The Use of Tranexamic Acid to Reduce the Need for Nasal Packing in Epistaxis (NoPAC): Randomized Controlled Trial

Adam Reuben, MB ChB*; Andrew Appelboam, MBBS; Kara N. Stevens, PhD; Jane Vickery, PhD; Paul Ewings, PhD; Wendy Ingram, PhD; Alison N. Jeffery, PhD; Richard Body, PhD; Malcolm Hilton, BM BCh; Jason Coppell, MBBS; Brian Wainman; Andy Barton, PhD

*Corresponding Author. E-mail: adam.reuben@nhs.net, Twitter: @adamreuben.

Study objective: Epistaxis is a common emergency department (ED) presentation and, if simple first aid measures fail, can lead to a need for anterior nasal packing. Tranexamic acid is an agent that contributes to blood clot stability. The aim of this study is to investigate the effectiveness of topical intranasal tranexamic acid in adult patients presenting to the ED with persistent epistaxis, and whether it reduces the need for anterior nasal packing.

Methods: From May 5, 2017, to March 31, 2019, a double-blind, placebo-controlled, multicenter, 1:1, randomized controlled trial was conducted across 26 EDs in the United Kingdom. Participants with spontaneous epistaxis, persisting after simple first aid and the application of a topical vasoconstrictor, were randomly allocated to receive topical tranexamic acid or placebo. The primary outcome was the need for anterior nasal packing of any kind during the index ED attendance. Secondary outcome measures included hospital admission, need for blood transfusion, recurrent epistaxis, and any thrombotic events requiring any hospital reattendance within 1 week.

Results: The study sample consisted of 496 participants with spontaneous epistaxis, persisting after simple first aid and application of a topical vasoconstrictor. In total, 211 participants (42.5%) received anterior nasal packing during the index ED attendance, including 111 of 254 (43.7%) in the tranexamic acid group versus 100 of 242 (41.3%) in the placebo group. The difference was not statistically significant (odds ratio 1.107; 95% confidence interval 0.769 to 1.594; P=.59). Furthermore, there were no statistically significant differences between tranexamic acid and placebo for any of the secondary outcome measures.

Conclusion: In patients presenting to an ED with atraumatic epistaxis that is uncontrolled with simple first aid measures, topical tranexamic acid applied in the bleeding nostril on a cotton wool dental roll is no more effective than placebo at controlling bleeding and reducing the need for anterior nasal packing. [Ann Emerg Med. 2021;■:1-10.]

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INTRODUCTION

Background

Epistaxis is an extremely common medical condition, accounting for up to 1 in 200 emergency department (ED) presentations in the United States[1] and, in one ED in the United Kingdom, an estimated 100 per 100,000 presentations per year.[2] Patients seeking medical attention are frequently elderly[3] and men.[4]

The majority of bleeding events will cease with simple first aid measures[5] (squeezing the soft part of the nose, applying ice to the bridge of the nose, or both), but additional measures, such as the use of topical vasoconstrictors, may be required. Chemical cautery with silver nitrate may also be used, but with profuse bleeding events it may be difficult to identify the bleeding site and successfully apply cautery.[6] If bleeding continues after these measures, patients will usually undergo anterior nasal packing.

Importance

Anterior nasal packing is an effective method of controlling persistent bleeding, leading to cessation in up to 85% of cases.[7] Insertion and removal of packs is uncomfortable for the patient but varies, depending on the type of pack used.[8-10] Nasal packs typically remain in situ for at least 24 hours, which causes ongoing pain (reported

Editor's Capsule Summary

What is already known on this topic

Tranexamic acid is an antifibrinolytic agent that reduces bleeding in certain populations.

What question this study addressed

Does topical tranexamic acid reduce the need for nasal packing among emergency department (ED) patients with epistaxis?

What this study adds to our knowledge

In this multicenter randomized trial of 496 patients, there was no difference in the need for nasal packing with topical tranexamic acid (43.7%) versus placebo (41.3%).

