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

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## Abstract

**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 (TXA) is an agent that contributes to blood clot stability. The aim of this study was to investigate the effectiveness of topical intranasal TXA in adult patients presenting to the ED with persistent epistaxis, and whether it reduced the need for anterior nasal packing.

**Methods:** From 5<sup>th</sup> May 2017 to 31<sup>st</sup> March 2019, a double blind, placebo controlled, multi-center, 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 TXA 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 re-attendance within one 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 111/254 (43.7%) in the TXA group versus 100/242 (41.3%) in the placebo group. The difference was not statistically significant (odds ratio 1.11, 95% confidence interval 0.77 to 1.59). Further, there were no statistically significant differences between TXA and placebo for any of the secondary outcome measures.

**Conclusions:** In patients, presenting to an ED with atraumatic epistaxis that is uncontrolled with simple first aid measures, topical TXA 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.

**Trial Registration:** ISRCTN34153772

## Introduction

### Background

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

The majority of bleeds will cease with simple first aid measures<sup>5</sup> (squeezing soft part of nose and/or application of ice to bridge of nose) but additional measures, such as the use of topical vasoconstrictors, may be required. Chemical cauterity with silver nitrate may also be used but with profuse bleeds it may be difficult to identify the bleeding site and successfully apply cauterity<sup>6</sup>. 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<sup>7</sup>. Insertion and removal of packs is uncomfortable for the patient, but varies depending on the type of pack used<sup>8–10</sup>. Nasal packs typically remain in situ for at least 24 hours, which causes ongoing pain (reported mean pain scores 0.5–3.5/10) and an uncomfortable sensation of nasal obstruction<sup>11</sup>. Once inserted, the hospital admission is on average 3 days for the majority of patients in the UK<sup>6</sup>. 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<sup>5</sup>.

Tranexamic acid (TXA) is an antifibrinolytic agent that contributes to blood clot stability. Large-scale trials have demonstrated TXA to be safe<sup>12</sup>, and shown to reduce blood loss after surgery when applied topically<sup>13,14</sup>. Whilst there have been a number of studies to date investigating the value of topical intranasal TXA in epistaxis<sup>15</sup>, 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 TXA 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 re-bleed<sup>16</sup>.

If topical TXA 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 TXA 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 or following 7 days follow-up; hospital admission and subsequent length of hospital stay; the requirement for blood products; re-bleed 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 paper<sup>17</sup>. We conducted a pragmatic 1:1 block randomized, double blind, parallel group, placebo controlled trial in 26 centers with type 1 EDs across the UK between 5<sup>th</sup> May 2017 and 31<sup>st</sup> March 2019. A Type 1 ED in the UK is defined as ‘a consultant led 24-hour service with full resuscitation facilities and designated accommodation for the reception of accident and emergency patients’<sup>18</sup>.

Patients presenting to the ED with epistaxis persisting after simple first aid (squeezing soft part of nose and/or application of ice to bridge of nose) were screened for eligibility. The patients or clinical staff carried out simple first aid measures for at least ten minutes, either prior to arrival, during transit or 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 pre-trial 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 following removal of the vasoconstrictor dental roll.

Upon 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 (TXA or matched placebo) as well as two 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 cauterity, 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 using either Merocel® (Medtronic Inc., Minneapolis, MN, USA) or Rapid Rhino® (ArthroCare Corp., Austin, Texas, USA) packs.

Any untoward or unintended response in a subject that was reported following the administration of the trial intervention during the index ED was classified as an adverse reaction (AR). This included occurrences that were 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 (SAE) were those that resulted in death or that were life-threatening, requiring hospitalization or prolonging existing hospitalization during or 7 days post the index ED attendance. Therefore, any adverse reaction deemed as serious was also counted as an SAE. The chief investigator examined all serious adverse events (SAEs), and determined their seriousness and relatedness to trial treatment whilst 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 following 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.

#### Randomization

To minimize delay of the participant's allocated treatment, the numbered packs were randomized to allocated groups, so that the treating clinician only had to select the next sequentially number pack. Random allocation of the packs was performed using computer based algorithm of variable pack 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 aged over 18 years, presenting to the ED, with persistent epistaxis were eligible for the study. Patients demonstrating hemodynamic instability, epistaxis occurring as a result of trauma, those with pre-hospital packing, with documented allergy to TXA or 'expected' by the Ear Nose and Throat (ENT) 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 unwilling to provide consent. As eligible participants presenting to 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 small minority (< 5%) of nosebleeds<sup>16</sup>, 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 TXA for topical (intranasal) use, prepared as a clear, colorless 100mg/mL solution. The comparator (placebo) was sterile water, which was indistinguishable from the TXA. Both were provided in identical glass vials.

