfarin were not reported, and length of stay outcomes would be expected to be

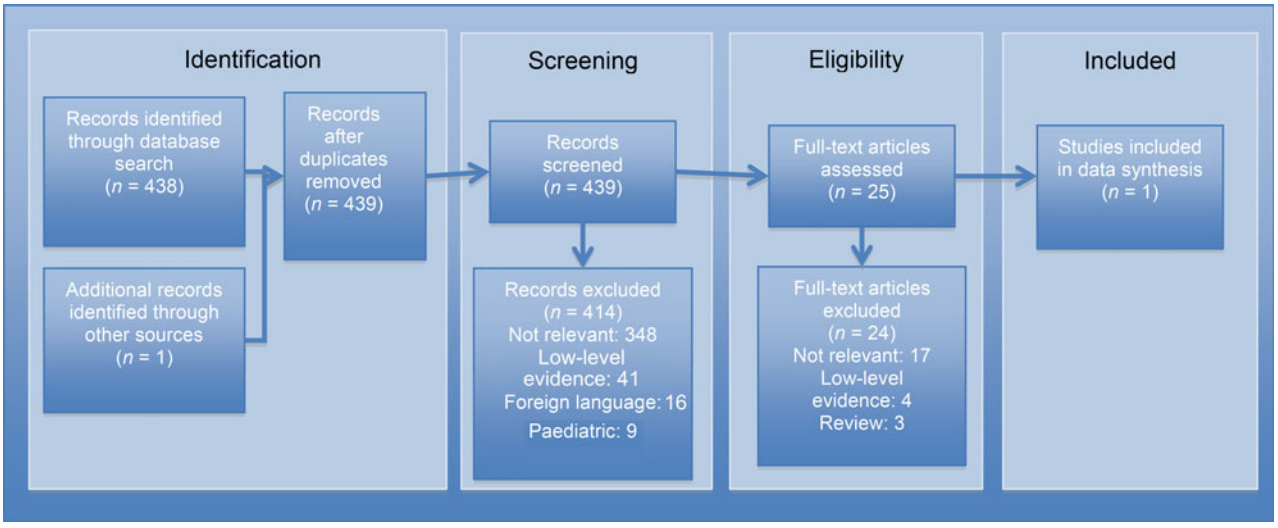

FIG. 1

Preferred Reporting Items for Systematic Reviews and Meta-Analyses ('PRISMA') diagram for the warfarin review, mapping the number of records identified, included and excluded during different review phases.

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influenced by variables other than treatment with warfarin. The incidence of re-bleeding was not stated.

Conclusions

The practice of temporarily discontinuing warfarin and/or reversing its effect in epistaxis cases is not evidence based. The above study suggests that this may not be necessary in all cases. Srinivasan *et al*. concluded that if the INR was within the therapeutic range, continuing anticoagulation was 'without risk of additional bleeding or compromise with epistaxis control'.[10] Since performing this literature search, a further study has supported this finding, concluding that warfarin can be continued in patients whose INR is within range.[11]

Several national organisations have published guidance on the management of bleeding in patients on warfarin.[7,12] These guidelines (Table I, Figure 2) are readily available, commonly incorporated into local hospital guidelines, and can be used for patients with epistaxis. The limited evidence available would support continuing warfarin in patients with epistaxis when the INR is within the therapeutic range, making a careful assessment of the underlying thrombotic and bleeding risks before anticoagulation is discontinued or reversed.

Direct oral anticoagulants

Direct oral anticoagulants are relatively new drugs, but their use is increasing, largely because of the lack of monitoring required.[13] The half-life of direct oral anticoagulants in patients with normal renal function is much shorter than warfarin, and estimated to be between 8 and 14 hours. Full anticoagulation occurs within 4 hours of ingestion, and takes 24–48 hours to subside after the last dose.[6,14,15] The management of bleeding in patients on these drugs is not well established. Novel agents to reverse direct oral anticoagulants are emerging. Idarucizumab has recently been licensed to reverse dabigatran in life-threatening haemorrhage. At present, there are no agents available to reverse other direct oral anticoagulants.[15,16]

Within this systematic review, we have focused on dabigatran, a direct thrombin inhibitor, and rivaroxaban and apixaban, which are factor Xa inhibitors. Observational studies have identified a high risk of receiving a blood transfusion following invasive procedures with use of dabigatran.[17,18]

TABLE I
EMERGENCY MANAGEMENT OF MAJOR BLEEDING IN PATIENTS ANTICOAGULATED WITH WARFARIN*

Emergency anticoagulation reversal in patients with major bleeding should be with 25–50 U/kg 4-factor prothrombin complex concentrate & 5 mg intravenous vitamin K
Recombinant factor VIIa is not recommended for emergency anticoagulation reversal
Fresh frozen plasma produces suboptimal anticoagulation reversal & should only be used if prothrombin complex concentrate is not available
Anticoagulation reversal for non-major bleeding should be with 1–3 mg intravenous vitamin K

*The British Committee for Standards in Haematology guidelines on oral anticoagulation with warfarin (fourth edition)[7]

Results and summary of evidence

No studies were identified which met the inclusion criteria and were relevant to the specific management of direct oral anticoagulants in epistaxis. Figure 3 illustrates the search and article selection process.

Conclusions

There is currently no evidence to define a specific treatment strategy for patients with epistaxis who are on direct oral anticoagulants. Management should follow generic bleeding guidance in patients taking these drugs. Given the short half-life and rapid time to full anticoagulation, management of significant bleeding should include stopping the offending drug in most cases, in addition to general haemostatic measures. In the case of major, life-threatening bleeding with dabigatran, idarucizumab use should be considered in discussion with local haematology services.

