

ORIGINAL ARTICLE

Efficacy and safety of topical tranexamic acid in the management of anterior epistaxis: a systematic review and meta-analysis

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ABSTRACT

Background: The effectiveness of topical tranexamic acid (TXA) for spontaneous anterior epistaxis remains uncertain. We evaluated its efficacy and safety compared with placebo or standard care.

Methodology: PubMed, Scopus, Web of Science, and Cochrane CENTRAL were searched through November 2025 for randomized controlled trials (RCTs) and comparative observational studies in adults with spontaneous anterior epistaxis. The primary outcome was bleeding cessation; secondary outcomes included overall hemostasis, rebleeding, resource utilization, and adverse events. Risk ratios (RRs) with 95% confidence intervals (CIs) were pooled using the Hartung–Knapp–Sidik–Jonkman random-effects model.

Results: Eleven studies (10 RCTs and 1 observational study; 1,811 patients) were included. TXA was associated with greater bleeding cessation within 10 minutes (RR 2.26, 95% CI 1.59–3.21), but this effect became non-significant after adjustment for publication bias, indicating uncertainty in rapid hemostatic efficacy. TXA improved overall hemostasis (RR 1.25, 95% CI 1.11–1.40), reduced rebleeding within 3 days (RR 0.39, 95% CI 0.28–0.55), and reduced ENT consultation (RR 0.54, 95% CI 0.38–0.75). No significant reductions were observed in nasal packing, hospital admission, or cauterization. Adverse events were comparable between groups.

Conclusions: Topical TXA appears safe and may reduce short-term rebleeding and ENT consultation, but its benefit for rapid initial bleeding cessation is uncertain because of publication bias and small-study effects. It should be considered an adjunct rather than a definitive first-line hemostatic treatment.

Keywords: Epistaxis, Tranexamic Acid, Topical TXA, Hemostasis, Rebleeding, Meta-Analysis, Emergency Medicine, otorhinolaryngology.

Introduction

Epistaxis is a common emergency department presentation, affecting up to 60% of the population, with 6% of cases requiring medical intervention [1,2]. The clinical burden is highest in elderly patients and those on antithrombotic medications, who often experience more severe bleeding [3,4]. Standard management begins with conservative measures like direct pressure and topical vasoconstrictors [5]. However, refractory cases often require anterior nasal packing, an effective but invasive procedure associated with significant patient discomfort,

pain, and complications like rebleeding upon removal, which has driven the search for less invasive alternatives [6,7].

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Topical tranexamic acid (TXA), an antifibrinolytic agent that promotes hemostasis by stabilizing clots, has emerged as a promising option due to its potent local effect and favorable safety profile [8,9]. The agent's efficacy is well-established across various medical fields, significantly reducing blood loss and transfusion requirements in major surgical procedures such as total joint arthroplasty [10]. This broad success in surgical blood management provides a strong rationale for evaluating its utility in more localized bleeding events like epistaxis. However, its clinical efficacy remains controversial. Several randomized controlled trials (RCTs) have reported that topical TXA leads to faster cessation of bleeding, reduced rebleeding rates, and higher patient satisfaction compared with standard care [11,12].

In contrast, the largest multicenter RCT to date, the NoPAC trial, found that topical TXA was no more effective than placebo in reducing the need for nasal packing, creating significant clinical uncertainty [13]. This clinical equipoise is reflected in current practice guidelines. The American Academy of Otolaryngology–Head and Neck Surgery provides only a weak recommendation (an “option”) for the use of topical TXA, citing the inconsistent and low-certainty evidence [5]. While a previous meta-analysis suggested a benefit, it was limited by the small number of available studies [14]. The recent publication of several large RCTs provides an opportunity to synthesize the current body of evidence more definitively and resolve this ongoing clinical debate. Thus, this systematic review and meta-analysis were conducted to thoroughly assess the effectiveness and safety of topical TXA against placebo or standard treatments for managing spontaneous anterior epistaxis in adult patients.

Methodology

Protocol and registration

The preparation and reporting of this systematic review and meta-analysis followed the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and Cochrane Handbook [15,16].

Eligibility criteria

RCTs and comparative observational studies were incorporated using the following Population, Intervention, Comparator, and Outcomes (PICO) framework: (P) We included studies enrolling adults (≥ 18 years) presenting with spontaneous, atraumatic anterior epistaxis. (I) The intervention was the topical administration of TXA in any formulation (e.g., injectable solution, gel, atomized spray) or dose. (C) The comparator group received either placebo (e.g., saline or sterile water) or standard care, including topical vasoconstrictors or anterior nasal packing. (O) Studies reporting on at least one of the pre-specified primary or secondary outcomes were included. We excluded studies that included patients aged less

than 18 years, conference abstracts, review articles, and foreign-language studies.

Information sources and search strategy

We performed an extensive literature search across the PubMed, Scopus, Web of Science, and Cochrane Central Register of Controlled Trials (CENTRAL) databases, covering all publications from their inception through November 2025.

Our search strategy utilized a combination of keywords and MeSH terms for concepts such as “epistaxis,” “nosebleed,” and “tranexamic acid.” In addition, we manually screened the reference lists from the included articles and other relevant reviews to identify any further eligible studies. The full, detailed search strategy for all databases is provided in Supplementary Table 1.

Study selection

The titles and abstracts of all identified records were screened against the eligibility criteria by two reviewers working independently. The full texts of potentially relevant articles were then retrieved and assessed in duplicate for final inclusion. Any disagreements between the reviewers at either stage were resolved through discussion and consensus or by consulting a senior reviewer. Moreover, we performed a manual screening of the references of the included studies and prior meta-analyses to ensure the inclusion of all relevant studies.

Data extraction

Data from the selected studies were extracted independently by two reviewers, who utilized a pre-piloted and standardized form for data collection. Extracted variables covered study ID (first author, year of publication), study design, country, and study groups, as well as details on patient characteristics (sample size, age, sex, comorbidities such as hypertension and diabetes, and baseline systolic and diastolic blood pressure). Information on intervention characteristics (topical TXA dose, formulation, and method of application), comparator details, inclusion criteria, and the use of antiplatelet or anticoagulant medications was also collected. Quantitative data for all pre-specified outcomes were extracted. Any discrepancies were resolved through discussion and consensus.