Trial treatment consisted of 4mL of TXA or placebo, given in up to two divided doses of 2mL. A cotton wool dental roll 9mm x 39mm 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 prior to assessment. Where epistaxis persisted, a second trial treatment (the remaining 2mL 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 rhinological practice. Pre-trial work demonstrated that, following

complete saturation, the mean absorption from a soaked dental rolls was approximately 200mg of TXA (half of the total trial dose).

The duration of 10 minutes per application was similar to that utilized in previous similar studies<sup>19–21</sup>, and would allow the application of two trial treatments without too significant a delay from definitive treatment should their application not be successful. Participants therefore received a topical application of either 200mg or 400mg of TXA, or placebo.

The treating clinicians were all hospital based practitioners. These were either doctors, 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 whilst in the ED. Given the adoption of the SOP 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.

### Outcomes

The primary outcome was the use of anterior nasal packing (of any type) at any time during the index ED attendance, irrespective of any other 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 where 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 re-attendance within one week. Additional treatments during the index ED episode for continued bleeding, and further ED hospital treatments required for epistaxis during the seven-day follow-up period, were also recorded.

### Sample Size

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

### **Analysis**

The trial is reported following the Consolidated Standards of Reporting Trials (CONSORT) statement and the relevant extensions<sup>22,23</sup>. Statistical analysis followed a pre-specified Statistical Analysis Plan agreed by the independent committees in the statistical program STATA<sup>24</sup>.

Participants' baseline characteristics were summarized by mean and standard deviation (SD) if continuous or frequency and percentage if categorical by allocated group.

The primary analysis of all outcomes followed the modified intention-to-treat (mITT) principle, where participants were analyzed according to their allocated group and included if they had provided an 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 indicated it should be summarized by median and interquartile-range and modelled using a negative binomial mixed effects regression model. Study center was included as a random effect in all models.

There were two pre-specified sensitivity analyses of the primary outcome. A Per Protocol (PP) 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 pre-planned, explorative, subgroup analysis of the primary outcome to investigate anticoagulant use at index ED attendance. This model included anticoagulant use and the interaction between anticoagulation usage and treatment group. There was no pre-planned subgroup analysis to distinguish between different agents. Whilst anticoagulant use was potentially important, differences would balance out with randomization.

The safety analysis included all participants who had at least one of the two 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 number of participants recruited by site are in Table S2 of the supplementary material. The CONSORT diagram in Figure 1 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 TXA and 242 (48.8%) to receive placebo. Table 1 presents the participant's characteristics by allocated group. There were more males than females allocated to the placebo group (58.7% placebo vs 50.4% TXA) and more participants taking anticoagulation medication in the placebo group (68.6% placebo vs 61.0% TXA).

### Main result

During the index ED attendance, 211 (42.5%) participants received anterior nasal packing for epistaxis. Of those allocated to receive TXA, 111 (43.7%) participants underwent packing in ED, compared to 100 (41.3%) participants 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 (CI) of 0.77 to 1.59) from the primary analysis. All of the pre-specified sensitivity analyses found there was no statistically significant difference between allocated groups, Table 2.

In the placebo group 166 (68.5%) and 155 (61.0%) in TXA group were taking anticoagulants. There was no evidence of a significant interaction with an odds ratio of 1.28 (95% CI: 0.59 to 2.81).

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

Twelve participants reported 14 adverse reactions (i.e. an adverse event reported within the index ED attendance), these included feeling faint, discomfort sensation in nostril, headache, nausea and vomiting, Table S3. Four of these adverse reactions were considered serious and included as serious adverse events (SAEs). Nine participants (3.5%) reported at least one adverse reaction in the TXA group and three (1.2%) in the placebo group, but the difference was not statistically significant.

