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The efficacy and application of tranexamic acid in emergency medicine: Emergency Medicine Association of Türkiye clinical policy- 2024

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Abstract:

The clinical policy of the Emergency Medicine Association of Türkiye (EMAT) provides guidance on the use of tranexamic acid (TXA) in emergency settings. TXA, an antifibrinolytic drug, is used to control bleeding by inhibiting plasminogen. Its applications have expanded from hemophilia and severe menstrual bleeding to include various forms of trauma and surgery-related bleeding. Despite its potential benefits, the use of TXA in emergency settings must be carefully evaluated due to its associated risks, including venous thromboembolism. This policy aimed to offer evidence-based recommendations on the indications and contraindications of TXA in different clinical scenarios encountered in the emergency departments. The guidelines were developed using the "Grading of Recommendations, Assessment, Development, and Evaluations" approach, incorporating systematic literature reviews, and expert consensus from the EMAT Research Committee. This document focuses on critical clinical questions regarding the efficacy and safety of TXA in situations such as gastrointestinal bleeding, multitrauma, traumatic brain injury, nontraumatic intracranial hemorrhage, hemoptysis, and epistaxis. By addressing these issues, the policy seeks to assist emergency physicians in making informed decisions about the use of TXA, ultimately aiming to improve the patient outcomes.

Keywords:

Brain injury, emergency department, epistaxis, gastrointestinal bleeding, hemoptysis, intracranial hemorrhage, policy, tranexamic acid, trauma

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Introduction

Tranexamic acid (TXA) is an antifibrinolytic drug known to facilitate thrombosis by inhibiting plasminogen, and it is used to stop or prevent bleeding in many serious cases due to this effect.[1] Initially, TXA was used primarily for hemorrhage prophylaxis or control in hemophilia patients and for managing severe menstrual bleeding. For a long time, it received Food and Drug Administration approval only for these two clinical scenarios.[2] Due to its low cost and relatively safe adverse effect profile, the use of TXA has become increasingly widespread over time. These include posttraumatic bleeding, postpartum bleeding, bleeding after surgical procedures (such as tonsillectomy), bleeding after tooth extraction (especially in hemophilia patients), gastrointestinal (GI) bleeding, and nasal bleeding. It is also used to stop bleeding in severe bleeding scenarios following excessive fibrinolysis secondary to fibrinolytic treatments.

Although TXA can be lifesaving in certain clinical situations due to its hemostatic effect, it must be used with caution because of its adverse effect profile. While some studies in the current literature show that TXA reduced the mortality, others reported that it did not improve survival.[3,4] Considering that some publications report significant adverse effects, such as an increase in venous thromboembolic events, TXA, like all other treatments, should be used with proper cost–benefit assessments.[4] The conflicting results reported in the literature may be due to methodological differences and errors in the studies, or because the effect of TXA may yield different results in different clinical settings. In this context, it is more appropriate to identify the clinical situations where TXA is effective and to use it selectively in those cases, rather than applying it to all bleeding scenarios.

This clinical policy was prepared by the Emergency Medicine Association of Türkiye-Research Committee (EMAT-Research Committee) in 2024. It aimed to provide an evidence-based approach and guide physicians on the use of TXA in different clinical scenarios by answering important clinical questions regarding the indications for its use in emergency settings. This clinical policy focuses on the emergency department (ED) uses of the drug, rather than providing a perspective on all indications of TXA.

Methods

This clinical policy was prepared based on the "Grading of Recommendations, Assessment, Development, and Evaluations" (GRADE) approach and by evaluating the evidence in the literature.[5] The recommendations in the guideline were formulated by considering the level of evidence in the literature. In cases where the evidence was insufficient or conflicting, the relevant clinical questions were answered by voting among the members of the EMAT-Research Committee Advisory Committee, based on a majority decision. This clinical policy guideline was first published on the EMAT website (https://tatd.org.tr/arastirma/), announced through social media, and published by the associated EMAT publications. Although the option to update the EMAT clinical policy guidelines earlier in case of a significant development remains open, it was decided that they will be routinely updated every 3 years.