Heparins and other parenteral anticoagulant agents

The use of heparins (unfractionated heparin and low molecular weight heparin) is commonplace amongst patients admitted to hospital, for the prophylaxis or treatment of thrombotic events. Unfractionated heparin acts via an antithrombin III dependent mechanism to inactivate thrombin (factor IIa) and factor Xa, and has a half-life of 45–90 minutes at therapeutic concentration. Low molecular weight heparin has a similar mechanism of action, but with a greater ratio of factor Xa to IIa inhibition and a longer half-life of approximately 4 hours.[16] Their differing pharmacokinetic properties mean unfractionated heparin usually requires continuous systemic intravenous (IV) administration, whereas low molecular weight heparin is administered predominately via the subcutaneous route on an intermittent dosing schedule. Other parenteral anticoagulant agents such as danaparoid, fondaparinux, argatroban and bivalirudin are primarily used when heparin is contraindicated.

Results and summary of evidence

No studies were identified which met the inclusion criteria and were relevant to the management of heparins and other parenteral anticoagulant agents in epistaxis. Figure 4 illustrates the search and article selection process.

Conclusions

In patients with epistaxis, generic guidance should be followed for the management of bleeding in relation to these drugs. Most hospitals have guidelines for the management of unfractionated heparin and low molecular weight heparin. Recommendations for the

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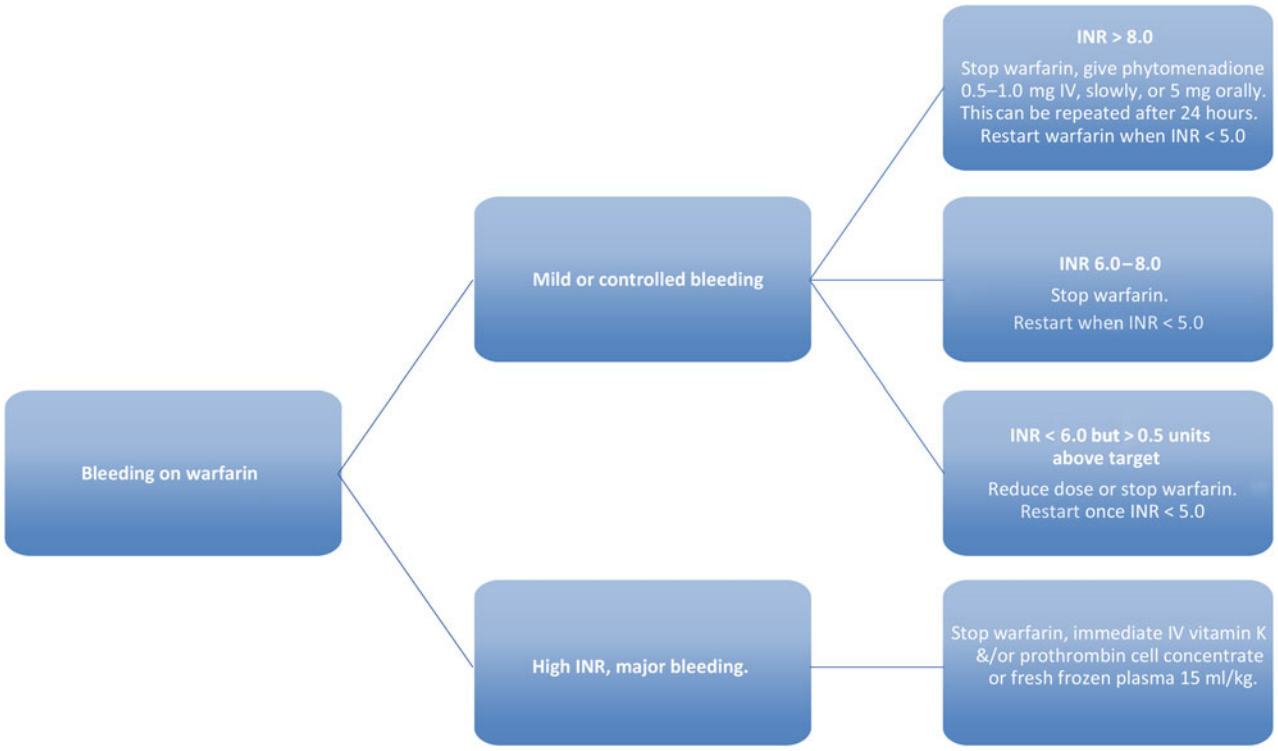

FIG. 2

Adaptation of National Institute for Health and Care Excellence guidelines on bleeding management in patients on warfarin.[12] INR = international normalised ratio; IV = intravenously

management of bleeding associated with other parenteral anticoagulant agents are provided in British Committee for Standards in Haematology guidance (Table II).[16]

Antiplatelet agents

Aspirin (cyclo-oxygenase inhibitor) and clopidogrel (adenosine diphosphate antagonist) are antiplatelet agents commonly used in the UK. Both drugs irreversibly inhibit platelet function, and 5–7 days off treatment is required to restore effectiveness.[12,16] Observational studies demonstrate an association between antiplatelet agent use and both the frequency and severity of epistaxis in patients taking these drugs.[1,19,20]

Results

Only one study could be included for analysis in the antiplatelet agent review (Appendix II). Figure 5 illustrates the search and article selection process. No randomised controlled trials were identified.