Fifteen participants reported 16 SAEs, including the four adverse reactions that were considered serious. All SAEs were deemed unlikely or not related to trial treatment. The SAEs 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, details in Table S4. The two significant medical events were systemic sepsis and syncope. Eleven SAEs occurred in eleven participants (4.3%) receiving TXA and five participants (2.1%) in the placebo group, with no statistical evidence of a difference between the groups in the number of reported SAEs.

## Limitations

The sample size calculation was based on a predicted packing rate of 95% for those where 'standard' treatment had failed, i.e. the population of patients who would have normally undergone immediate nasal packing. The packing rate in the NoPAC study fell a long way short of this: 41.3% patients received packing in the placebo group, compared with 43.7% in the TXA 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 CONSORT diagram (figure 1) the main reason a participant was excluded from the study was unavailability of a research nurse. Therefore, as the sample of participants were not randomly selected and restricted to times a research nurse was available in the ED, the participants included in this study was 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 are unlikely to be responsive to standard measures to stop bleeding. No formal diagnosis of posterior or anterior epistaxis was recorded during the index ED or 7 day follow-up. However, four cases of posterior packing were reported, two 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 TXA selected (up to 200mg per application) would appear to be less than that used in some of the previous studies, where packs or dental rolls were soaked in up to 500mg of TXA and

this could account for a perceived lack of benefit. In a number of these studies, whilst a larger volume and dose of TXA was used to soak the packing material, the amount actually taken up by the pack prior to insertion is not detailed. There is little to suggest that the entire volume is 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 TXA would not have resulted in any more being absorbed. The pre-trial 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.

Whilst the SOP recommended insertion of an anterior nasal pack as the next step for patients where 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, following initial measures and trial treatments, Table S5. It is likely that whilst 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 TXA 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 TXA provides more rapid control of hemorrhage as compared with standard management<sup>15</sup>, and a reduced need for anterior nasal packing, our study demonstrates 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.

The NoPAC study is the largest single study to date to investigate the role of topical intranasal TXA as an adjunct to standard therapy for patients with spontaneous epistaxis. Our study design was pragmatic with minimum deviation from standard UK ED practice in order to maximize recruitment and reflect real life practice in this challenging environment.

Follow-up data were available for all 496 patients recruited, either from direct patient contact, from scrutiny of the hospital notes, or both. The availability of follow up data for 100% of those recruited and the rigor of the methodology helps to give confidence to the real world accuracy of the results. Whilst the NoPAC methodology is both robust and pragmatic, it is important to recognize that this design is based on standard UK practice and that this differs in many respects to that in other countries, such that some of the results may not be directly transferrable.

Although outpatient strategies have increasingly been adopted over 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 the hospital wards, with 50% staying in hospital for 2 days or more. Whilst techniques for packing have changed in recent years, this proportion is in keeping with previous published data<sup>21</sup> and reflects, for most, the age, associated comorbidities and social circumstances of those recruited rather than the need to control on-going bleeding.

However, despite the fact 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 TXA has a clinically important benefit in this context.

Numerous studies have investigated a possible role for TXA 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, hence none of the existing literature accurately reflects current UK practice in this area, where, as shown high proportions of patients undergo anterior nasal packing where first aid fails and require subsequent hospital admission.

Akkan et al. (2019)<sup>19</sup> carried out a single center, prospective study in patients presenting with epistaxis who were subsequently randomized to one of 3 trial treatment groups – nasal compression with TXA, nasal compression with matched placebo or anterior nasal packing. Of 135 patients enrolled, they found topical TXA to be as effective as anterior nasal packing at terminating bleeding in 15 minutes and superior to saline placebo. Treatment with TXA led to a significant reduction in subsequent re-bleeding compared with anterior nasal packing and saline placebo. Whilst this would seem to provide reasonable support for the use of topical TXA in epistaxis, this study was conducted in only one center with a small sample size. Although participants and clinicians were blinded to TXA or placebo, they were not blinded to anterior nasal packing.

Zahed et al. (2013)<sup>20</sup> performed one of the first investigations of topical TXA 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 TXA 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 using topical TXA compared with anterior nasal packing. This study differed to NoPAC as 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. (2018)<sup>21</sup> also reported the results of another randomized controlled trial of topical intranasal TXA compared to anterior nasal packing soaked in epinephrine and lidocaine in 124 patients taking antiplatelet drugs. The study was conducted in two EDs, with a primary outcome of bleeding cessation after 10 minutes. The results of this study also favored TXA, but had similar limitations with a small sample size and blinding was not possible.