How this is relevant to clinical practice

Topical tranexamic acid is unlikely to reduce the need for nasal packing among ED patients with epistaxis.

mean pain scores 0.5 to 3.5/10) and an uncomfortable sensation of nasal obstruction.[11] Once the pack is inserted, hospital admission is on average 3 days for the majority of patients in the United Kingdom.[6] This reflects the average age of patients with epistaxis, the number of associated comorbidities, and the high proportion of associated use of oral anticoagulant medications, which requires longer periods of observation.[5]

Tranexamic acid is an antifibrinolytic agent that contributes to blood clot stability. Large-scale trials have demonstrated it to be safe[12] and shown it to reduce blood loss after surgery when applied topically.[13,14] Although there have been a number of studies to date investigating the value of topical intranasal tranexamic acid in epistaxis,[15] most of which would seem to favor its use, the studies are variable in their methodology, with small sample sizes. A meta-analysis of topical tranexamic acid did not find a statistically significant difference in the cessation of bleeding in 30 minutes, but did demonstrate a higher rate of discharge within 2 hours and fewer episodes of rebleeding.[16]

If topical tranexamic acid is an effective treatment for epistaxis that fails to resolve with simple measures, it could reduce the need for nasal packing and subsequent hospital admission.

Goals of This Investigation

The primary objective of the study was to test the effectiveness of topical intranasal tranexamic acid in reducing the need for anterior nasal packing in adult patients presenting to the ED with spontaneous atraumatic epistaxis in a UK ED setting. The secondary objectives investigated need for anterior nasal packing during the index ED visit or after 7 days' follow-up, hospital admission and subsequent length of hospital stay, the requirement for blood products, rebleeding rate, and any adverse events, including thrombotic complications.

MATERIALS AND METHODS

Study Design and Setting

Full details of the study design are described in the protocol article.[17] We conducted a pragmatic, 1:1, block-randomized, double-blind, parallel-group, placebo-controlled trial in 26 centers with type 1 EDs across the United Kingdom between May 5, 2017, and March 31, 2019. A type 1 ED is defined as "a consultant led 24-hour service with full resuscitation facilities and designated accommodation for the reception of accident and emergency patients."[18]

Patients presenting to the ED with epistaxis persisting after simple first aid (squeezing the soft part of the nose, applying ice to the bridge of the nose, or both) were screened for eligibility. The patients or clinical staff carried out simple first aid measures for at least 10 minutes before arrival, during transit, or during triage. Persistent epistaxis was defined as the continued presence of blood on the upper lip after wiping, emanating from the nares.

After initial assessment and screening, eligible patients were treated with a topical vasoconstrictor, applied on a cotton wool dental roll in the affected nostril for 10 minutes, held in place by a purpose-designed disposable nasal clip. A standard operating procedure was used to guide the pretrial treatment, with the choice of vasoconstrictor decided by the treating clinician according to local guidelines and availability.

During vasoconstrictor therapy, participants provided informed consent to participate in the trial. Confirmation of final eligibility was persistent bleeding after removal of the vasoconstrictor dental roll.

On confirmation of final eligibility, participants were given the treatment contained within the next sequentially numbered pack. The packs contained a sealed vial of the trial solution (tranexamic acid or matched placebo), as well as 2 dental rolls. Treating clinicians and participants were blinded to the treatment allocation.

Further management of continuing epistaxis was given according to local departmental protocols at the discretion of the treating clinician. Further treatment included silver nitrate cautery, anterior nasal packing, or other topical

applications. Participants whose bleeding was controlled were managed according to their individual needs in line with departmental protocols. Anterior nasal packing was carried out according to local guidelines with either Merocel (Medtronic Inc., Minneapolis, MN) or Rapid Rhino (ArthroCare Corp., Austin, TX) packs.

Any untoward or unintended response in a subject that was reported after the administration of the trial intervention during the index ED visit was classified as an adverse reaction (Table E1, available online at http://www.annemergmed.com). This included occurrences not necessarily caused by or related to that product. Participants were routinely asked about any additional symptoms during their time in the ED. Serious adverse events were those that resulted in death or that were life threatening, requiring hospitalization or prolonging existing hospitalization during or 7 days after the index ED attendance. Therefore, any adverse reaction deemed serious was also counted as a serious adverse event. The chief investigator examined all serious adverse events and determined their seriousness and relatedness to trial treatment while blinded to treatment allocation.

Patients were followed up at 7 days with a structured telephone call to establish whether any additional treatments for epistaxis had been required after the index event. If a participant could not be contacted, the research nurse reviewed the hospital notes to ascertain the relevant information.