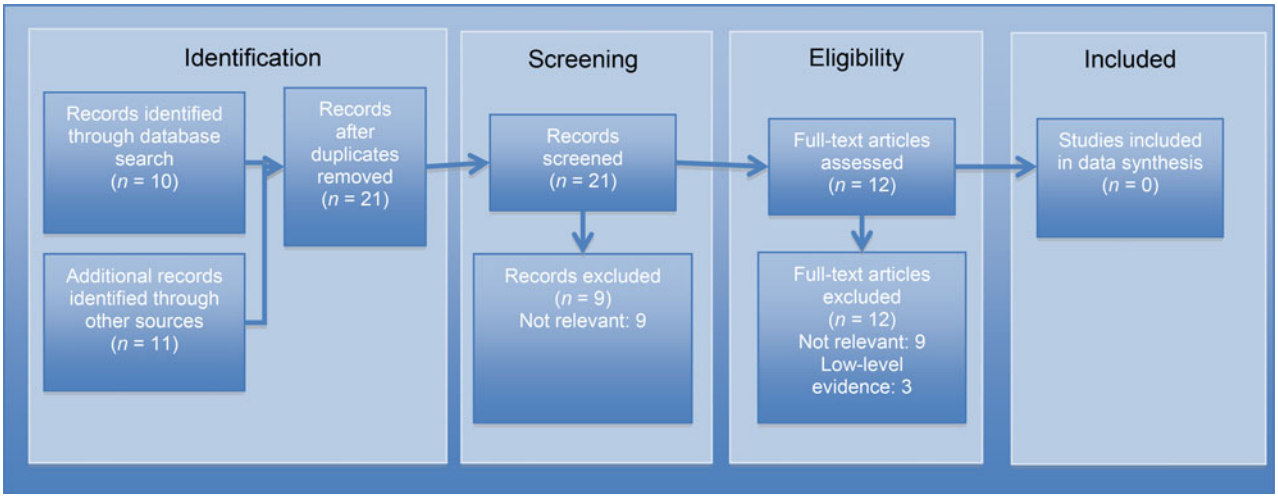

FIG. 3

Preferred Reporting Items for Systematic Reviews and Meta-Analyses ('PRISMA') diagram for the direct oral anticoagulant review, mapping the number of records identified, included and excluded during different review phases.

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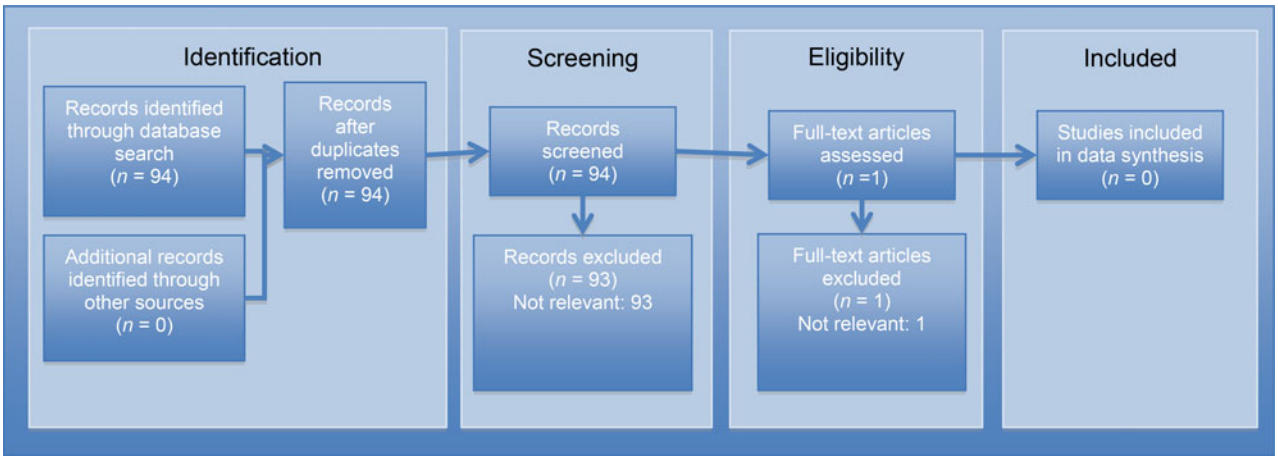

FIG. 4

Preferred Reporting Items for Systematic Reviews and Meta-Analyses ('PRISMA') diagram for the heparins review, mapping the number of records identified, included and excluded during different review phases.

Summary of evidence

An interventional study compared outcomes in patients who discontinued antiplatelet agents with those who continued.[21] Antiplatelet agents were continued in patients with controlled or minor bleeding, and baseline assessment and treatment outcome were compared with a retrospective control group managed by discontinuing these drugs. There was no statistically significant difference between the groups in rates of re-bleeding, re-packing, blood transfusion, surgical intervention or re-admission ($p < 0.05$).

Limitations

The above study was described as an audit by the authors; however, there was no established 'gold standard' for management. The control group did not receive treatment at the same time as the intervention group, introducing the risk of other differences in management affecting the result.

Conclusions

High-quality evidence for or against stopping antiplatelet medication in patients presenting with epistaxis is lacking. There may be significant morbidity associated with withholding these drugs (e.g. post-cardiac stenting), and generic guidance for bleeding associated with these drugs should be followed.[15,22] Continuing antiplatelet agents in patients with controlled or non-severe bleeding should be considered. This approach is supported by the irreversible effect of these agents on platelets, with discontinuation unlikely to influence the acute event. Recent UK National Blood Transfusion Committee guidelines recommend the consideration of platelet transfusion only in those on antiplatelet medication with critical bleeding.[23]

Tranexamic acid

Tranexamic acid is an antifibrinolytic agent which acts on plasminogen and is used to reduce blood loss. It is effective if given within the initial 3 hours

TABLE II
MANAGEMENT OF BLEEDING IN PATIENTS ANTICOAGULATED WITH HEPARINS AND OTHER PARENTERAL ANTICOAGULANTS*

Anticoagulant	Management of bleeding
Fondaparinux, bivalirudin or argatroban	There is no specific antidote for fondaparinux, bivalirudin or argatroban. Management of bleeding should be through cessation of treatment & general haemostatic measures Recombinant factor VIIa should be considered for critical bleeding Exceptionally, haemodialysis, haemofiltration or plasmapheresis may be considered for critical bleeding secondary to bivalirudin
Unfractionated heparin (UFH)	Stopping an UFH infusion & general haemostatic measures are often sufficient to stop or prevent bleeding Protamine sulphate (1 mg per 80–100 units UFH) will fully reverse UFH, but should be given slower than 5 mg/minute to minimise risk of adverse reactions Maximum recommended dose of 50 mg protamine is sufficient to reverse UFH in most settings
Low molecular weight heparin (LMWH)	LMWH administration within 8 hours: give protamine sulphate (1 mg per 100 anti–Xa units of LMWH). If ineffective, consider further protamine sulphate 0.5 mg per 100 anti–Xa units LMWH administration greater than 8 hours prior: consider smaller doses of protamine Consider recombinant factor VIIa if there is continued life-threatening bleeding despite protamine sulphate & time frame suggests a residual effect from LMWH contributing to bleeding