The NoPAC study is not the first to contest a role for the use of TXA in epistaxis. Tibbelin et al. (1994)<sup>25</sup> published their investigation into the use of a gel form of TXA in 68 patients with epistaxis compared with matched placebo. They found no statistically significant difference between the groups, although identified a trend towards a reduction in re-bleeds in the TXA group. However, the sample size is small, and investigated a different method of delivering TXA.

In their systematic review of TXA in epistaxis, Gottlieb et al. (2019)<sup>16</sup> found no difference in cessation of bleeding within 30 minutes, but that demonstrated that there were more patients discharged within 2 hours of arrival and lower re-bleeding rates associated with the use of TXA. However, this review limited by the inclusion of only three studies with variation in control groups and primary outcomes.

What is apparent from previous studies is the safety profile of topical TXA, with few if any adverse effects reported. Those reported are relatively minor (nausea, vomiting, 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 TXA in epistaxis may be beneficial. There may well be value in looking at different doses of topical TXA, examining the higher doses used in some of the previous studies, 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 longer periods of application.

In summary, in patients presenting to the Emergency Department with atraumatic epistaxis that is uncontrolled with simple first aid measures and topical vasoconstrictor, topical TXA 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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## Competing interests' declaration

All authors have completed the ICMJE uniform disclosure forms at [www.icmje.org/coi\\_disclosure.pdf](http://www.icmje.org/coi_disclosure.pdf) and declare: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

## Contributor statement

AR, AA, JV, RB, MH, JC and AB were responsible for the conception and design of this research. WI AJ contributed to protocol development and, with BW, undertook analysis and interpretation of data. PE and KS were responsible for statistical data analysis. All authors contributed to the interpretation of the results, drafting and reviewing the manuscript, and all authors approve this version of the manuscript. AR is guarantor of the research and accepts full responsibility for the conduct of the study.