Determining the clinical questions

The EMAT-Research Committee identified the clinical policy topics that needed to be prioritized. Selected topics' clinical questions were gathered from the doctors nationwide. Announcements were made using the EMAT website (https://tatd.org.tr/arastirma/) and social media tools, and clinical questions were collected using Google Forms. Within the specified time frame (60 days), the collected clinical questions were ranked by the EMAT-Research Committee, oversight committee members using a 9-point Likert scale based on the priority of the need for answers (1–3: noncritical and unimportant outcomes, 4–6: noncritical but important outcomes, and 7–9: critical outcomes). As a result of the voting, it was decided that both noncritical but important outcomes and critical outcomes should be addressed based on the evidence.

Systematic literature review and selection of the studies

For each clinical question, a systematic literature review was conducted using the SCOPUS, MEDLINE, and WOS databases with the specified keywords, and the findings were shared in the relevant section of the clinical question.

The articles obtained from the systematic literature review for each clinical question were separately transferred to Rayyan software (Rayyan Systems Inc, Cambridge, MA).[6] Two blinded reviewers independently assessed whether the articles were related to the clinical question by reading the abstracts. Articles on which the two reviewers disagreed were evaluated by a third reviewer, who made the final decision.

Classification of the evidence

For each critical question, the included articles were critically reviewed by at least two researchers, and the evidence was graded using the GRADEpro software (McMaster University and Evidence Prime Inc, 2021) and the GRADE approach (very low, low, moderate, and

high levels of evidence). The risk of bias assessment was conducted using the Cochrane RoB-2 and Robins-E tools (low bias, moderate/some concerns bias, and high bias level). The risk of bias assessment was performed by two blinded reviewers. Articles where the reviewers had conflicting decisions were evaluated by a third reviewer, who made the final decision.

Determining recommendation levels from evidence levels

Based on the evidence tables created using the GRADE approach, recommendations were developed according to the appropriate recommendation levels. The levels of recommendations are defined in Table 1.

This clinical policy is a recommendation document aimed at physicians working in EDs. The scope of patients includes adults presenting to EDs, with pediatric patients excluded from the guide. The EMAT clinical policy reflects the official views of EMAT as they contain evidence-based answers and the recommendations from the current literature. However, they are not definitive and final recommendations for physicians. EMAT respects the experiences of physicians and the preferences of patients when making the final decision.

Noncritical but Important Clinical Questions

Noncritical but important clinical questions and their evidence-based answers are presented in detail below, along with a discussion of the literature. A summary of all the recommendations included in this clinical policy is shown in Table 2.

Scenario 1: Is tranexamic acid an effective and safe treatment option in the emergency management of patients with acute gastrointestinal bleeding?

Strong opposing recommendation: TXA does not provide any benefit in terms of critical clinical outcomes such as mortality and rebleeding in patients with acute GI bleeding. In addition, considering the increased risk of venous thromboembolism, as a panel, we do not recommend the use of TXA in patients with acute upper or lower GI bleeding (high level of evidence).

Moderate recommendation: None.

Weak recommendation: None.

Rationale and background for the recommendation

Acute GI bleeding is one of the common causes of significant morbidity and mortality in the ED. While endoscopic methods to identify and stop the bleeding source form the cornerstone of managing patients with GI bleeding, various treatments such as fluid resuscitation, proton pump inhibitors, somatostatin, and erythromycin can also be used in appropriate indications in the early period.[7,8] In addition to these treatments, another practice that continues to be debated is the use of TXA, an antifibrinolytic. The European Society of Gastrointestinal Endoscopy in its 2021 "*Non-variceal Upper GI Bleeding Guideline*" did not recommend the use of TXA, whereas the National Institute for Health and Care Excellence in its 2016 "*Guideline for Upper GI*