*The British Committee for Standards in Haematology guidelines on the management of bleeding in patients on antithrombotic agents[16]

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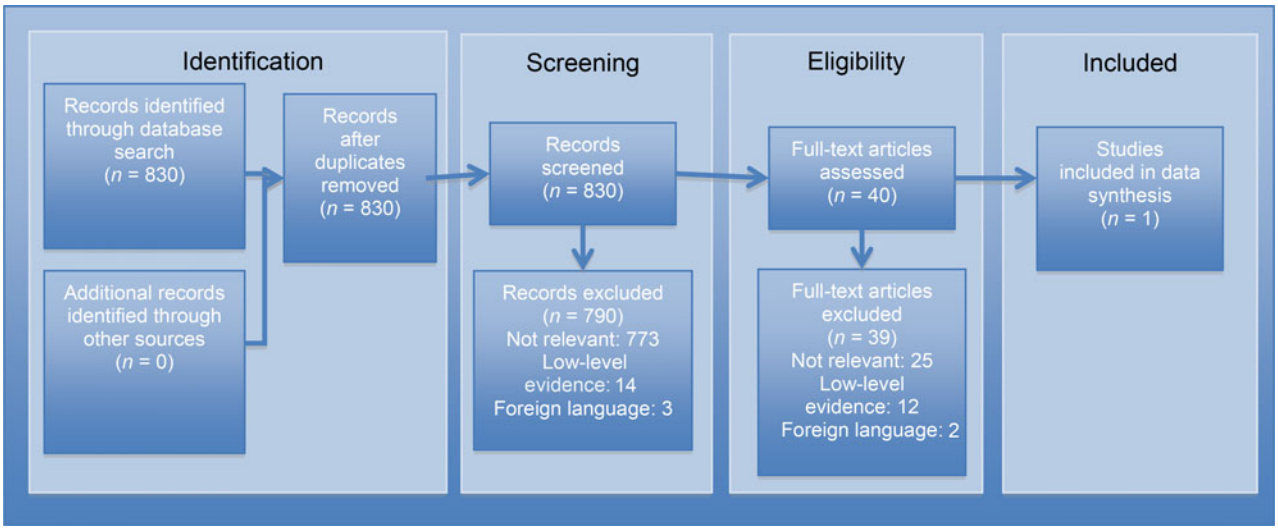

FIG. 5

Preferred Reporting Items for Systematic Reviews and Meta-Analyses ('PRISMA') diagram for the antiplatelet review, mapping the number of records identified, included and excluded during different review phases.

of haemorrhage.[24] The Clinical Randomization of an Antifibrinolytic in Significant Hemorrhage ('CRASH-2') study established the evidence base for use in major trauma,[25] and the World Maternal Antifibrinolytic ('WOMAN') trial established the evidence base for use in major obstetric haemorrhage.[26] It is also recommended to minimise bleeding perioperatively,[27] and is frequently used in menorrhagia. It is commonly used to treat epistaxis both systemically and topically.

Results

Four studies could be included for analysis in the tranexamic acid review (Appendix III). Figure 6 illustrates the search and article selection process. Four randomised controlled trials were identified, two using topical tranexamic acid[28,29] and two using oral tranexamic acid.[30,31]

Summary of evidence

Petruson studied all patients admitted to a single-centre hospital with epistaxis and treated with a posterior Foley catheter or anterior gauze pack from February to December 1971.[30] Patients were randomised to receive tranexamic acid 1 g orally, three times a day (31 patients) or placebo (37 patients) for 10 days. Bleeding severity, length of stay (4.4 days *vs* 6 days) and bleeding recurrence (52 per cent *vs* 81 per cent) were significantly lower in the tranexamic acid treatment group.

White and O'Reilly identified 89 adult patients presenting to one hospital with epistaxis from December 1984 to January 1986.[31] The patients were randomised to receive treatment with tranexamic acid 1 g orally, three times a day, or oral placebo three times a day for 10 days. There was no significant difference in rebleed rate between the treatment (47 per cent) and placebo (57 per cent) arms overall, or at 24 hours or 5 days. There was no significant reduction in length of stay.

Tibbelin *et al*. conducted a multicentre trial, randomising adult patients presenting with epistaxis to receive either 15 ml 10 per cent tranexamic acid topically (30 patients) or 15 ml glycine topically (38 patients).[28] There was no significant difference between the two groups in the primary outcome measures: frequency of bleeding that was arrested within 30 minutes (60 per cent in the tranexamic acid group *vs* 76 per cent in the placebo group), and re-bleeding within 8 days (44 per cent in the tranexamic acid group *vs* 66 per cent in the placebo group) and 30 days.

Zahed *et al*. studied patients presenting to a single-centre emergency department with spontaneous anterior epistaxis.[29] The patients in the study group ($n = 107$) had a 15 cm piece of cotton pledget soaked in 10 per cent tranexamic acid placed in the nasal cavity, which was removed after the arrest of bleeding. The control group received the usual treatment of a pledget soaked in 2 per cent lidocaine plus adrenaline 1:100 000 (109 patients) for 10 minutes, followed by the placement of an anterior nasal pack with tetracycline coating, which was removed on day 3. The results showed a significant increase in bleeding arrest in the tranexamic acid group (71 per cent *vs* 31.2 per cent; odds ratio = 2.27, $p < 0.001$) and earlier discharge from the emergency department. There was no significant difference in re-bleeding rate between the two groups at 24 hours or 7 days.