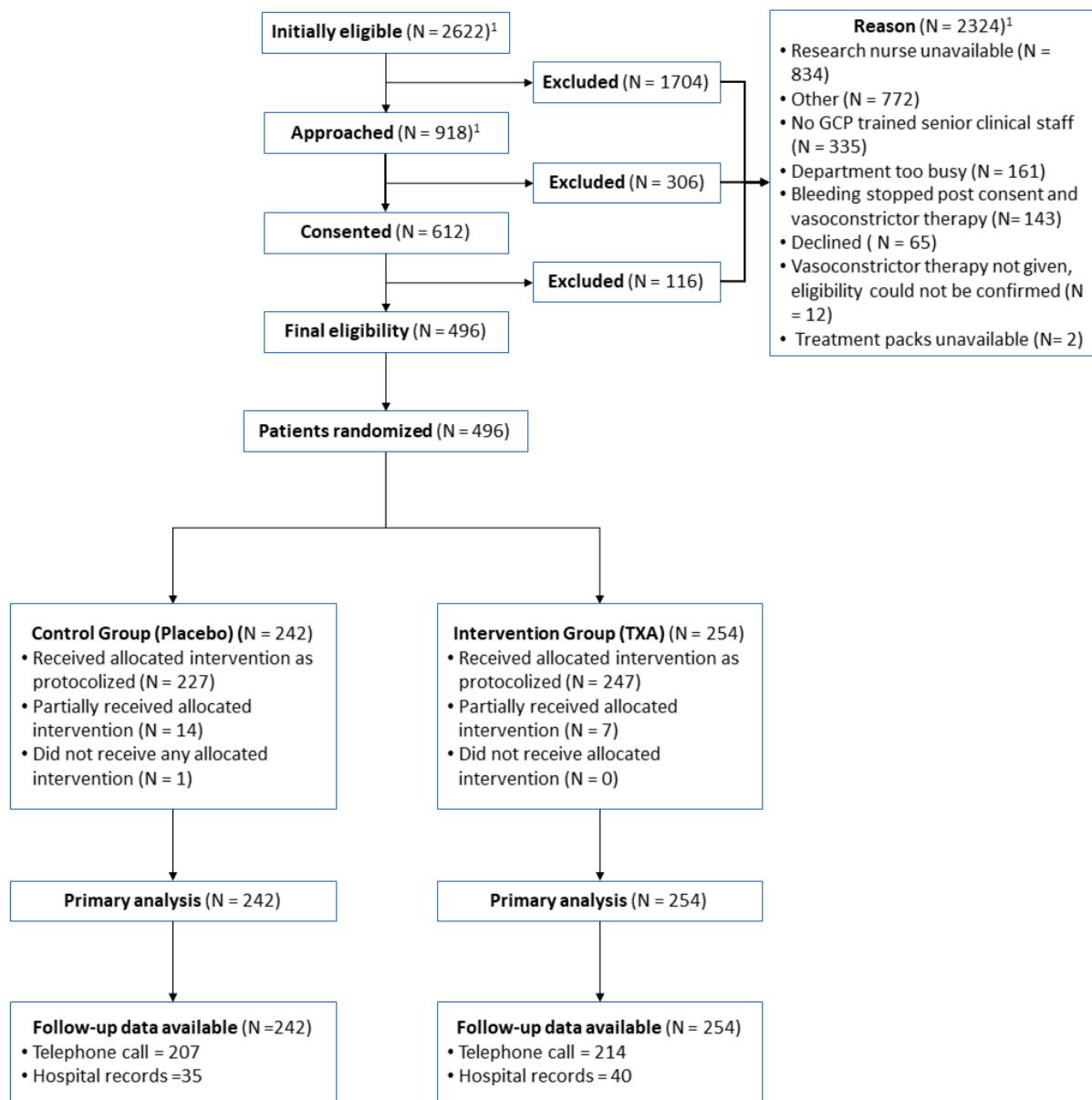
## Referenced

1. Pallin DJ, Chng YM, McKay MP, Emond JA, Pelletier AJ, Camargo CA. Epidemiology of epistaxis in US emergency departments, 1992 to 2001. *Ann Emerg Med*. Published online 2005. doi:10.1016/j.annemergmed.2004.12.014
2. O'Donnell M, Robertson G, McGarry GW. A new bipolar diathermy probe for the outpatient management of adult acute epistaxis. *Clin Otolaryngol Allied Sci*. Published online 1999. doi:10.1046/j.1365-2273.1999.00311.x
3. Walker TWM, MacFarlane T V., McGarry GW. The epidemiology and chronobiology of epistaxis: An investigation of Scottish hospital admissions 1995-2004. *Clin Otolaryngol*. Published online 2007. doi:10.1111/j.1749-4486.2007.01530.x
4. Fishpool SJC, Tomkinson A. Patterns of hospital admission with epistaxis for 26,725 patients over an 18-year period in Wales, UK. *Ann R Coll Surg Engl*. Published online 2012. doi:10.1308/003588412X13373405386691
5. National ENTTRN. Epistaxis 2016: national audit of management. *J Laryngol Otol*. 2017;131(12):1131-1141. doi:10.1017/S002221511700202X
6. Barr GD. Silver nitrate cauterity and epistaxis. *Arch Emerg Med*. Published online 1989. doi:10.1136/emj.6.3.233
7. Pope LE, Hobbs CG. Epistaxis: an update on current management. *Postgr Med J*. 2005;81(955):309-314. doi:10.1136/pgmj.2004.025007
8. Singer AJ, Blanda M, Cronin K, et al. Comparison of nasal tampons for the treatment of epistaxis in the emergency department: A randomized controlled trial. *Ann Emerg Med*. Published online 2005. doi:10.1016/j.annemergmed.2004.10.002
9. Badran K, Malik TH, Bellosio A, Timms MS. Randomized controlled trial comparing Merocel® and Rapid-Rhino® packing in the management of anterior epistaxis. In: *Clinical Otolaryngology*. ; 2005. doi:10.1111/j.1365-2273.2005.01019.x
10. Moumoulidis I, Draper MR, Patel H, Jani P, Price T. A prospective randomised controlled trial comparing Merocel and Rapid Rhino nasal tampons in the treatment of epistaxis. *Eur Arch Oto-Rhino-Laryngology*. Published online 2006. doi:10.1007/s00405-006-0047-5
11. Pringle MB, Beasley P, Brightwell AP. The use of Merocel nasal packs in the treatment of epistaxis. *J Laryngol Otol*. 1996;110(6):543-546. doi:10.1017/s0022215100134218
12. Montroy J, Hutton B, Moodley P, et al. The efficacy and safety of topical tranexamic acid: A systematic review and meta-analysis. *Transfus Med Rev*. Published online 2018. doi:10.1016/j.tmrv.2018.02.003
13. Ker K, Edwards P, Perel P, Shakur H, Roberts I. Effect of tranexamic acid on surgical bleeding: systematic review and cumulative meta-analysis. *BMJ*. 2012;344:e3054. doi:10.1136/bmj.e3054
14. Roberts I, Shakur H, Coats T, et al. The CRASH-2 trial: a randomised controlled trial and economic evaluation of the effects of tranexamic acid on death, vascular occlusive events and transfusion requirement in bleeding trauma patients. *Health Technol Assess*. 2013;17(10):1-79.