The study was approved by the South West–Central Bristol Research Ethics Committee, in accordance with the Declaration of Helsinki. The trial was managed by the Peninsula Clinical Trials Unit and was overseen by a trial steering committee and an independent data monitoring committee.

To minimize delay of a participant's allocated treatment, the numbered packs were randomized to allocated groups so that the treating clinician only had to select the next sequentially numbered pack. Random allocation of the packs was performed with a computer-based algorithm of variable bock sizes of 2 or 4, which was stratified by center. The site research teams, trial manager, and trial management group strictly audited the sequential use of packs.

Selection of Participants

Patients older than 18 years and presenting to the ED with persistent epistaxis were eligible for the study. Patients demonstrating hemodynamic instability, with epistaxis occurring as a result of trauma, with out-of-hospital packing, with documented allergy to tranexamic acid, or "expected" by the ear, nose, and throat in-patient team for specialist treatment were excluded. Other exclusion criteria included known or suspected nasopharyngeal malignancy, previous inclusion in the study, pregnancy, hemophilia, and inability or unwillingness to provide consent. Because eligible participants presenting to the ED with epistaxis were not randomly selected for the study, the participants included were a convenience sample.

Given that the initial presentations of anterior and posterior epistaxis are clinically indistinguishable, no efforts were made to discriminate between the two during initial assessment. Posterior epistaxis accounts for the minority (<5%) of nosebleeds,[16] and the ED management in the first instance is the same as for anterior. The randomization process was considered sufficiently robust such that both groups would be similarly affected.

Interventions

The intervention was tranexamic acid for topical (intranasal) use, prepared as a clear, colorless solution at 100 mg/mL. The comparator (placebo) was sterile water, which was indistinguishable from the tranexamic acid. Both were provided in identical glass vials.

Trial treatment consisted of 4 mL of tranexamic acid or placebo, given in up to 2 divided doses of 2 mL. A 9×39-mm cotton wool dental roll soaked in approximately half of the trial solution was gently inserted into the bleeding nostril by the responsible treating clinician. The dental roll was held in place with a disposable nasal clip and left in situ for 10 minutes. When epistaxis persisted, a second trial treatment (the remaining 2 mL of trial solution) was applied in the same manner, on a second dental roll held in place with a nasal clip.

The dental rolls used in this study form part of the standard mode of application of topical intranasal medications in UK emergency and rhinologic practice. Pretrial work demonstrated that, after complete saturation, the mean absorption from a soaked dental roll was approximately 200 mg of tranexamic acid (half of the total trial dose).

The duration of 10 minutes per application was similar to that used in previous studies[19-21] and allowed the application of 2 trial treatments without too significant a delay from definitive treatment should their application not be successful. Participants therefore received a topical application of either 200 or 400 mg of tranexamic acid, or placebo.

The treating clinicians were all hospital-based practitioners. These were either physicians, ranging in experience from junior house officers to consultants, or

specialist emergency nurse practitioners. These practitioners were responsible for all aspects of the patient's treatment in the ED. Given the adoption of the standard operating procedure in advance, there was no stratification or analysis according to the grade or type of treating clinician on the basis that the approach was considered both straightforward and standardized, such that it could be equally applied irrespective of clinician.

Outcome Measures

The primary outcome was the use of anterior nasal packing (of any type) at any time during the index ED attendance, irrespective of any additional treatments used after application of the trial treatment. The use of packing was at the discretion of the treating clinician, with alternative treatments considered when bleeding was minor.

Secondary outcome measures included hospital admission for further treatment of epistaxis, need for blood transfusion, recurrent epistaxis, and any thrombotic events requiring hospital reattendance within 1 week. Additional treatments during the index ED episode for continued bleeding, and further ED hospital treatments required for epistaxis during the 7-day follow-up period, were also recorded.

The sample size calculation assumed that patients with persistent epistaxis, in which simple measures and vasoconstrictors had failed to control the bleeding, would ordinarily proceed to nasal packing. We anticipated that the majority of patients (95%) would require packing. The study aimed to detect a 10% absolute reduction in packing rate, which we believed was the minimum improvement that would realistically inform clinical practice. This difference required 207 patients per group, assuming a corrected χ^2 test result powered at 90% and with a significance level of 5%. The total recruitment target was 450 to allow any subsequent loss to follow-up.