Risk of bias assessment

Two reviewers independently evaluated the methodological quality and risk of bias for the included RCTs with the revised Cochrane Risk of Bias 2 (RoB-2) tool [17]. Each domain was judged as “low risk,” “some concerns,” or “high risk” of bias. The quality of the included observational study was evaluated using the Newcastle-Ottawa Scale (NOS), which assesses patient selection, comparability of groups, and outcome assessment [18]. Disagreements were resolved through discussion to reach a final consensus.

Outcome measures

The primary outcome was stopping bleeding, analyzed as a time-dependent event at three distinct intervals: within 10 minutes, between 10 and 20 minutes, and after 20 minutes of treatment application.

Secondary efficacy outcomes included achieving hemostasis at any point during the initial ED visit and the incidence of rebleeding (analyzed within 3 days and after 3 days). Measures of treatment failure and resource utilization included the need for subsequent hospital admission, nasal packing, cauterization, and otorhinolaryngology (ENT) consultation. The safety outcome was the incidence of any reported adverse events.

Statistical analysis

All statistical analyses were performed using R (version 4.3.1; R Foundation for Statistical Computing, Vienna,

Austria) with the meta package. For all dichotomous outcomes, the risk ratio (R.R) with 95% confidence intervals (C.I) was calculated. To accommodate the anticipated clinical and methodological diversity across the studies, and in light of the high heterogeneity observed, we applied the Hartung–Knapp–Sidik–Jonkman random-effects model for all pooled analyses. The between-study variance (τ^2) was estimated using the Restricted Maximum-Likelihood method. We also report the 95% prediction interval (PI) for clinically central outcomes to illustrate the range of expected effects in future studies. Statistical heterogeneity was assessed using the Chi-square (χ^2) test (with $p < 0.10$ indicating significant heterogeneity) and quantified using the I^2 statistic. I^2 values of $<25\%$, $25\%–75\%$, and $>75\%$ were interpreted as representing low, moderate, and substantial heterogeneity, respectively.

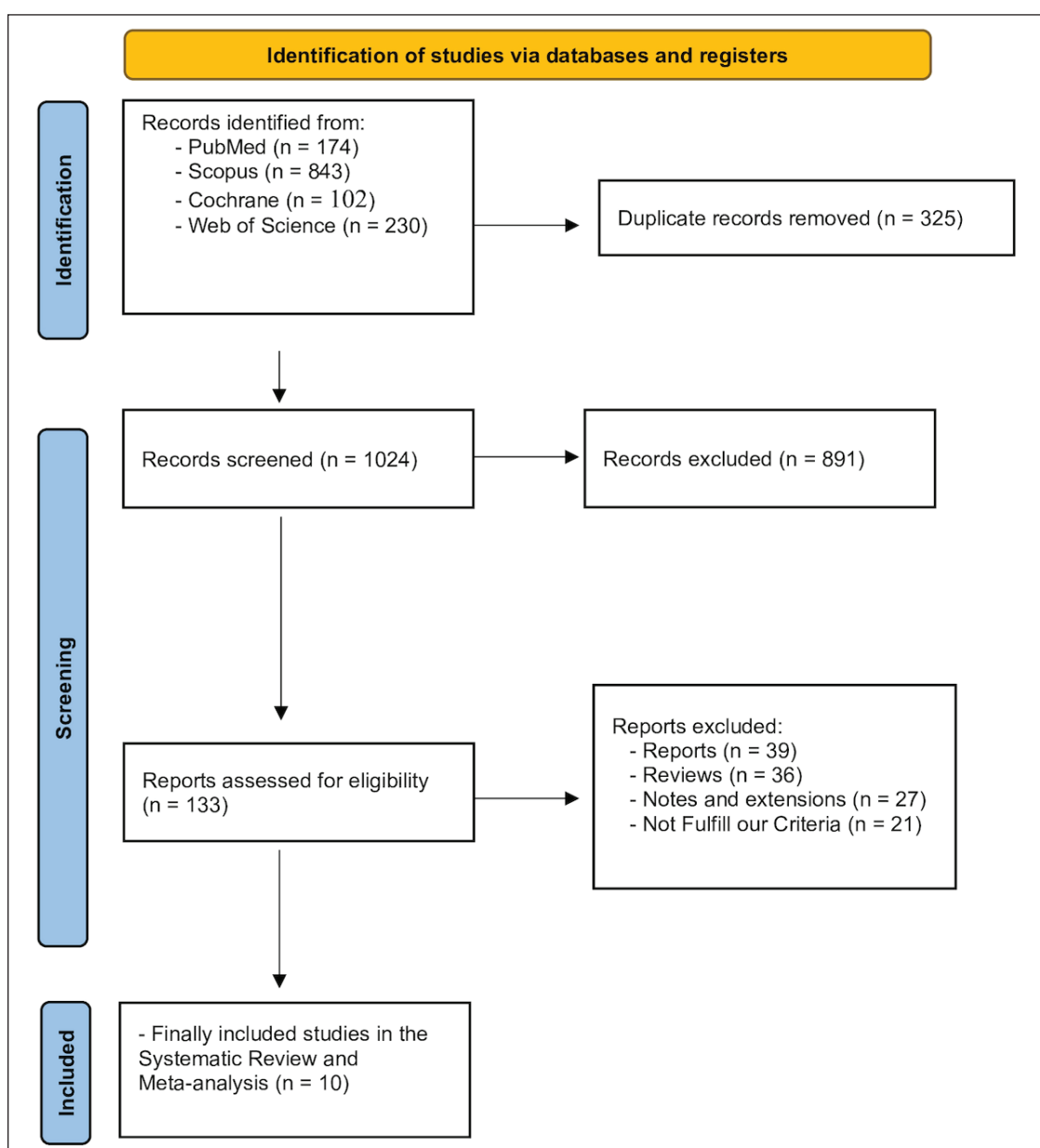


Figure 1. PRISMA 2020 flow diagram illustrating the study identification, screening, and inclusion process.