doi:10.3310/hta17100

15. Joseph J, Martinez-Devesa P, Bellorini J, Burton MJ. Tranexamic acid for patients with nasal haemorrhage (epistaxis). *Cochrane Database Syst Rev*. Published online 2018.  
doi:10.1002/14651858.CD004328.pub3
16. Gottlieb M, DeMott JM, Peksa GD. Topical Tranexamic Acid for the Treatment of Acute Epistaxis: A Systematic Review and Meta-analysis. *Ann Pharmacother*. 2019;53(6):652-657.  
doi:10.1177/1060028018820625
17. Reuben A, Appelboam A, Barton A, et al. Novel use of tranexamic acid to reduce the need for Nasal Packing in Epistaxis (NoPac) randomised controlled trial: research protocol. *BMJ Open*. 2019;9(2):e026882. doi:10.1136/bmjopen-2018-026882
18. Health and Social Care Information Centre. NHS Data Model and Dictionary. Admission Method. Published 2013. Accessed October 5, 2020.  
[http://www.datadictionary.nhs.uk/data\\_dictionary/attributes/a/add/admission\\_method\\_de.asp?shownav=1](http://www.datadictionary.nhs.uk/data_dictionary/attributes/a/add/admission_method_de.asp?shownav=1)
19. Akkan S, Corbacioglu SK, Aytar H, Emektar E, Dagar S, Cevik Y. Evaluating Effectiveness of Nasal Compression With Tranexamic Acid Compared With Simple Nasal Compression and Merocel Packing: A Randomized Controlled Trial. *Ann Emerg Med*. 2019;74(1):72-78.  
doi:10.1016/j.annemergmed.2019.03.030
20. Zahed R, Moharamzadeh P, Alizadeharasi S, Ghasemi A, Saeedi M. A new and rapid method for epistaxis treatment using injectable form of tranexamic acid topically: a randomized controlled trial. *Am J Emerg Med*. 2013;31(9):1389-1392. doi:10.1016/j.ajem.2013.06.043
21. Zahed R, Mousavi Jazayeri MH, Naderi A, Naderpour Z, Saeedi M. Topical Tranexamic Acid Compared With Anterior Nasal Packing for Treatment of Epistaxis in Patients Taking Antiplatelet Drugs: Randomized Controlled Trial. *Acad Emerg Med*. Published online 2018.  
doi:10.1111/acem.13345
22. Schulz KF, Altman DG, Moher D, Group C. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *BMJ*. 2010;340:c332. doi:10.1136/bmj.c332
23. Zwarenstein M, Treweek S, Gagnier JJ, et al. Improving the reporting of pragmatic trials: an extension of the CONSORT statement. *BMJ*. 2008;337:a2390. doi:10.1136/bmj.a2390
24. StataCorp. Stata Statistical Software: Release 14. Published online 2015.
25. Tibbelin A, Aust R, Bende M, et al. Effect of local tranexamic acid gel in the treatment of epistaxis. *ORL J Otorhinolaryngol Relat Spec*. 1995;57(4):207-209. doi:10.1159/000276741

## Tables and Figures



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

Figure 1: CONSORT diagram of the NoPAC trial starting from all participants who met the study inclusion criteria. GCP = Good clinical practice, TXA = Tranexamic acid.