Limitations

Assessment of bias highlighted a lack of disclosure of randomisation method in Tibbelin and colleagues' trial.[28] Concealment and blinding were not well described in the trials by Tibbelin *et al*.,[28] Petruson,[30]

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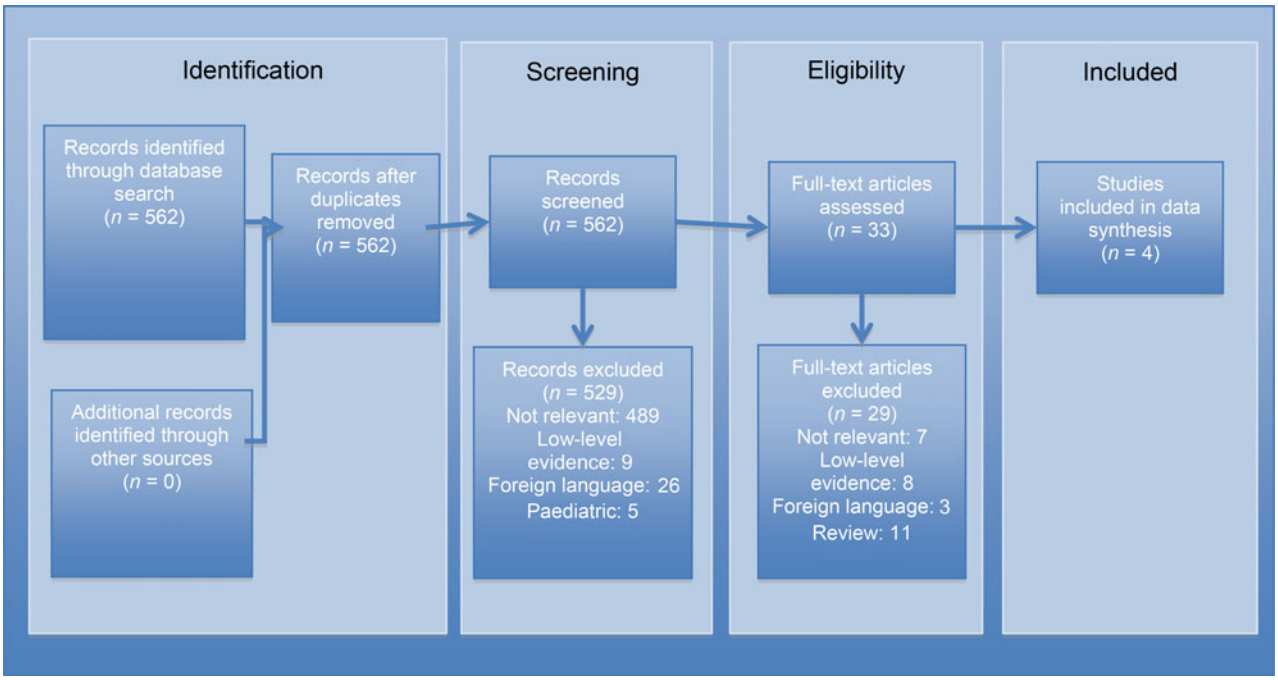

FIG. 6

Preferred Reporting Items for Systematic Reviews and Meta-Analyses ('PRISMA') diagram for the tranexamic acid review, mapping the number of records identified, included and excluded during different review phases.

or White and O'Reilly.[31] Moreover, Zahed *et al.* acknowledged that the tranexamic acid and placebo treatments had different appearances.[29] Patient exclusion criteria differed between the trials, and none were mentioned in Petruson's study.[30] Comparison of baseline characteristics between tranexamic acid and placebo groups were not stated in the studies by Petruson,[30] or White and O'Reilly.[31] The baseline characteristics of the two groups in Zahed and colleagues' study were comparable, apart from a previous history of epistaxis, which was significantly higher in the tranexamic acid group (58 per cent in the tranexamic acid group *vs* 13.5 per cent in the placebo group).[29] Tibbelin and colleagues recognised that the baseline bleeding severity was higher in the tranexamic acid group compared to the placebo group.[28] Correction with a linear logistic model was applied, but it is unclear whether this will have eliminated all confounding factors. Both oral tranexamic acid trials[30,31] contained low case numbers.

Conclusions

The limited number of included studies involved different patient populations, and all studies had significant threats to validity. This may explain the lack of consensus on the value of either oral or topical tranexamic acid in the management of epistaxis. Further studies are needed. Until there is clear evidence for tranexamic acid use in epistaxis, more general recommendations for its use in bleeding should be followed. As an example, the National Institute for Health and Care Excellence (NICE) clinical guideline (on blood transfusion, 'NG24')[27] suggests considering the use of tranexamic acid in adults undergoing surgery if they are expected to have at least moderate blood loss (greater than 500 ml).

Transfusion of blood and blood products

The requirement for transfusion of blood components has recently been reviewed by NICE[27] and the National Blood Transfusion Committee.[23] The evidence supports limiting red cell transfusions, and using a haemoglobin threshold of 70 g/l for most patients and clinical situations. Additional recommendations are made for the transfusion of platelets, fresh frozen plasma and cryoprecipitate. Advice specifically for major haemorrhage is covered in the British Committee for Standards in Haematology guideline: a practical guide for the haematological management of major haemorrhage.[32] Observational studies relating to transfusion in epistaxis have considered risk factors, the length of hospital stay, and the incidence and volume of blood transfused.

Summary of evidence

No randomised controlled trials or interventional studies were identified that were relevant to the specific management of blood transfusion in epistaxis. Figure 7 illustrates the search and article selection process.

Conclusions

Hospitals should have generic guidance for the transfusion management of patients with bleeding, based on national recommendations, and these should be followed for patients with epistaxis. To facilitate the appropriate use of blood by busy clinicians, a blood