To investigate potential sources of heterogeneity in the primary outcome, we performed pre-specified subgroup analyses stratified by: (1) study design (RCTs vs. observational studies) and (2) the type of comparator used in the control group (placebo, packing alone, or packing with vasoconstrictor). Meta-regression analyses were conducted to explore the influence of mean patient age and the proportion of male patients on the treatment effect. A leave-one-out sensitivity analysis was also performed to assess the robustness of the primary outcome finding. Publication bias was assessed visually using funnel plots and quantitatively using Egger’s linear regression test and the trim-and-fill method. Based on the representative control risk from included RCTs, we calculated the absolute risk reduction (ARR) or absolute risk increase (ARI), and the number needed to treat (NNT). A two-tailed *p*-value of < 0.05 was considered statistically significant for all analyses.

Results

A total of 1,349 publications were initially identified through database searching. Following the exclusion of 325 duplicates, 1024 unique publications were subjected to title and abstract screening, which resulted in the exclusion of 891 irrelevant records. The eligibility of the remaining 133 articles was then evaluated through a full-text assessment. This final step led to the inclusion of 11 studies that met all criteria. The final analysis drew upon data from ten randomized controlled trials and a single observational study, which together included 1,811 patients. The study identification and selection process is summarized in Figure 1.

Characteristics of included studies

The 11 included studies were published between 1995 and 2024 and were conducted across several countries, including Iran, Turkey, the USA, the UK, and Sweden [11–13,19–26]. The total sample size was 1811 patients (877 in the TXA group and 934 in the control group). All studies enrolled adult patients with spontaneous anterior epistaxis. The patient populations varied, with some studies specifically including patients on antiplatelet or anticoagulant therapy, while others excluded them.

The application of topical TXA varied significantly across studies. Doses ranged from 300 mg to 1000 mg per application. Formulations included injectable solutions soaked onto cotton or gauze packing, a pre-formulated gel, and an atomized spray. Control interventions were also diverse, including placebo (saline or sterile water), vasoconstrictors (phenylephrine or oxymetazoline), and various types of anterior nasal packing (e.g., Merocel, gauze). The follow-up duration ranged from 24 hours to 10 days. A summary of the baseline characteristics for the included studies is presented in Tables 1 and 2, [11–13, 19–26].

Risk of bias assessment

The ten RCTs were assessed for risk of bias using the Revised ROB-2. Overall, eight studies were judged to be at a low risk of bias. Two studies were judged to be at

Table 1. Summary characteristics of included studies.

Study ID	Arms	Sample size	Study design	Country	Antiplatelet / anticoagulant use	Topical TXA dose	Formulation used	Inclusion criteria	Nasal packing type (Merocel, tampon, gauze)	Follow up	Conclusion
Akkan [23]	TXA	45	RCT	Turkey	Antiplatelets	500 mg	Injectable form (500 mg ampoule) diluted in 5 ml normal saline, sprayed with an atomizer	Patients >18 years with active, spontaneous anterior epistaxis.	Merocel 2000	1 day	TXA with external compression is as effective as Merocel packing at stopping bleeding and superior to Merocel in decreasing rebleeding rates.
	Control	90									
Amini [24]	TXA	50	RCT	Iran	Both	500 mg	Injectable form (500 mg in 5 ml) soaked in a wad of cotton	Patients in the ED with epistaxis who were taking antiplatelet drugs (aspirin, clopidogrel, or both).	Cotton wad	3 days	Topical TXA is an appropriate treatment for bleeding cessation and reducing re-bleeding and duration of hospital stay in patients with epistaxis who take antiplatelet agents.
	Control	50									
Arikan [25]	TXA	101	RCT	Turkey	Both	1000 mg and 500 mg	Injectable solution (250 mg/2.5 ml) used to soak gauze	Patients >18 years who presented to the emergency department with epistaxis and provided written consent.	Gauze (soaked with TXA or saline)	1 day	000 mg of TXA is recommended due to its superiority in achieving earlier bleeding control and decreasing the rate of recurrent bleeding, with a low incidence of side effects.
	Control	51									