Primary Data Analysis

The trial is reported following the Consolidated Standards of Reporting Trials statement and the relevant extensions.[22,23] Statistical analysis followed a prespecified statistical analysis plan agreed by the independent committees in the statistical program Stata.[24]

Participants' baseline characteristics were summarized by mean and SD if continuous or frequency and percentage if categoric by allocated group.

The primary analysis of all outcomes followed the modified intention-to-treat principle, in which participants were analyzed according to their allocated group and included if they had provided the outcome measure.

Most of the outcomes (including the primary) were binary, which are summarized as frequencies and percentages, and comparisons between allocated groups was by mixed-effect logistic regression models. Visual inspection of the length of hospital stay distribution showed it had a strong positive skew. Therefore, it was summarized by median and interquartile range and modeled with a negative binomial mixed-effects regression model. Study center was included as a random effect in all models.

There were 2 prespecified sensitivity analyses of the primary outcome: a per-protocol population, which excluded any participant who did not have the second dose of treatment when indicated; and a modified primary outcome, to include any use of anterior nasal packing within the 7-day follow-up period. The data monitoring committee requested a post hoc analysis of participants who received 10 minutes of topical vasoconstrictor therapy and the indicated dose of trial treatment.

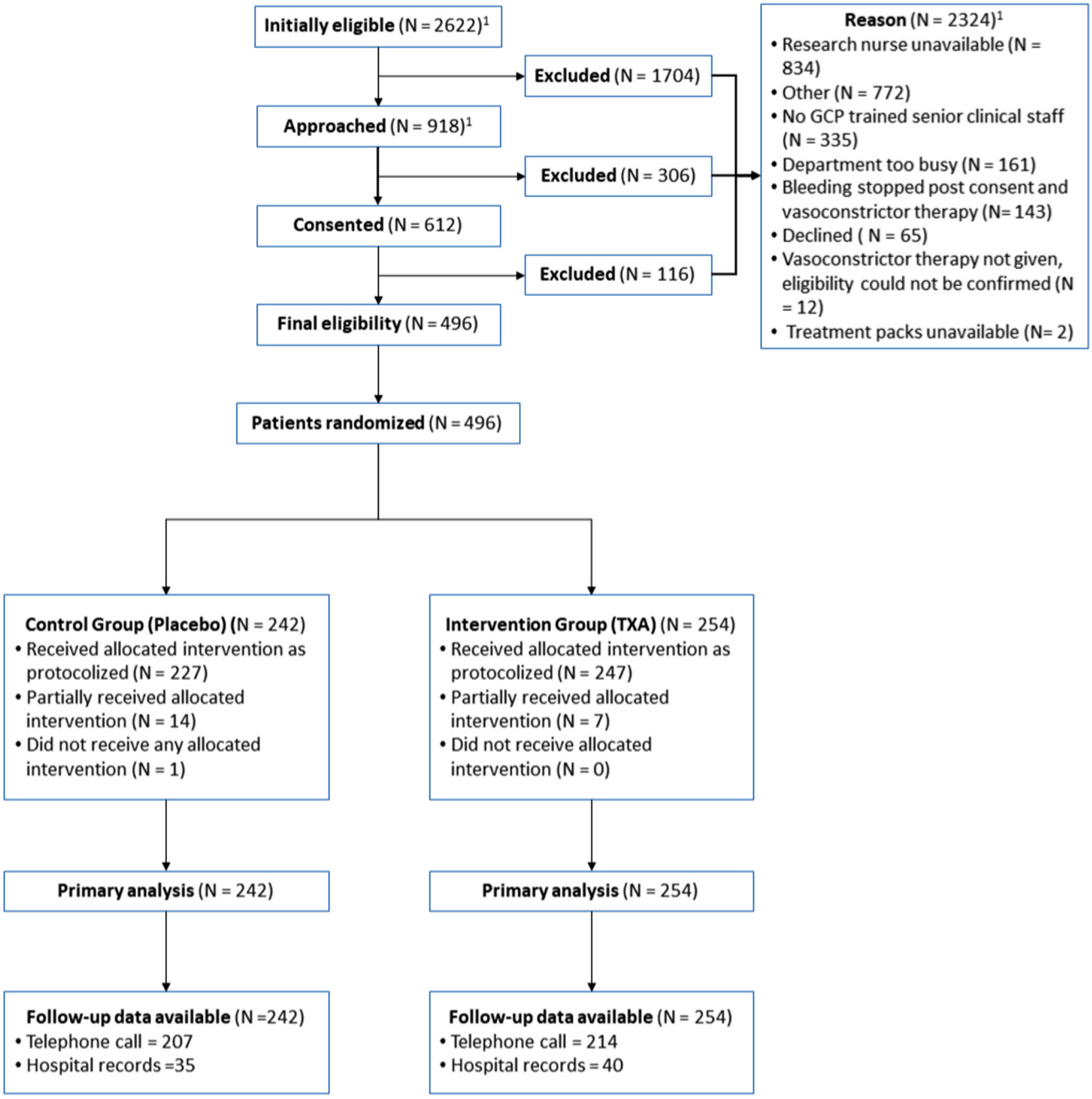
There was one preplanned, explorative, subgroup analysis of the primary outcome to investigate anticoagulant use at the index ED attendance. This model included anticoagulant use and the interaction between anticoagulation usage and treatment group. There was no preplanned subgroup analysis to distinguish between different agents. Although anticoagulant use was potentially important, differences would balance out with randomization.