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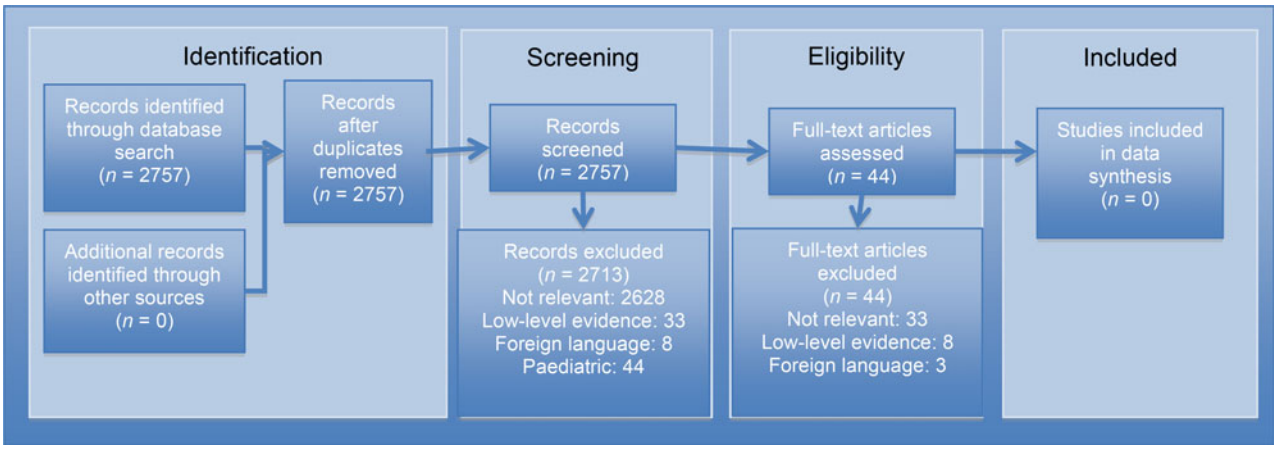

FIG. 7

Preferred Reporting Items for Systematic Reviews and Meta-Analyses ('PRISMA') diagram for the transfusion review, mapping the number of records identified, included and excluded during different review phases.

component smart phone application has been developed which contains National Blood Transfusion Committee recommendations.[33]

Summary conclusion

There is little published evidence addressing haematological factors that may complicate epistaxis treatment. However, the management of major bleeding and transfusion practice is well documented in national guidance from multiple sources. These guidelines include advice on anticoagulants, antiplatelet agents and tranexamic acid. In the absence of specific evidence, these guidelines should be applied in the management of epistaxis. There is a need for further research, and in particular studies examining the role of early intervention with topical or systemic tranexamic acid in epistaxis management.

Acknowledgement

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APPENDIX I
SUMMARY OF STUDIES INCLUDED IN WARFARIN REVIEW

Study (year)	Method	Participants	Interventions	Outcome measures	Results	Bias grade/results & assessment details
Non-RCTs with comparators Srinivasan *et al.*[10] (1997)	– 20 consecutive patients on warfarin admitted to hospital were studied – During same time period, 95 patients not on warfarin were admitted – From this pool, 20 were matched by age & sex – Single-centred study – Details from both groups were recorded to compare baseline characteristics: predisposing factors (trauma, URTI, hypertension); previous admissions with epistaxis; past medical history; NSAID use – BP was periodically measured – In warfarin group, indication for warfarin, treatment duration & suggested INR range were noted, & INR was measured – Treatment proceeded along standard lines	– 20 consecutive patients on warfarin admitted with epistaxis to hospital over 7-month period – 20 controls from pool of 95 patients not on warfarin admitted during same period were selected by matching for age & sex	'Standard treatment' was provided to both groups: – Patients with anterior bleeds with identified bleeding points were cauterised with silver nitrate, &, if successful, admitted for 24 h bed rest & observation – If unsuccessful or no bleeding point identified, BIPP packing was inserted under topical anaesthesia with 10% cocaine & pack left in situ for 36–48 h. If this failed, a Foley catheter was inserted as a posterior pack – For patients taking warfarin, if INR was within suggested range, it was continued. If INR was higher, warfarin was temporarily stopped & FFP given. Warfarin was restarted when INR level came within range – Red cell concentrate was given if haemoglobin was <10 g/dl (both groups)	Length of stay, epistaxis management escalation, bleeding complications	– No significant difference in mean length of stay between warfarin group (mean of 2.80 days, SD = 1.5) & control group (mean of 2.75 days, SD = 1.2) ($p = 0.93$, unpaired *t*-test) – Patients with posterior bleed had longer mean stay (warfarin group = 3.8 days, controls = 3.2 days) than those with anterior bleed (warfarin group = 1.7 days, controls = 1.8 days) ($p < 0.0001$, unpaired *t*-test) – Warfarin group: INR was above suggested range in 15% patients (3/20) – Authors concluded it is safe to continue warfarin treatment in epistaxis patients if INR is within suggested therapeutic range, 'without risk of additional bleeding or compromise with epistaxis control' – No incidences of re-bleeding in either group	MINORS; max grade of 24 Grade: 20 – Calculation of group size not reported – Control group stated to be matched but not explicitly reported – Clear comparison of outcomes in terms of treatments provided & lengths of stay – End point (length of hospital stay) has a large number of variables affecting it. – No mention of re-admission rate – Re-bleed rate not measured – Very small study group – would be difficult to measure any differences in blood transfusion rate & other in-patient interventions

RCT = randomised controlled trial; MINORS = methodological index for non-randomised studies; URTI = upper respiratory tract infection; NSAID = non-steroidal anti-inflammatory drugs; BP = blood pressure; INR = international normalised ratio; h = hours; BIPP = bismuth iodine paraffin paste; FFP = fresh frozen plasma; SD = standard deviation

APPENDIX II
SUMMARY OF STUDIES INCLUDED IN ANTIPLATELET AGENTS REVIEW

Study (year)	Method	Participants	Interventions	Outcome measures	Results	Bias grade/results & assessment details
Non-RCTs with comparators						MINORS; max grade of 24
Biggs *et al.*[21] (2013)	– A 2-staged observational study, comparing management of epistaxis patients with regard to antiplatelet & anticoagulant agents before & after implementation of a new treatment algorithm – The number of patients with epistaxis admitted on antiplatelet & anticoagulant medications was noted, & those who had their medication continued, stopped or dose altered were identified. Outcomes for each category were reported & compared – A standardised treatment algorithm was introduced & observation repeated, noting any change in frequency & outcome of above observations – This algorithm included continuing antiplatelet agents in controlled or minor bleeding	100 sequential patients admitted to single centre with epistaxis	Antiplatelet agents were continued in patients with controlled or minor bleeding in second cycle – Baseline assessment findings & treatment outcome were compared with a control group previously managed by discontinuing these drugs from first cycle	Number of patients presenting with epistaxis according to drug group & BP status	There was no statistically significant difference between groups in rates of re-bleeding, re-packing, blood transfusion, surgical intervention or re-admission ($p < 0.05$)	Grade: 20 – Article is described as being an audit; however, first cycle has no defined or established 'gold standard' – Control group did not receive treatment at same time as intervention group, introducing risk of other differences in management affecting result