Study ID	Arms	Sample size	Study design	Country	Antiplatelet / anticoagulant use	Topical TXA dose	Formulation used	Inclusion criteria	Nasal packing type (Merocel, tampon, gauze)	Follow up	Conclusion
Birmingham [19]	TXA	30	Observational	USA	Both	500 mg (in 29 patients), and 100 mg (in 1 patient)	Injectable solution (500 mg) soaked onto cotton pledgets or nasal tampons, and (1 patient received 100 mg aerosolized)	Patients in ED with epistaxis refractory to first-line agents (e.g., oxymetazoline, lidocaine, or epinephrine).	Merocel, rhinorockets, surgical, floreal	7 days	No significant difference in ED LOS. However, TXA was associated with a reduction in resource utilization (fewer ENT consults and nasal packing), suggesting it may provide more effective bleeding control.
	Control	92									
Hosseinalhashemi [12]	TXA	120	RCT	Iran	Antiplatelets	500 mg	Injectable solution (5 ml of 100 mg/mL) soaked on a cotton pledget	Adult patients >18 years with active spontaneous atraumatic anterior epistaxis not controlled by 10 mins of simple measures (compression, ice, etc.).	Cotton pledget	7 days	Intranasal topical TXA is associated with a lower rate of need for anterior nasal packing and a shortened stay in the ED; it may be considered part of the treatment for atraumatic anterior epistaxis.
	Control	120									
Reuben [13]	TXA	254	RCT	UK	Anticoagulant	400 mg	Injectable solution (100 mg/mL) applied on a cotton wool dental roll.	Adults >18 years with spontaneous epistaxis persisting after simple first aid AND application of a topical vasoconstrictor.	Merocel or rapid rhino	7 days	Topical tranexamic acid is no more effective than placebo at controlling bleeding and reducing the need for anterior nasal packing.
	Control	242									
Shahidi 2021 [20]	TXA	60	RCT	Iran	No	500 mg	Injectable (500 mg per 5 ml) soaked on a 15-cm-long gauze	Patients with idiopathic anterior epistaxis or previous epistaxis, bleeding from only one nasal passage.	Gauze	7 days	The results indicate the beneficial effects of TA in reducing bleeding time in patients with epistaxis.
	Control	60									
Tibbelin [26]	TXA	30	RCT	Sweden	Antiplatelets	15 ml of 10% gel	10% Tranexamic acid gel (in 15 ml plastic syringes)	Patients >18 years with an ongoing nosebleed at the time of gel application.	NA	10 days	Tranexamic acid was no better than placebo in the early treatment of nose bleedings, but the gel itself seemed to have a beneficial effect.
	Control	38									
Whitworth [21]	TXA	18	RCT	USA	Both	300 mg	3 ml of intravenous TXA (1000 mg/10 mL) applied via atomizer	Patients >18 years of age presenting to the ED with new or acute anterior epistaxis.	Nasal tampon or nasal packing	2 days	The topical application of the intravenous preparation of TXA is more effective than topical oxymetazoline for achievement of hemostasis in anterior epistaxis.
	Control	20									
Zahed [11]	TXA	107	RCT	Iran	No	500 mg	Injectable (500 mg in 5 ml) soaked on a 15-cm cotton pledget	Patients with ongoing idiopathic or recurrent anterior epistaxis	cotton pledget	7 days	Topical application of injectable form of tranexamic acid was better than anterior nasal packing in the initial treatment of idiopathic anterior epistaxis
	Control	109									
Zahed [22]	TXA	62	RCT	Iran	Both	500 mg	Injectable form (500 mg in 5 mL) soaked on a 15-cm cotton pledget	Patients in the ED with acute anterior epistaxis currently taking antiplatelet drugs (aspirin, clopidogrel, or both)	cotton pledget	7 days	Topical TXA resulted in faster bleeding cessation, less rebleeding at 1 week, shorter ED LOS, and higher patient satisfaction compared with ANP.
	Control	62									

Abbreviations: TXA: Tranexamic Acid, RCT: Randomized Controlled Trial, ED: Emergency Department, ENT: Ear, Nose, and Throat, ANP: Anterior Nasal Packing, LOS: Length of Stay, UK: United Kingdom, USA: United States of America.

Table 2. Baseline characteristics of included studies.

Study ID	Arms	Sample size	Age, (y), mean (SD)	Male, n (%)	HTN, n (%)	DM, n (%)	SBP, mmHg, mean (SD)	DBP, mmHg, mean (SD)
Akkan [23]	TXA	45	59.7 (19.1)	24 (53.4)	21 (46.6)	5 (11.1)	146 (24.5)	80.3 (14.6)
	Control	90	57.7 (16.1)	17 (37.7)	24 (53.4)	7 (15.5)	148.7 (26)	82.3 (18.4)
Amini [24]	TXA	50	61.3 (19.1)	24 (53.4)	21 (46.6)	7 (15.5)	146.7 (34.5)	81.3 (15.3)
	Control	50	NA	29 (58)	5 (10)	7 (14)	NA	NA
Arikan [25]	TXA	101	NA	23 (46)	13 (26)	5 (10)	NA	NA
	Control	51	56.7 (27.2)	21 (70)	9 (30)	NA	NA	NA
Birmingham [19]	TXA	30	56.7 (27.2)	21 (70)	9 (30)	NA	NA	NA
	Control	92	54.3 (27.9)	40 (43.5)	30 (33)	NA	NA	NA
Hosseinihashemi [12]	TXA	120	52 (13.5)	66 (55)	NA	NA	133.3 (11.3)	78 (6.8)
	Control	120	54 (12.8)	60 (50)	NA	NA	131.7 (11.26)	76.7 (3.8)
Reuben [13]	TXA	254	70.1 (15.6)	128 (50.4)	153 (60.2)	33 (13)	150.2 (27.9)	85.8 (18.4)
	Control	242	72.3 (13.9)	142 (58.7)	149 (61.6)	38 (15.7)	150.7 (25.8)	87 (15.3)
Shahidi [20]	TXA	60	52.1 (7.6)	40 (66.7)	NA	NA	141.5 (12.6)	85.4 (7.3)
	Control	60	50.4 (7)	38 (63.3)	NA	NA	148.9 (12.4)	89.7 (7.7)
Tibbelin [26]	TXA	30	53 (16.2)	21 (70)	NA	NA	NA	NA
	Control	38	59.75 (15.7)	28 (73.7)	NA	NA	NA	NA
Whitworth [21]	TXA	18	71.4 (14.6)	9 (50)	NA	NA	NA	NA
	Control	20	65.8 (14.9)	9 (45)	NA	NA	NA	NA
Zahed [11]	TXA	107	50.4 (19)	67 (62.6)	NA	NA	NA	NA
	Control	109	54 (15.5)	57 (52.3)	NA	NA	NA	NA
Zahed [22]	TXA	62	58.5 (16.1)	36 (58.5)	NA	NA	NA	NA
	Control	62	60.7 (12.2)	38 (60.7)	NA	NA	NA	NA

Abbreviations: SD: Standard Deviation, HTN: Hypertension, DM: Diabetes Mellitus, SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure, mmHg: Millimeters of Mercury, TXA: Tranexamic Acid, PANP: Phenylephrine-Assisted Nasal Packing, NA: Not Available.