Table 1: The levels of recommendations

Level of recommendation	Recommendation
Strong recommendation	Recommendations supported by moderate to high levels of evidence, indicating that the benefits of the practice significantly outweigh the risks
	Recommendations where the majority of panel members agree that the practice is evidently beneficial, even if based on low levels of evidence, especially for critical outcomes
Moderate recommendation	Recommendations supported by conflicting moderate or high levels of evidence on whether the benefits of the practice outweigh its risks
	Recommendations supported by low or very low levels of evidence indicating that the benefits outweigh the harms
Weak recommendation	Recommendations supported by conflicting low or very low levels of evidence about whether the benefits of the practice outweigh the harms
	Recommendations where panel members disagree on the benefits of the practice
Level of recommendation	**Recommendation**
Strong recommendation	Recommendations supported by moderate to high levels of evidence, indicating that the benefits of the practice significantly outweigh the risks
	Recommendations where the majority of panel members agree that the practice is evidently beneficial, even if based on low levels of evidence, especially for critical outcomes
Moderate recommendation	Recommendations supported by conflicting moderate or high levels of evidence on whether the benefits of the practice outweigh its risks
	Recommendations supported by low or very low levels of evidence indicating that the benefits outweigh the harms
Weak recommendation	Recommendations supported by conflicting low or very low levels of evidence about whether the benefits of the practice outweigh the harms
	Recommendations where panel members disagree on the benefits of the practice

Table 2: Summaries of all recommendations

Level of recommendation	Recommendation	Level of evidence
Scenario-1: Use of TXA in patients with GI system bleeding		
Is TXA an effective and safe treatment option in the emergency management of patients with acute GI bleeding?		
Strong against recommendation	TXA treatment does not provide benefits in terms of important clinical outcomes such as mortality and rebleeding in patients with acute lower and upper GI bleeding. In addition, considering the increased risk of venous thromboembolism, as a panel, we do not recommend the use of TXA in patients with acute upper or lower GI bleeding	High
Scenario-2: Use of TXA in trauma patients		
Is TXA, given in addition to standard treatments, an effective and safe treatment option in patients with multitrauma who are bleeding or at high risk of bleeding?		
Moderate recommendation	We recommend administering IV TXA in the early period, either prehospital or on arrival at the hospital, as it is beneficial for mortality in multitrauma patients who are bleeding or at high risk of bleeding. In EDs or prehospital settings, TXA should be administered within the first 3 h after trauma, with an initial 1-g IV bolus followed by a 1-g infusion over 8 h	Moderate
Moderate recommendation	Considering the subgroup analysis results of the CRASH-3 study, which has the largest sample size related to the management of patients with TBI, we recommend the administration of TXA to patients with moderate TBI (GCS 9–12) and those with mild TBI (GCS 13–15) who have any intracranial hemorrhage, as it may offer a mortality benefit. Specifically, we suggest a 1-g IV bolus followed by a 1-g infusion over 8 h within the first 3 h after trauma for these patients	Moderate
Weak recommendation	Considering all TBI patients regardless of severity, the routine early administration of TXA does not appear to have an effect on 28-day mortality and neurological outcomes. However, given the safety profile of TXA in traumatic patients and the indirect evidence in favor of the drug from the subgroup analysis results of the CRASH-3 study, TXA administration within the first 3 h (1-g IV bolus followed by 1-g infusion over 8 h) may be considered in patients with severe TBI (GCS <9)	Low
Weak recommendation	Due to the lack of evidence on the benefits of TXA in patients with mild TBI (GCS 13–15) without intracranial hemorrhage, we do not recommend the routine use of TXA in this patient group	Very low
Scenario-3: Use of TXA in patients with nontraumatic acute intracranial hemorrhage?		
Is IV TXA, used in addition to standard care, an effective and safe treatment option in patients with nontraumatic acute intracranial hemorrhage?		
Moderate recommendation	In patients with acute nontraumatic ICH, early administration of IV TXA treatment does not lead to a significant increase in the frequency of side effects. However, it also does not have a positive effect on outcomes such as hematoma expansion, mortality, and neurological sequelae. Therefore, as panel members, we do not recommend the routine use of IV TXA treatment in patients with acute nontraumatic ICH	Moderate
Weak recommendation	In patients with acute nontraumatic SAH, early administration of IV TXA treatment does not lead to a significant increase in the frequency of side effects; however, it does not appear to have an improving effect on neurological outcomes. Therefore, we do not recommend the routine use of early TXA in the management of SAH patients	Low
Scenario-4: Use of TXA in patients with hemoptysis		
Should TXA be used in addition to standard care in patients with hemoptysis?		
Weak recommendation	TXA treatment may be considered for patients with nonmassive hemoptysis requiring hospitalization or procedures such as bronchoscopy in the ED, as no significant adverse effects have been reported	Very low
Weak recommendation	Studies evaluating the efficacy of nebulized TXA suggest that the nebulized route appears superior to other methods of delivery. However, due to the small sample sizes of the studies and the IV TXA doses being well below standard, the panel does not make a recommendation on which treatment route to prefer	Very low
Weak recommendation	Despite encountering varying doses in studies and daily practice for IV TXA administration, the panel considers it more reasonable to follow the protocol of 1-g IV bolus followed by 1-g IV infusion over 8 h, as we have more information on the safety profile of this regimen	Very low
Weak recommendation	There is insufficient evidence regarding the efficacy of TXA treatment in the management of patients with massive hemoptysis. However, considering the indirect evidence provided by low-level studies in patients with nonmassive hemoptysis, the use of TXA may be considered in cases where interventions such as embolization or bronchoscopy are likely to be delayed	Very low
Scenario-5: Use of TXA in patients with epistaxis		
Is the application of local TXA plus compression, as an alternative to standard interventions, an effective and safe treatment option in patients with epistaxis (nosebleeds)?		