RCT = randomised controlled trial; MINORS = methodological index for non-randomised studies; BP = blood pressure

APPENDIX III
SUMMARY OF STUDIES INCLUDED IN TRANEXAMIC ACID REVIEW

Study (year)	Method	Participants	Interventions	Outcome measures	Results	Bias grade/results & assessment details
RCTs Petruson[30] (1974)	– Patients presenting to single hospital with epistaxis were treated with posterior Foley catheter &/or anterior gauze tampon – Random number generator assigned patients to treatment or placebo groups. Patients were randomised to receive TXA 1 g orally 3 times/day (31 patients) or placebo (37 patients) for 10 days – 'Bleeding points' were awarded twice a day by author (daytime) or by on-call ENT doctor at clinic (non-daytime): 0 = no bleeding; 1 = unimportant bleeding; 2 = small bleeding, not treated; 4 = repeated small bleedings, not treated; 6 = bleeding requiring treatment	– All patients hospitalised for epistaxis from February to December 1971 – 68 patients in total; 31 in TXA treatment arm & 37 in placebo arm	– Tablet administration began 1 h after hospitalisation & continued 3 times/day for 10 days – TXA dose was 1 g orally 3 times/day *vs* placebo – Foley catheter balloon drained 12–24 h after bleeding stopped – Catheter removed 3–6 h later – If no bleeding within 12–24 h, anterior gauze tampon taken away until fresh blood evident; repeated every 3–6 h until completely removed	– Cumulative 'bleeding points' to give bleeding severity score at days & 5 days & total score – Length of stay – Recurrent epistaxis	– Bleeding severity total score, & scores after 3 days & 5 days of treatment, were significantly lower in treatment group *vs* placebo group – Length of stay was significantly shorter for treatment group patients (4.4 days *vs* 6.0 days) – Number of patients with ≥1 recurrent bleed was significantly lower in treatment group (52% *vs* 81% total; 6% *vs* 41% after 3 days treatment; 0 *vs* 10% after 5 days treatment)	Cochrane Risk of Bias – Random sequence generation: low risk – Allocation concealment: unclear risk – Blinding of participants & personnel: unclear risk – Blinding of outcome assessment: unclear risk – Incomplete outcome data: unclear risk – Selective reporting: low risk – Other: low risk – Random numbers used for randomisation – Labels on tablet bottles bore only patient's number – No comment on appearance of tablet & whether drug & placebo matched – All patients hospitalised in time period were selected, but no description of whether any outcome data missing

Tibbelin *et al.*[28] (1995)	– Multi-centred trial of all adult patients presenting with epistaxis – Patients received 15 ml 10% TXA topically (30 patients) or 15 ml glycine topically (38 patients) – Patients' history (including predisposing factors), bleeding source location, bleeding severity & concomitant therapy were recorded – Treatment gel or same volume of placebo was administered in plastic syringes – Gels were applied in same way by investigator – If bleeding was not arrested within 30 min of gel application, 'traditional therapy' was instituted	– Patients ≥18 y with ongoing nosebleed at time of gel application – 68 patients in total; 30 in TXA treatment arm & 38 in glycine treatment arm – Exclusions: known impaired haemostasis, skull &/or nose fracture, & nasal septum perforation – Predisposing factors (including acetylsalicylic acid use, URTI signs) were comparable between groups. Bleeding site location was also comparable	– Treatment gel = 15 ml of 10% TXA – Placebo = 15 ml glycine – Both interventions had same preservatives & thickeners, looked identical, were hypertonic & had same pH & storage temperature – Applied to affected nostril, after it had been examined to check clean & free of clot – After gel application, piece of cotton was placed in nostril & patients instructed not to blow gel out for 30 min	– Time taken to arrest bleeding – Re-bleeding within 30 min, 8 days & 30 days – Adverse events – Inconvenience or complications associated with gel application	– Bleeding intensity, as baseline variable, was different between groups: a significantly higher relative frequency of moderate to severe bleeding (as recorded prior to start of treatment) in TXA group. Linear logistic model was fitted to data to adjust for this group difference – No significant differences between study & control groups for frequency of bleeding arrested within 30 min (60% TXA *vs* 76% placebo) – No significant differences for re-bleeding within 10 days (44% TXA, 66% placebo) or 8 h (11% TXA, 31% placebo) – No serious adverse events were recorded; 3 patients in each of study & placebo groups reported a 'bad taste'	– Random sequence generation: unclear risk – Allocation concealment: unclear risk – Blinding of participants & personnel: low risk – Blinding of outcome assessment: unclear risk – Incomplete outcome data: unclear risk – Selective reporting: low risk – Other: unclear risk – Randomisation technique not described – Concealment not described, other than that gels looked identical – Attrition rate not explicitly stated – Difference in baseline parameter of bleeding severity – difficult to interpret impact of model used to adjust for this