The safety analysis included all participants who had at least 1 of the 2 dental rolls soaked in the allocated solution fully inserted into their nose (even if removed before the intended 10 minutes).

RESULTS

Characteristics of Study Subjects

Details of the number of participants recruited by site are in Table E2 (available online at http://www.annemergmed.com). The Consolidated Standards of Reporting Trials diagram in the Figure depicts the flow of participants through the study, all initially eligible patients who met the study inclusion criteria. The reasons for exclusion were obtained from site summary data. In total, 496 participants were randomized, 254 (51.2%) to receive tranexamic acid and 242 (48.8%) to receive placebo. Table 1 presents the participants' characteristics by allocated group. There were more men than women allocated to the placebo group (58.7% placebo versus 50.4% tranexamic acid) and more participants receiving anticoagulation medication in the placebo group (68.6% placebo versus 61.0% tranexamic acid).



[1] Reasons for exclusions obtained from site summary data which did not identify the stage patients were excluded and some patients provided multiple reasons.

Figure. Consolidated Standards of Reporting Trials diagram of the NoPAC trial starting from all participants who met the study inclusion criteria. GCP, Good clinical practice; TXA, tranexamic acid.

Main Results

During the index ED attendance, 211 participants (42.5%) received anterior nasal packing for epistaxis. Of participants allocated to receive tranexamic acid, 111 (43.7%) underwent packing in the ED compared with 100 (41.3%) in the placebo group. There was no statistically significant difference in the rate of anterior nasal packing between allocated groups, with an odds ratio of 1.11 (95% confidence interval 0.77 to 1.59) from the primary analysis. All of the prespecified sensitivity analyses found there was no statistically significant difference between allocated groups (Table 2).

Table 1. Summary characteristics of participants in the NoPAC trial by allocated group (placebo or tranexamic acid) and for total study population.

Characteristic	Placebo, Mean (SD) (N=242)	TXA, Mean (SD) (N=254)
Age, y	72.3 (13.9)	70.1 (15.6)
Systolic blood pressure, mm Hg	150.7 (25.8)	150.2 (27.9)
Diastolic blood pressure, mm Hg	87 (15.3)	85.8 (18.4)
Pulse, beats/min	82.2 (16.6)	82.6 (17.2)
	No. (%)	**No. (%)**
Men	142 (58.7)	128 (50.4)
Anticoagulant medication	166 (68.6)	155 (61.0)
Hypertension	149 (61.6)	153 (60.2)
Ischemic heart disease	59 (24.4)	49 (19.3)
Diabetes	38 (15.7)	33 (13.0)
Thromboembolic disease	16 (6.6)	26 (10.2)
Alcoholic liver disease	1 (0.4)	2 (0.8)
Any bleeding disorder	8 (3.3)	5 (2.0)

Data are presented as mean and SD for continuous variables, and frequency (N) and percentage for categoric variables.

In the placebo group, 166 were receiving anticoagulants (68.5%), as were 155 (61.0%) in tranexamic acid group. There was no evidence of a significant interaction, with an odds ratio of 1.28 (95% confidence interval 0.59 to 2.81).