Contd...

Table 2: Contd...

Weak recommendation	After the application of local TXA and external nasal compression, although there are conflicting results between anterior nasal packing and placebo applications, no result indicates that TXA treatment is inferior. Considering the discomfort associated with anterior nasal packing application and studies showing no serious adverse effects, we believe that local application of TXA could be a potential alternative for emergency physicians in the management of epistaxis in EDs	Low
Weak recommendation	Due to conflicting and insufficient evidence regarding the method of delivery for TXA application and the optimal drug dose, we do not make any specific recommendations and suggest adhering to local protocols	

TXA: Tranexamic acid, GI: Gastrointestinal, IV: Intravenous, TBI: Traumatic brain injury, ICH: Intracerebral hemorrhage, ED: Emergency department, SAH: Subarachnoid hemorrhage

Bleeding in Patients Over 16" and the American College of Gastroenterology in its 2021 "*Guideline for Upper GI and Ulcer Bleeding*" do not have a recommendation regarding the use of TXA.[7-9] However, since the efficacy of TXA has been demonstrated in different clinical scenarios, there are differing opinions among physicians about whether it can be used in patients with GI bleeding. This guide aimed to provide evidence-based recommendations to emergency physicians for the early management of acute GI bleeding with TXA in patients encountered in the EDs.

Selection of studies

A systematic literature review conducted with the pertinent keywords [Supplementary File 1] (https://turkjemergmed.com/pages/2024-4-issue-supplementary-files) identified a total of 206 studies. Out of the 28 studies related to the research question, only 13 randomized controlled trials (RCTs) were included following an assessment, as there was a sufficient number of RCT designs [Supplementary File 2] (https://turkjemergmed.com/pages/2024-4-issue-supplementary-files).

The bias assessment conducted using the Cochrane RoB-2 tool revealed that one article had a low risk of bias, two articles had a moderate risk of bias, and ten articles had a high risk of bias [Figure 1]. It was determined that the three articles with low and moderate risks of bias were not suitable for meta-analysis due to the differences in treatment arms or outcomes. When addressing the relevant clinical question, priority was given to the three RCTs with low and moderate risks of bias. A summary of the studies is presented in Supplementary File 3 (https://turkjemergmed.com/pages/2024-4-issue-supplementary-files).