Continued

Appendix III *Continued*

Study (year)	Method	Participants	Interventions	Outcome measures	Results	Bias grade/results & assessment details
White & O'Reilly[31] (1988)	– All admitted patients with epistaxis were randomised to receive TXA 1 g orally 3 times/day or placebo orally 3 times/day for 10 days post-presentation – Medical history, clinical findings & usual medication were recorded on admission – Local treatment (cautery, anterior nasal packing, posterior nasal packing) was commenced to control bleeding & method used was recorded – Treatment allocation was 'double blinded' according to a previously determined randomisation code – Nasal packing was removed at 24 h after all bleeding had stopped – Patients were discharged from hospital altering having been free of bleeding for at least a further 24 h – All patients were reviewed at 3 weeks to record re-bleeds or complications	– All epistaxis patients ≥18 years admitted to Victoria Infirmary from December 1984 to January 1986 – 89 adult patients in total; single-centred – Exclusions: recent (last 2 years) history of vascular thrombosis or thromboembolic disease, evidence of renal insufficiency, history of medication known to interfere with coagulation process (e.g. aspirin, dipyridamole, warfarin), massive haematuria, & oral contraceptive use	– Treatment group: oral TXA 1 g 3 times/day – Control group: placebo tablets 3 times/day – Treatment (both groups) started within 1 h of admission & continued for 10 days	– Re-bleeding events at 24 h, 5 days and total number – Re-bleed severity (mild, moderate, severe) – Length of hospital stay – Side effects	– No significant difference in total number of patients experiencing re-bleeding (47% TXA *vs* 57% control). No difference after 24 h (31% TXA *vs* 45% placebo), nor after 5 days (20% TXA *vs* 20% placebo) – No significant difference in number of patients experiencing re-bleeding after excluding those patients who re-bled only within first 24 h – No difference in number of patients with severe (type 3) re-bleeds – Number with mild (type 1) re-bleeds showed some decrease in treatment group (13 *vs* 28 patients; chi square trends = 4.9; $p = 0.03$) – No significant difference in mean length of hospital stay (5.42 days TXA group, 5.42 days placebo group). Modal hospitalisation time was 1 day shorter in treatment group (3 *vs* 4 days)	– Random sequence generation: low risk – Allocation concealment: unclear risk – Blinding of participants & personnel: unclear risk – Blinding of outcome assessment: low risk – Incomplete outcome data: low risk – Selective reporting: low risk – Other: unclear risk – Previously determined randomisation code – Method of allocation concealment not described – Insufficient information regarding similarities between treatment & placebo tablets – 89/96 patients completed course of treatment & returned for follow up – Pre-specified outcomes reported – Classification of re-bleed severity (type 1 mild, type 2 moderate, type 3 severe) could be somewhat subjective

Zahed *et al.*[29] (2013)	– Single-centre trial – Patients with anterior epistaxis presenting to ED allocated to receive: 15 cm piece of cotton pledget soaked in 10% TXA (107 patients) removed after arrest of bleeding, or control treatment of a pledget soaked in 2% lidocaine plus adrenaline 1:100 000 (109 patients) for 10 min followed by anterior pack with tetracycline covering removed on day 3 – Treatment allocation: previously determined randomisation code using computer software. Treatment boxes filled with medication & pledgets were randomised & blinded & stored in a remote location inaccessible from ED – Treatment was carried out by ED doctors trained in pledget & nasal packing application in a 2-h workshop – ED doctors undertook follow up for re-bleeding & complications by telephone call or revisiting schedule	– Patients presenting to ED with ongoing anterior epistaxis – 216 patients in total; 107 in TXA treatment arm & 109 in lidocaine plus adrenaline control arm – Exclusions: epistaxis following major trauma; posterior epistaxis; known history of bleeding disorder (e.g. thrombocytopenia, haemophilia) or platelet disorder; INR >1.5; evidence of shock; & visible bleeding vessel – Basic baseline characteristics (e.g. age, sex, INR, platelet count, prothrombin time, partial thromboplastin time) were comparable, but epistaxis history was significantly higher in TXA treatment group (58.1% *vs* 13.5%)	– In TXA group, a 15 cm piece of cotton pledget soaked in injectable form of TXA (500 mg in 5 ml) was inserted in nostril of bleeding side. It was removed after bleeding arrest was determined by examining blood-soaked pledgets & oropharynx – In anterior nasal packing group, usual shrinkage, with a cotton pledget soaked in adrenaline (1:100 000) plus lidocaine (2%) for 10 min, & packing, with several cotton pledgets covered with tetracycline, were performed in nostril of bleeding side – Nasal packing removed after 3 days – Routine anterior nasal packing & cautery, if needed, were considered as rescue treatment for TXA group & cautery for anterior nasal packing group	– Taken time to arrest bleeding (recorded in 5 min intervals) – Rate of initial haemostasis within 10 min from treatment onset – Rate of re-bleeding within 24 h & 7 days – Length of ED stay – Patient satisfaction rate evaluated by a 0–10 scale	– Within 10 min of treatment, bleeding arrest was significantly higher in TXA treatment group (71% *vs* 31.2%, OR = 2.27; 95% CI = 1.68–3.06; $p < 0.001$) – Discharge from ED in ≤2 h was higher in TXA treatment group (95.3% *vs* 6.4%, OR = 14.8; 95% CI = 7.2–30.4; $p < 0.001$) – Complications (nausea, vomiting, intolerance) reported – no group difference (4.7% TXA group *vs* 11% control group) – Re-bleeding in first 24 h showed no significant difference (4.7% TXA, 12/8% control; OR = 0.46; CI = 0.14–0.98; $p = 0.034$) – Re-bleeding in 1 week showed no significant difference (2.8% TXA *vs* 11% control; OR = 0.26; 95% CI = 0.07–0.88; $p = 0.018$) – Satisfaction rate was higher in TXA group (8.5 ± 1.7) compared with control anterior nasal packing group (4.4 ± 1.8) ($p < 0.001$)	– Random sequence generation: low risk – Allocation concealment: low risk – Blinding of participants & personnel: high risk – Blinding of outcome assessment: low risk – Incomplete outcome data: low risk – Selective reporting: low risk – Other: low risk – Computer generated random numbers – ED doctors presented with sequential unmarked boxes, in order determined by randomisation by research nurses – As acknowledged by authors, doctors & patients were not truly blinded, as medications differed in consistency, colour & smell, & there were a different number of pledgets in groups – Investigators performing analysis were not same as those performing nasal packing – No patients lost to follow up – CONSORT diagram present

RCT = randomised controlled trial; TXA = tranexamic acid; h = hours; URTI = upper respiratory tract infection; min = minutes; ED = emergency department; OR = odds ratio; CI = confidence interval; CONSORT = Consolidated Standards of Reporting Trials