Results of the secondary outcomes analyses are presented in Table 3. Because only one participant in the placebo group reported a thrombotic event, no comparative analysis was performed on this outcome. Two participants in the tranexamic acid group had missing data for recurrent epistaxis. There was no statistically significant difference between tranexamic acid and placebo in any of the secondary outcomes.

Twelve participants reported 14 adverse reactions (ie, an adverse event reported within the index ED attendance); these included feeling faint, sensation in the nostril, headache, nausea, and vomiting (Table E3, available online at http://www.annemergmed.com). Four of these adverse reactions were considered serious and included as serious adverse events. Nine participants in the tranexamic acid group (3.5%) reported at least 1 adverse reaction and 3 (1.2%) did so in the placebo group, but the difference was not statistically significant.

Fifteen participants reported 16 serious adverse events, including the 4 adverse reactions that were considered serious. All serious adverse events were deemed unlikely to be related or not related to trial treatment. The serious adverse events comprised 11 hospitalizations (which did not follow from the index ED for treatment of epistaxis or recurrent epistaxis), 3 deaths, and 2 significant medical events (Table E4, available online at http://www.annemergmed.com). The 2 significant medical events were systemic sepsis and syncope. Eleven serious adverse events occurred in 10 participants (4.3%) receiving tranexamic acid and 5 serious adverse events occurred in 5 participants (2.1%) in the placebo group, with no statistical evidence of a difference between the groups in the number of reported serious adverse events.

LIMITATIONS

The sample size calculation was based on a predicted packing rate of 95% for patients for whom standard treatment had failed (ie, the population of patients who would have normally undergone immediate nasal packing). The packing rate in the The Use of Tranexamic Acid to Reduce the Need for Nasal Packing in Epistaxis (NoPAC) study did not meet this percentage: 41.3% of patients received packing in the placebo group compared with 43.7% in the tranexamic acid group. Therefore, the study may have been underpowered.

The study was pragmatically designed such that recruitment of participants could occur at all times in the ED. However, it was evident from the Consolidated

Table 2. Results of the primary and sensitivity analyses of the primary outcome.

Primary Outcome Analysis	Placebo N (%)	TXA N (%)	Difference in % (95% CI)	Odds Ratio (95% CI)
Packing in ED *Primary analysis* (N = 496)	100 (41.3)	111 (43.7)	2.4 (-6.3 to 11.1)	1.11 (0.77 to 1.59)
Sensitivity Analyses				
Packing in ED *Per Protocol analysis* (N = 474)	90 (39.6)	106 (42.9)	3.3 (-5.6 to 12.1)	1.16 (0.79 to 1.68)
Packing in and post ED *Pre-specified analysis* (N = 496)	117 (48.3)	134 (52.8)	4.4 (-4.4 to 1.32)	1.20 (0.82 to 1.75)
Packing in ED *Post hoc analysis* (N = 466)	89 (39.7)	106 (43.8)	4.1 (-4.9 to 13.0)	1.20 (0.84 to 1.73)

Table 3. Results of the primary analyses of the secondary outcomes.

Outcome	Placebo N (%)	TXA N (%)	Difference (95% CI)	Odds Ratio (95% CI)
ED epistaxis treatment (N = 496)	147 (60.7)	157 (61.8)	1.1 (-7.5 to 9.6)	1.05 (0.73 to 1.52)
Epistaxis treatment (N = 496)	174 (69.0)	184 (72.4)	0.5 (-7.4 to 8.4)	1.04 (0.70 to 1.56)
Hospital admission (N = 496)	110 (45.5)	110 (43.3)	-2.1 (-10.9 to 6.6)	0.92 (0.64 to 1.32)
Length of hospital stay (N = 220)	2.0 (2.0)†	2.2 (3.2)†	0.05* (-0.19 to 0.28)	N/A
Blood Transfusion (N = 496)	6 (2.5)	7 (2.8)	0.3 (-2.5 to 3.1)	1.11 (0.37 to 3.37)
Recurrent epistaxis (N = 494)	39 (16.1)	49 (19.4)	3.3 (-34.0 to 10.1)	1.26 (0.79 to 2.00)

Standards of Reporting Trials diagram (Figure) that the main reason a participant was excluded from the study was unavailability of a research nurse. Therefore, because the sample of participants was not randomly selected and was restricted to times a research nurse was available in the ED, the participants included in this study were a convenience sample and could be subject to selection bias.