Overview of studies and measures of outcome

In the existing studies, the effectiveness of TXA was primarily examined; however, there were variations in the outcome measures and the selection of comparison groups.

The largest study on this topic, and the only one with a low risk of bias, is the HALT-IT study published in 2020. The HALT-IT study, conducted in 15 countries and 164 hospitals, involved adult patients with severe upper or lower acute GI bleeding (those at risk of mortality, hypotensive, tachycardic or with signs of shock, or those requiring transfusion or urgent endoscopy and/or surgical intervention). The study compared intravenous (IV) TXA and placebo, with the primary outcome being 5-day mortality due to bleeding, whereas 24-h and 28-day mortality and rebleeding rates were also analyzed. The study, which included a total of 12,009 patients, used a modified intention-to-treat analysis, with the analyses conducted on the 11,952 patients who received the initial treatment. Bleeding-related death within 5 days of randomization occurred in 222 (4%) patients in the TXA group and in 226 (4%) patients in the placebo group and no statistically significant difference was found (relative risk [RR]: 0.99, 95% confidence interval [CI]: 0.82–1.18).[4] No statistically significant difference was found between the groups in terms of secondary outcomes (bleeding-related death within 24 h, bleeding-related death within 28 days, rebleeding within 24 h, rebleeding within 5 days, and rebleeding within 28 days).[4]

The HALT-IT study is one of the rare studies where a broad adverse effect profile was also analyzed. Arterial thromboembolic events (myocardial infarction or stroke) were found to be similar in the TXA group and the placebo group (42 [0.7%] vs. 46 [0.8%], RR: 0.92, 95% CI: 0.60–1.39). Venous thromboembolic events (deep vein thrombosis or pulmonary embolism) were found to be statistically significantly higher in the TXA group compared to the placebo group (48 [0.8%] vs. 26 [0.4%], RR: 1.85, 95% CI: 1.15–2.98). In summary, the HALT-IT study found that TXA did not provide any benefits in preventing mortality and rebleeding and was associated with harmful effects concerning venous thromboembolism. The HALT-IT authors even warned the relevant authorities that the license for TXA in GI bleeding should be reconsidered.[4]

Of the 13 RCTs examining the use of TXA in GI bleeding, two were found to have a moderate risk of bias. The first study of the two RCTs trials with a moderate risk of bias is the one conducted by Smith *et al*., which involved 100 patients and was published in 2018. This study was performed on adult patients with lower GI bleeding. In the study, TXA was administered orally and compared