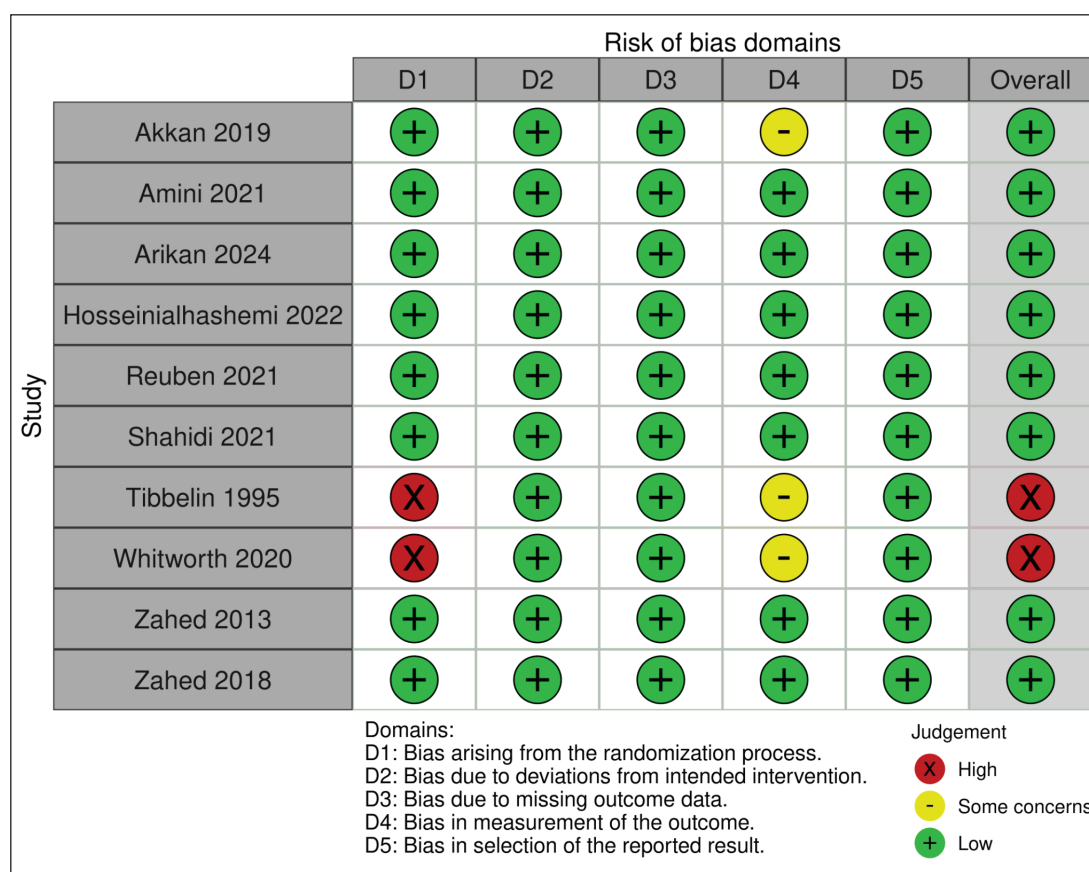


Figure 2. Risk of bias summary for included randomized controlled trials, assessed using the cochrane risk of bias 2 (rob-2) tool.

a high risk of bias, primarily due to concerns related to the randomization process and potential for selection bias (Figure 2).

The single observational study, Birmingham [19], was assessed using the NOS and was rated as high quality, as shown in Supplementary Table 2.

Primary outcome

The primary pooled analysis revealed a time-dependent efficacy for topical TXA in stopping bleeding. A significant benefit was observed within the first 10 minutes of treatment, with TXA use significantly increasing the rate of bleeding cessation compared to control (RR = 2.26, 95% CI [1.59, 3.21], $p < 0.0001$). However, heterogeneity was substantial ($I^2 = 79\%$, $\tau^2 = 0.1015$, $p < 0.0001$), and the 95% PI was [0.82, 6.23]. This early effect was not sustained in pooled analyses of later time points, including the 10-to-20-minute interval (RR = 0.46, 95% CI [0.19, 1.14], $p = 0.0925$; $I^2 = 89.6\%$, $\tau^2 = 0.5286$, 95% PI [0.01, 18.71]) and bleeding lasting longer than 20 minutes (RR = 0.47, 95% CI [0.13, 1.63], $p = 0.2329$; $I^2 = 76.2\%$, $\tau^2 = 0.6440$, 95% PI [0.00, 210188.19]) (Figure 3).

Based on a representative control event rate of 30.4% for bleeding cessation within 10 minutes from the included RCTs, treatment with topical TXA corresponds to an ARI of 46.4%, yielding an NNT of 2.6 (95% CI [1.5, 5.6].

Visual inspection of the funnel plot for the primary outcome suggested asymmetry (supplementary Figure

1). This asymmetry was further corroborated by the Doi plot, which yielded an LFK index of 5.19 (supplementary Figure 2) and was confirmed by Egger’s linear regression test, which was statistically significant ($t = 3.01$, $df = 5$, $p = 0.0298$), indicating the presence of small-study effects (supplementary Figure 3). Furthermore, the trim-and-fill analysis imputed three potentially missing studies on the left side of the funnel plot. After imputation, the adjusted pooled effect size was substantially reduced and became non-significant (RR = 1.16, 95% CI [0.63, 2.13]), suggesting that the primary finding may be inflated due to publication bias (supplementary Figure 4). Consequently, the current evidence is insufficient to confidently conclude that topical TXA provides a reliable benefit for immediate bleeding cessation within 10 minutes.

A leave-one-out sensitivity analysis showed that no single study disproportionately influenced the overall effect for the primary outcome, confirming the robustness of the finding (supplementary Figure 5).

Subgroup analysis based on the comparator group showed that TXA did not demonstrate a statistically significant difference in any subgroup as follows: placebo (RR = 1.04, 95% CI [0.77, 1.41], $p = 0.7826$; $I^2 = 74\%$, $\tau^2 = 0.0562$; 95% PI [0.31, 3.50]), packing alone (RR = 1.50, 95% CI [0.62, 3.62], $p = 0.3652$; $I^2 = 71.4\%$, $\tau^2 = 0.3845$; 95% PI [0.01, 25161.55]), and packing combined with a vasoconstrictor (RR = 4.94, 95% CI [0.97, 25.03], $p = 0.0539$; $I^2 = 77.4\%$, $\tau^2 = 1.7892$; 95% PI [0.01, 4298.27]) (Figure 4).