It is possible that some participants included in the study had "posterior" epistaxis, bleeding from high up in the nasal cavity, such that they were unlikely to be responsive to standard measures to stop bleeding. No formal diagnosis of posterior or anterior epistaxis was recorded during the index ED visit or 7-day follow-up. However, 4 cases of posterior packing were reported, 2 in each allocated group, which would indicate a balance in the randomization process. However, without a formal diagnosis we cannot verify if this was the case, and their presence may have manifested as an artificial apparent failure of treatment.

The dose of topical tranexamic acid selected (up to 200 mg per application) would appear to be less than that used in some of the previous studies, in which packs or dental rolls were soaked in up to 500 mg of tranexamic acid, and this could account for a perceived lack of benefit. In a number of these studies, although a larger volume and dose of tranexamic acid was used to soak the packing material, the amount actually taken up by the pack before insertion is not detailed. There is little to suggest that the entire volume was soaked up. The dental rolls used in the NoPAC study were completely saturated with each application of trial solution, such that a greater dose of tranexamic acid would not have resulted in any more being absorbed. The pretrial work demonstrated that only a small proportion of the volume applied was actually absorbed by the nasal mucosa. Therefore, applications of greater doses or volumes are unlikely to lead to greater absorption.

Although the standard operating procedure recommended insertion of an anterior nasal pack as the next step for patients when epistaxis could not be stopped, it is evident that this was not always necessary. Further investigation of the data found that 25% of patients had their epistaxis managed with silver nitrate cautery, after initial measures and trial treatments (Table E5, available online at http://www.annemergmed.com). It is likely that although simple measures such as digital pressure, vasoconstrictor, and up to 20 minutes of further pressure were not always sufficient to terminate active hemorrhage, they may have contributed to control such that nasal packing was not required and other measures were able to control the bleeding.

DISCUSSION

This randomized controlled trial of 496 participants investigated the effectiveness of topical intranasal tranexamic acid in patients presenting to the ED with spontaneous epistaxis uncontrolled with simple first aid measures and topical vasoconstrictor. Although previous studies have suggested that use of tranexamic acid provides more rapid control of hemorrhage compared with standard management,[15] and a reduced need for anterior nasal packing, our study demonstrated no benefit. The results of our study show that there is no statistically significant difference between the groups for any of the primary or secondary outcome measures.

To our knowledge, the NoPAC study is the largest single study to date to investigate the role of topical intranasal tranexamic acid as an adjunct to standard therapy for patients with spontaneous epistaxis. Our study design was pragmatic, with minimum deviation from standard UK ED practice to maximize recruitment and reflect actual practice in this challenging environment.

From direct patient contact, scrutiny of the hospital notes, or both, follow-up data were available for all 496 patients recruited. The availability of follow-up data for 100% of patients recruited and the rigor of the methodology bolster confidence about the real-world accuracy of the results. Although the NoPAC methodology is both robust and pragmatic, this design is based on

standard UK practice, which differs in many respects from that in other countries, such that some of the results may not be directly transferrable.

Although outpatient strategies have increasingly been adopted during the past decade for patients with epistaxis controlled by the placement of anterior nasal packs, almost half of the patients in this study were admitted to hospital wards, with 50% staying in the hospital for 2 days or more. Although techniques for packing have changed in recent years, this proportion is in keeping with previously published data[21] and reflects, for most of those recruited, their age, associated comorbidities, and social circumstances rather than the need to control ongoing bleeding.

However, despite that the packing rate in the control group was considerably different from that assumed in the sample size calculation, the results suggest it is very unlikely that tranexamic acid has a clinically important benefit in this context.

Numerous studies have investigated a possible role for tranexamic acid as an adjunct to standard treatment for the management of spontaneous epistaxis. There is clear international variation in practice, which may account for the differences in outcomes between previous studies and that demonstrated in the NoPAC study. There are no existing UK-based studies, to our knowledge. The NoPAC study differs from most of the existing studies in this area by virtue of the selection of anterior nasal packing as the primary outcome measure, in which bleeding cessation is most often selected. This may account for some of the perceived differences in outcome.