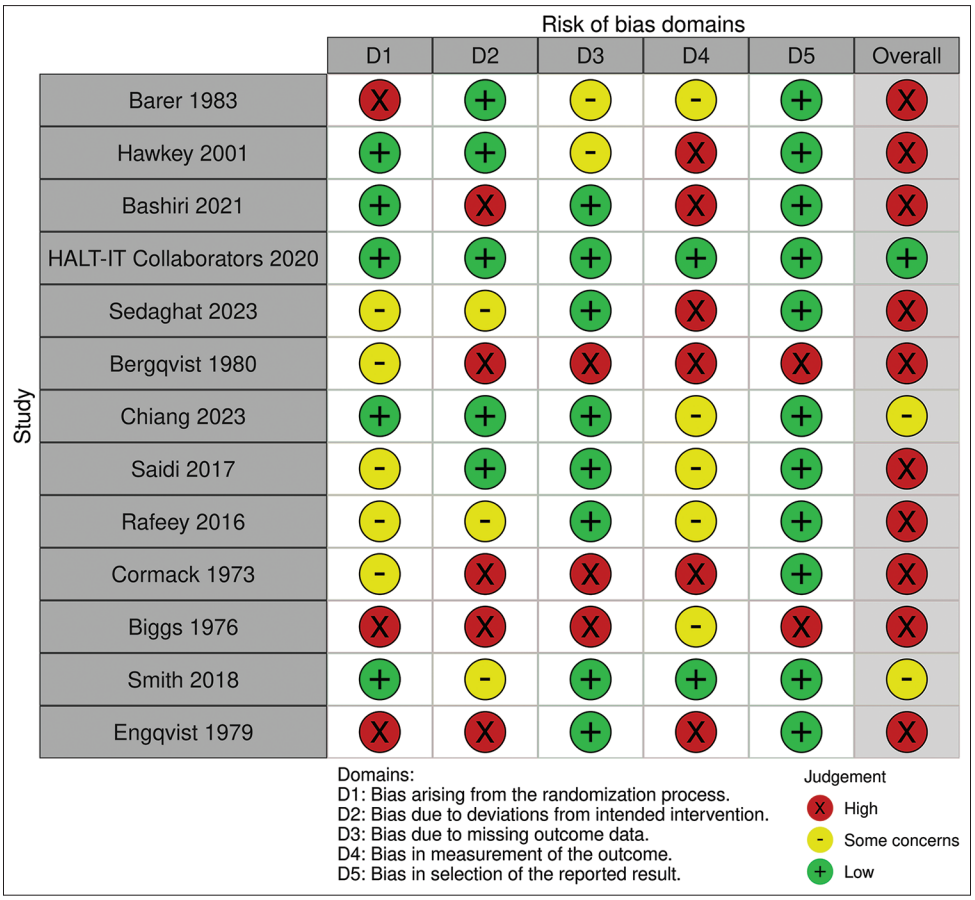

Figure 1: Traffic light charts for gastrointestinal bleeding articles (RoB-2 bias assessment)

with a placebo, evaluating endpoints such as hemoglobin drop, transfusion requirement, length of hospital stay, readmission, and complications. No statistically significant difference was found between the groups for any of the outcomes (hemoglobin drop, proportions and amounts of transfusion, length of hospital stay, readmission, and complications).[10]

In the second study with a moderate risk of bias, dated 2023 and conducted with adult patients over 20 years of age, patients with endoscopically confirmed GI bleeding were included. Early treatment failure within 4 days of the first endoscopy was evaluated as the primary outcome. In this study, which included 60 patients, early treatment failure was reported to be significantly less in the TXA group (6.7% vs. 30%, P = 0.042). Both univariate and multivariate analyses found early treatment failure to be less in the TXA group; however, it is noteworthy that the 95% CIs were quite wide in both analyses (univariate analysis: RR, 0.17; 95% CI, 0.03–0.85; P = 0.032 and multivariate analysis: RR, 0.10; 95% CI, 0.01–0.87; P = 0.037).[11]

Among the 13 RCTs investigating the use of TXA in GI bleeding, all 10 studies with a high risk of bias were conducted on patients with upper GI bleeding. In six of these, TXA was administered IV to the intervention group, in two it was administered orally (PO), and in two it was administered through a nasogastric tube. While TXA was compared with a placebo in most of these studies, one study compared it with saline and epinephrine, another with placebo and cimetidine, and yet another with lansoprazole, placebo, and a combination of TXA and lansoprazole.[7-16]

In 8 out of the 10 studies with high-risk bias, the groups were compared in terms of mortality rates. Seven studies found no difference; however, one study conducted on 775 patients found that mortality was statistically significantly lower in the TXA group compared to the placebo group (6.3% vs. 13.5%, difference in proportions: 7.2% [95% CI: 1.7–12.7]).[12,14,16-21]

In six studies, the groups were compared in terms of the need for emergency surgery, and none found a statistically significant difference between the groups.[7,8,11,13-15]

In eight studies, the groups were compared in terms of the need for blood transfusion. Five studies found no statistically significant difference, whereas two studies found a lower need for blood transfusion in the TXA group, and one study found a statistically significant higher need for blood transfusion in the TXA group.[7-10,12,14-16]

The comparison of groups in terms of rebleeding was conducted in seven studies with a high risk of bias and in one study with a low risk of bias. No statistically significant difference was found in six of these eight studies, whereas two studies found a statistically significant difference in favor of TXA.[4,7-11,15,16]

Only two studies examined the outcome of continued bleeding, and neither found a statistically significant difference.[12,19]