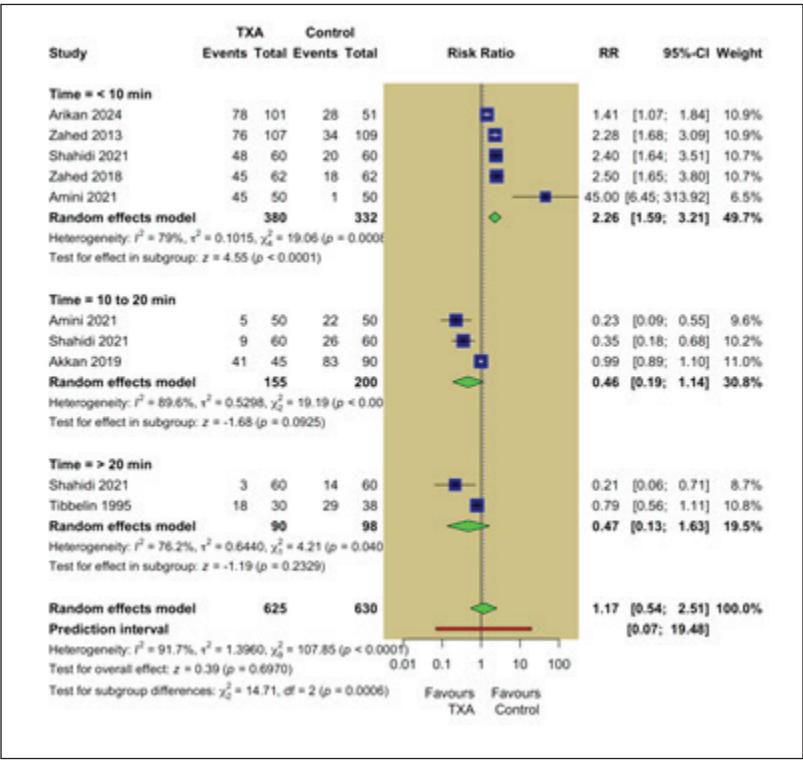


Figure 3. Forest plot comparing the effect of topical tranexamic acid (TXA) versus control on stopping bleeding at different time intervals (10 minutes, 10–20 minutes, and 20 minutes).

To explore sources of heterogeneity, we conducted meta-regression analyses. Neither the proportion of male patients in the TXA group ($p = 0.98$) nor the mean age of patients ($p = 0.62$) was found to be a significant moderator of the treatment effect for the primary outcome (supplementary Figures 6 and 7).

Secondary outcomes

Secondary efficacy outcomes

Our pooled analysis showed that patients who were treated with TXA significantly achieved complete hemostasis (RR = 1.25, 95% CI [1.11, 1.40], $p = 0.0002$; $I^2 = 47.7\%$, $\tau^2 = 0.0001$, 95% PI [0.97, 1.62]) (Figure 5).

Additionally, the effect of topical TXA on rebleeding was time-dependent. A statistically significant reduction in rebleeding was observed within the first 3 days of treatment; patients in the TXA group had a lower risk

of rebleeding during this period compared to the control group (RR = 0.39, 95% CI [0.28, 0.55], $p = 0.0001$; $I^2 = 0\%$, $\tau^2 = 0$; 95% PI [0.26, 0.59]). In contrast, for rebleeding events occurring after 3 days, the pooled analysis did not find a statistically significant difference between the groups (RR = 0.60, 95% CI [0.35, 1.02], $p = 0.0589$; $I^2 = 64.5\%$, $\tau^2 = 0.3008$, 95% PI [0.82, 6.23]) (Figure 6).

Based on a representative control event rate for rebleeding of 18% (calculated from the control arms of the RCT subgroup), the use of topical TXA was associated with an ARR of 12.2%, corresponding to an NNT of 10.1 (95% CI [7.6 to 21.4]).

Subgroup analysis according to study design revealed that this effect was consistently significant among RCTs (RR = 0.46, 95% CI [0.29, 0.75], $p = 0.0016$; $I^2 = 63.4\%$, $\tau^2 = 0.2489$; 95% PI [.13, 1.67]), not the observational study (supplementary Figure 8).

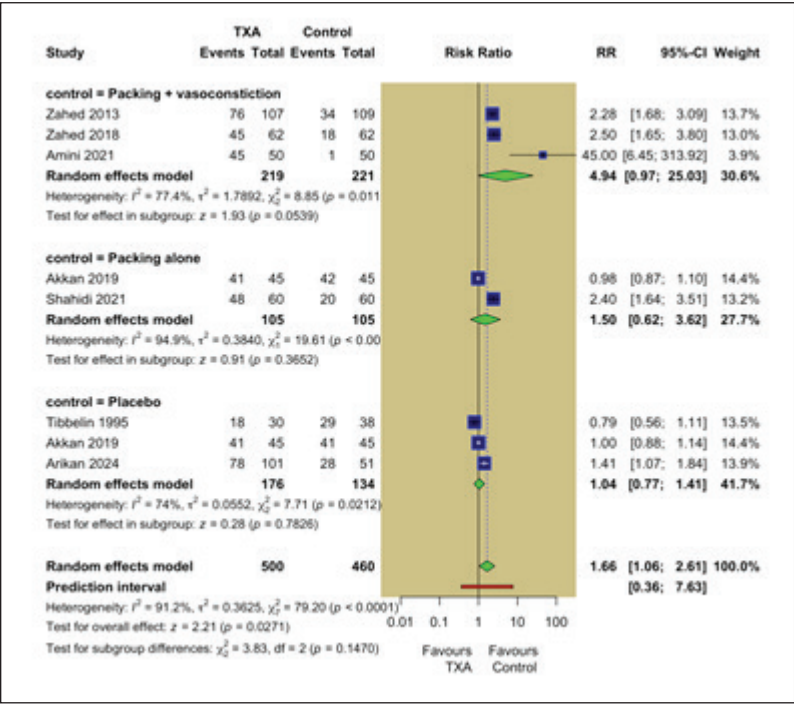


Figure 4. Forest plot of subgroup analysis for stopping bleeding, stratified by the type of comparator (Placebo vs. Packing Alone vs. Packing with Vasoconstrictor).