Akkan et al[19] carried out a single-center, prospective study in patients presenting with epistaxis who were subsequently randomized to 1 of 3 trial treatment groups: nasal compression with tranexamic acid, nasal compression with matched placebo, or anterior nasal packing. Of 135 patients enrolled, they found topical tranexamic acid to be as effective as anterior nasal packing at terminating bleeding in 15 minutes and superior to saline solution placebo. Treatment with tranexamic acid led to a significant reduction in subsequent rebleeding compared with anterior nasal packing and saline solution placebo. Although this would seem to provide reasonable support for the use of topical tranexamic acid in epistaxis, this study was conducted in only one center with a small sample size. Although participants and clinicians were blinded to tranexamic acid or placebo, they were not blinded to anterior nasal packing.

Zahed et al[20] performed one of the first investigations of topical tranexamic acid in a single ED. The primary outcome was bleeding cessation within 10 minutes, and the study recruited 216 participants who were randomized to receive either tranexamic acid or anterior nasal packing with a dental roll that was soaked in lidocaine and adrenaline, followed by tetracycline ointment. The authors reported a significant benefit with topical tranexamic acid compared with anterior nasal packing. This study differed from NoPAC because patients receiving anticoagulant therapy were excluded and blinding was not possible because of the differences between the smell, coating, and number of dental rolls used.

In a subsequent study, Zahed et al[21] also reported the results of another randomized controlled trial of topical intranasal tranexamic acid compared with anterior nasal packing soaked in epinephrine and lidocaine in 124 patients receiving antiplatelet drugs. The study was conducted in 2 EDs, with a primary outcome of bleeding cessation after 10 minutes. The results of this study also favored tranexamic acid, but had similar limitations, with a small sample size and inability to blind.

The NoPAC study is not the first to contest a role for the use of tranexamic acid in epistaxis. Tibbelin et al[25] published their investigation into the use of a gel form of tranexamic acid in 68 patients with epistaxis compared with matched placebo. They found no statistically significant difference between the groups, although they identified a trend toward a reduction in rebleeding events in the tranexamic acid group. However, the sample size was small, and they investigated a different method of delivering tranexamic acid.

In their systematic review of tranexamic acid in epistaxis, Gottlieb et al[16] found no difference in cessation of bleeding within 30 minutes, but demonstrated that there were more patients discharged within 2 hours of arrival and lower rebleeding rates associated with the use of tranexamic acid. However, this review was limited by the inclusion of only 3 studies with variation in control groups and primary outcomes.

What is apparent from previous studies is the safety profile of topical tranexamic acid, with few if any adverse effects reported. Those reported have been relatively minor (nausea, vomiting, and feeling faint). The safety profile demonstrated in the NoPAC study reinforces this, with similarly low numbers of adverse events and none deemed significant.

In view of this conflicting evidence, some further evaluation of the role of tranexamic acid in epistaxis may be beneficial. There may well be value in investigating different doses of topical tranexamic acid; examining the higher doses used in some of the previous studies; examining alternative methods of administration that may more effectively fill the external

nares, bringing the topical drug into contact with a greater area of the nasal mucosa; and investigating longer periods of application.

In summary, in patients presenting to the ED with atraumatic epistaxis that is uncontrolled with simple first aid measures and topical vasoconstrictor, topical tranexamic acid applied in the bleeding nostril on a cotton wool dental roll is no more effective than placebo at controlling bleeding and reducing the need for anterior nasal packing.

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Author affiliations: From the Royal Devon and Exeter NHS Foundation Trust, Exeter, England (Reuben, Appelboam, Hilton, Coppell); Medical Statistics Group (Stevens) and Peninsula Clinical Trials Unit (Vickery, Ingram, Jeffery, Wainman), Faculty of Health, Medicine, Dentistry and Human Sciences, University of Plymouth University, Plymouth, England; National Institute of Health Research (NIHR) Research Design Service South West, United Kingdom (Ewings, Barton); Taunton and Somerset NHS Foundation Trust, Taunton, Somerset, England (Ewings); and the Division of Cardiovascular Science, The University of Manchester, and the Emergency Department, Manchester University NHS Foundation Trust, Manchester, England (Body).

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All authors attest to meeting the four ICMJE.org authorship criteria: (1) Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND (2) Drafting the work or revising it critically for important intellectual content; AND (3) Final approval of the version to be published; AND (4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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