	<b>Placebo</b> (N = 242)	<b>TXA</b> (N = 254)	<b>Total</b> (N = 496)
	<b>Mean (SD)</b>	<b>Mean (SD)</b>	<b>Mean (SD)</b>
<b>Age (years)</b>	72.3 (13.9)	70.1 (15.6)	71.2 (14.8)
<b>Systolic Blood Pressure (mm Hg)</b>	150.7 (25.8)	150.2 (27.9)	150.4 (26.9)
<b>Diastolic Blood Pressure (mm Hg)</b>	87 (15.3)	85.8 (18.4)	86.4 (17.0)
<b>Pulse (bpm)</b>	82.2 (16.6)	82.6 (17.2)	82.4 (16.9)
	<b>N (%)</b>	<b>N (%)</b>	<b>N (%)</b>
<b>Male</b>	142 (58.7)	128 (50.4)	270 (54.4)
<b>Anticoagulant Medication</b>	166 (68.6)	155 (61.0)	321 (64.7)
<b>Hypertension</b>	149 (61.6)	153 (60.2)	302 (60.9)
<b>Ischemic Heart Disease</b>	59 (24.4)	49 (19.3)	108 (21.8)
<b>Diabetes</b>	38 (15.7)	33 (13.0)	71 (14.3)
<b>Thrombo-embolic disease</b>	16 (6.6)	26 (10.2)	42 (8.5)
<b>Alcoholic Liver Disease</b>	1 (0.4)	2 (0.8)	3 (0.6)
<b>Any bleeding disorder</b>	8 (3.3)	5 (2.0)	13 (2.6)

Table 1: Summary characteristics of participants in the NoPAC trial by allocated group (placebo or Tranexamic Acid (TXA)) and for total study population. Mean and standard deviation (SD) for continuous variables, frequency (N) and percentage for categorical variables.

<b>Primary Outcome Analysis</b>	<b>Placebo</b> N (%)	<b>TXA</b> N (%)	<b>Odds Ratio</b> (95% CI)
Packing in ED <i>Primary analysis</i> (N = 496)	100 (41.3)	111 (43.7)	1.11 (0.77 to 1.59)
<b>Sensitivity Analyses</b>			
Packing in ED <i>Per Protocol analysis</i> (N = 474)	90 (39.6)	106 (42.9)	1.16 (0.79 to 1.68)
Packing in and post ED <i>Pre-specified analysis</i> (N = 496)	117 (48.3)	134 (52.8)	1.20 (0.82 to 1.75)
Packing in ED <i>Post hoc analysis</i> (N = 466)	89 (39.7)	106 (43.8)	1.20 (0.84 to 1.73)

Table 2: Results of the primary and sensitivity analyses of the primary outcome. Frequency (N) and percentage (%) by allocated group (placebo or Tranexamic Acid (TXA)). Odds ratio and 95% confidence intervals (CI) for allocated group difference estimated from the mixed effects, regression model fitted to the binary outcome packing status (packed = yes/no), adjusted for recruiting site as a random effect.

Outcome	Placebo N (%)	TXA N (%)	Odds Ratio (95% CI)
ED epistaxis treatment (N = 496)	147 (58.3)	157 (61.8)	1.05 (0.73 to 1.52)
Epistaxis treatment (N = 496)	174 (69.0)	184 (72.4)	1.04 (0.70 to 1.56)
Hospital admission (N = 496)	110 (45.5)	110 (43.3)	0.92 (0.64 to 1.32)
Length of hospital stay* (N = 220)	2.0 (1.0 – 3.0) <sup>†</sup>	1.5 (1.0 – 2.0) <sup>†</sup>	0.05* (-0.19 to 0.28)
Blood Transfusion (N = 496)	6 (2.5)	7 (2.8)	1.11 (0.37 to 3.37)
Recurrent epistaxis (N = 494)	39 (16.1)	49 (19.4)	1.26 (0.79 to 2.00)

ED epistaxis treatment - Participant given treatment for epistaxis given during index ED (yes/no)

Epistaxis treatment - Participant given treatment given for epistaxis given during the index ED or subsequent 7 days (yes/no)

\* mixed effects generalized linear model fitted to count data with a log link, assuming a negative binomial distribution

<sup>†</sup> median (IQR) number of days

*Table 3: Results of the primary analyses of the secondary outcomes. Frequency (N) and percentage (%) by allocated group (placebo or Tranexamic Acid (TXA)). Between allocated group difference and 95% confidence intervals (CI) estimated from the mixed effects, logistic regression model for binary outcomes (yes/no) or mixed effects log link generalized linear model for count data, adjusted for recruiting site as a random effect.*