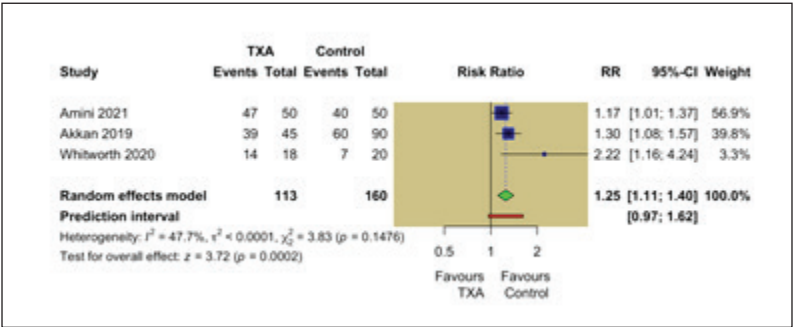


Figure 5. Forest plot comparing the effect of topical tranexamic acid (TXA) versus control on achieving complete hemostasis.

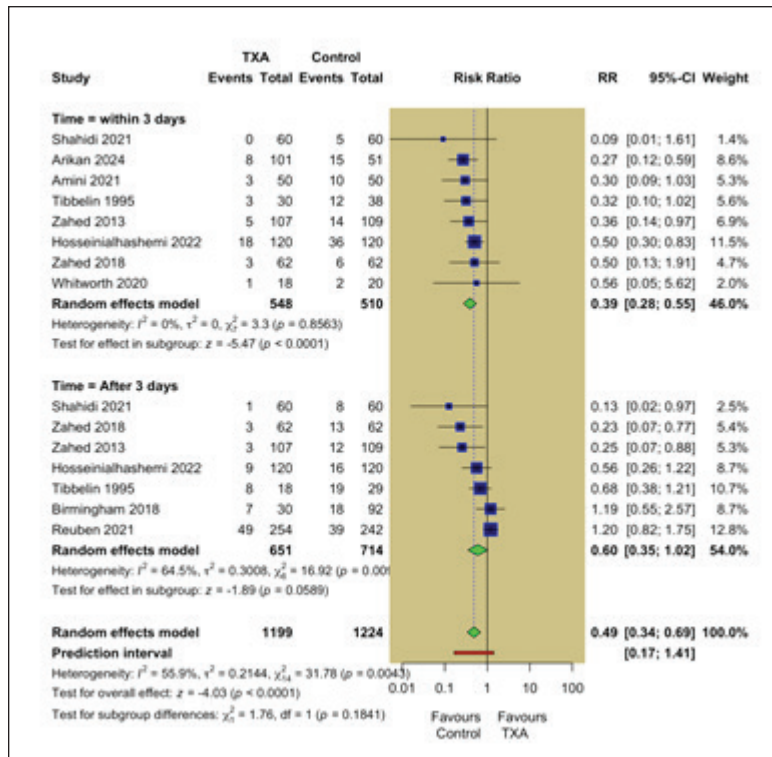


Figure 6. Forest plot comparing the effect of topical tranexamic acid (TXA) versus control on the incidence of rebleeding (within 3 days and after 3 days).

A subgroup analysis by comparator type was performed. Although the overall test for subgroup differences was not significant ($p = 0.8156$), the benefit of TXA was most pronounced and was only statistically significant when compared against packing with a vasoconstrictor (RR = 0.45, 95% CI [0.30, 0.67], $p < 0.0001$; 95% PI [0.26, 0.79]), a subgroup which exhibited no heterogeneity ($I^2 = 0\%$, $\tau^2 = 0$). In contrast, no significant benefit was observed against packing alone (RR = 0.43, 95% CI [0.11, 1.63]; 95% PI [0.01, 67.36]; $I^2 = 76.6\%$, $\tau^2 = 0.9189$) or placebo (RR = 0.69, 95% CI [0.19, 2.50]; 95% PI [0.01, 464071.05]; $I^2 = 77.7\%$, $\tau^2 = 0.6866$), suggesting the overall effect is primarily driven by studies with an active vasoconstrictor control (supplementary Figure 9).

Meta-regression analysis identified mean patient age as a significant moderator of this effect ($p = 0.00253$), indicating that the efficacy of TXA in preventing rebleeding diminishes as the average age of the study population increases (supplementary Figure 10). The proportion of male patients was not a significant factor ($p = 0.861$) (supplementary Figure 11).

Treatment failure and resource utilization

Our analysis of treatment failure and resource utilization outcomes revealed that while topical TXA did not reduce the need for subsequent invasive interventions, it did decrease the need for specialist consultation. There was no significant difference in the need for nasal packing (RR = 0.84, 95% CI [0.63, 1.12], $p = 0.2279$; $I^2 = 62.4\%$, $\tau^2 = 0.0468$; 95% PI [0.36, 1.93]) (supplementary Figure 12), hospital admission (RR = 0.94, 95% CI [0.77,

1.13], $p = 0.5081$; $I^2 = 0.0\%$, $\tau^2 = 0$, 95% PI [0.62, 1.43]) (supplementary Figure 13), or cauterization (RR = 0.97, 95% CI [0.80, 1.17], $p = 0.7417$; $I^2 = 44.4\%$, $\tau^2 = 0.0062$; 95% PI [0.56, 1.66]) (supplementary Figure 14). In contrast, treatment with TXA led to a statistically significant 27.3% of ARR in the need for ENT consultation (RR = 0.54, 95% CI [0.38, 0.75], $p = 0.0003$; 95% PI [0.25, 1.13]). This finding was consistent across studies, with no statistical heterogeneity observed ($I^2 = 0\%$, $\tau^2 = 0$) (supplementary Figure 15).

Safety outcomes

In terms of safety, the pooled analysis of adverse events from six studies revealed no statistically significant difference when comparing the topical TXA and control groups (R.R = 1.00, 95% C.I [0.46, 2.21], $p = 0.9931$; $I^2 = 56.8\%$, $\tau^2 = 0.5390$; 95% PI [0.12, 8.63]) (Supplementary Figure 16).

Discussion

Summary of key findings

This systematic review and meta-analysis assessed the efficacy and safety of topical TXA compared to standard care or placebo for the management of spontaneous anterior epistaxis in adults. Our findings indicate that the apparent rapid bleeding control within the first 10 minutes of topical TXA application is highly uncertain. This specific outcome demonstrated substantial heterogeneity, very wide PIs, and lost statistical significance after adjusting for potential publication bias. Importantly, our

analysis confirmed that initial TXA application did not significantly reduce the need for subsequent invasive interventions such as nasal packing, hospital admission, or cauterization.

However, TXA demonstrated clear benefits in other key outcomes. It significantly improved the overall rate of complete hemostasis and substantially reduced the risk of rebleeding within the first 3 days after initial treatment. This protective effect against rebleeding was less pronounced in older patient populations. Furthermore, TXA use led to a significant reduction in the need for specialist ENT consultations. Despite these advantages, the initial benefits of TXA did not translate into a decreased need for subsequent invasive interventions, as there were no significant reductions in the rates of nasal packing, hospital admission, or cauterization. Finally, the safety profile of topical TXA was comparable to control interventions, with no significant increase in adverse events.

Interpretations of main findings

TXA stabilizes the fibrin clot by inhibiting plasminogen activation and limiting local fibrinolysis [27,28]. Although this mechanism provides a strong biological rationale for rapid hemostasis, our publication-bias analyses indicate that the magnitude of the early effect is likely overestimated. Therefore, rapid bleeding cessation should not be considered a consistent clinical benefit of topical TXA [29–31].

The rapid effect observed in our analysis is consistent with multiple RCTs, which highlight this immediate benefit, especially when the injectable form is applied topically, delivering a high drug concentration directly to the target area [11,24]. This finding aligns with the previous meta-analysis, which also reported superior bleeding cessation at first assessment [14].

Despite the theoretical benefit for initial hemostasis, topical TXA did not significantly reduce the need for anterior nasal packing. The large NoPAC trial enrolled a more refractory population who had already failed first aid and topical vasoconstrictor therapy, which may partly explain the difference from earlier smaller trials [13]. These findings suggest that topical TXA should be viewed as an adjunctive therapy rather than a reliable replacement for nasal packing [11,22].

The significant reduction in rebleeding within the first 3 days is biologically consistent with TXA-mediated stabilization of the fibrin clot [22,24,32]. This benefit was not maintained after 3 days, suggesting that the main effect of topical TXA is concentrated in the acute phase. Meta-regression also indicated that the reduction in rebleeding may diminish with increasing patient age [33,34].

A notable finding was the significant reduction in ENT consultations, despite no corresponding decrease in nasal packing or hospital admission rates. This may reflect a change in emergency physician behavior; the rapid and effective initial control of bleeding likely increases clinician confidence to manage the patient without immediate specialist escalation [25]. Even if packing is

eventually required, the initial stabilization may allow for a more controlled management pathway within the emergency department. The observational study by Birmingham [19] reported a similar reduction in ENT consults, suggesting this reflects a real-world impact on resource utilization.

Finally, the safety profile of topical TXA was confirmed to be excellent, with no increase in adverse events. This is attributed to its local administration, which results in minimal systemic absorption [35]. By confining the drug's action to the nasal mucosa, the risk of systemic side effects, particularly thromboembolic events, is largely obviated [36]. This favorable safety profile, consistently reported across all included studies, is a critical advantage, making it a safe initial treatment for a broad range of patients presenting with epistaxis.

Strengths and limitations

The primary strength of this meta-analysis is its comprehensive and up-to-date nature, incorporating several recent and large-scale RCTs, including the pivotal NoPAC trial. This has allowed for a more robust and nuanced synthesis of the current evidence. The inclusion of over 1800 patients provides substantial statistical power for our analysis. Furthermore, the methodological quality of the included studies was generally high, with the majority of RCTs judged to be at a low risk of bias. Our use of pre-specified subgroups and sensitivity analyses also adds to the robustness of our findings.

However, several limitations must be acknowledged. First, there was substantial clinical and statistical heterogeneity in the primary outcome analysis. This heterogeneity stems from considerable variations across the included studies in TXA dosage (ranging from 300 mg to 1000 mg), formulation (injectable solution, gel, and atomized spray), and comparator interventions (placebo, vasoconstrictors, or anterior nasal packing). This variability makes it challenging to determine an optimal application method or dose. Our publication bias analysis for the primary outcome indicated significant small-study effects. After adjustment using the trim-and-fill method, the initially significant effect of TXA on stopping bleeding within 10 minutes was rendered non-significant. This is a major limitation of the current body of evidence and suggests that the true effect may be modest or null.

Clinical implications and advances in knowledge

Topical TXA appears most useful as an adjunctive therapy rather than a definitive first-line hemostatic intervention. The strongest evidence supports a reduction in short-term rebleeding and ENT consultation, whereas its effect on rapid initial hemostasis remains uncertain because of publication bias. It also does not reliably reduce the subsequent need for nasal packing, hospital admission, or cauterization.

Conclusion

Topical TXA appears safe and may reduce short-term rebleeding and the need for ENT consultation, but its

effect on rapid initial hemostasis remains uncertain because of heterogeneity and publication bias. It does not significantly reduce nasal packing, hospital admission, or cauterization and should therefore be considered an adjunct rather than a definitive first-line treatment. Further large, high-quality RCTs are needed to clarify its effect on initial bleeding cessation.

Conflict of interest

There is no conflict of interest or a financial to disclose. All authors have notified and willing to publish in this journal.

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Supplementary content (If any) is available online.

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