In three studies, the groups were compared in terms of the length of hospital stay; two found no difference, whereas one study found a statistically significant difference in favor of TXA.[13-15]

As discussed in detail above, the results of studies with low and moderate risks of bias indicate that TXA does not provide significant benefits in patients with both upper and lower GI bleedings and may even increase the risk of venous thromboembolism. Although some studies reported the benefits in favor of TXA for certain outcomes, these findings were low level of evidence due to the small sample sizes and high risk of bias in these studies. Even though the three studies with low and moderate risks of bias were not suitable for meta-analysis, the very large sample size in the HALT-IT study (12,009 patients), which has a low risk of bias, alone makes the results of this study highly significant [Supplementary File 4] (https://turkjemergmed.com/pages/2024-4-issue-supplementary-files).

Scenario 2: Is tranexamic acid, given in addition to standard care, an effective and safe treatment option in patients with multitrauma who are bleeding or at high risk of bleeding?

Strong recommendation: None.

Moderate recommendation:

1. In patients with bleeding or at high risk of bleeding due to multitrauma, we recommend administering IV TXA in the prehospital setting or early after hospital arrival, due to evidence suggesting it is beneficial for mortality. We recommend administering TXA within the first 3 h after trauma as a 1-g IV bolus followed by a 1-g IV infusion over 8 h (moderate level of evidence)
2. Considering the subgroup analysis results of the CRASH-3 study, which has the largest sample size related to the management of patients with traumatic brain injury (TBI), we recommend the administration of TXA to patients with moderate TBI (Glasgow Coma Scale [GCS] 9–12) and those with mild TBI (GCS 13–15) who have any intracranial hemorrhage, as it may offer a mortality benefit. Specifically, we suggest a 1-g IV bolus followed by a 1-g infusion over 8 h within the first 3 h after trauma for these patients (moderate level of evidence).

Weak recommendation:

3. Considering all TBI patients regardless of severity, the routine early administration of TXA does not appear to have an effect on 28-day mortality and neurological outcomes. However, given the safety profile of TXA in traumatic patients and the indirect evidence in favor of the drug from the subgroup analysis results of the CRASH-3 study, TXA administration within the first 3 h (1-g IV bolus followed by 1-g infusion over 8 h) may be considered in patients with severe TBI (GCS <9) (low level of evidence)
4. Due to the lack of evidence on the benefits of TXA in patients with mild TBI (GCS 13–15) without intracranial hemorrhage, we do not recommend the routine use of TXA in this patient group (very low level of evidence).

Rationale and background for the recommendations

Trauma remains one of the leading causes of mortality worldwide, with approximately four million deaths annually attributed to trauma according to the World Health Organization.[22] Consequently, risk stratification in trauma patients and innovations in diagnosis and treatment continue to be hot topics of current research. Notably, the impact of TXA on outcomes in various trauma populations has been investigated in large, multicenter studies that have gained significant attention in recent years. However, due to the nature of these studies, they exhibit methodological differences.

In this guideline, trauma patients are examined in two separate categories: "general trauma" and "head trauma," based on the focus of existing studies. The aim was to provide evidence-based recommendations on the effects of TXA on various outcomes in these patient groups.

Selection of studies

A literature review using keywords related to trauma and TXA identified a total of 62 studies [Supplementary File 1] (https://turkjemergmed.com/pages/2024-4-issue-supplementary-files). After applying exclusion criteria, a total of 18 RCTs were selected for evaluation[23-39] [Supplementary File 2] (https://turkjemergmed.com/pages/2024-4-issue-supplementary-files). Given the sufficient number of RCTs, it was decided that evidence-based responses to the questions in this guideline would rely solely on RCTs.

Following the bias assessment using the Cochrane RoB-2 tool, all five studies under the general trauma category were rated as low risk of bias,[23-27] whereas of the 13 studies under the head trauma category, 9 were rated as high risk of bias, 2 as moderate risk of bias, and 2 as low risk of bias[28-39] [Figure 2]. A detailed summary of the studies is presented in Supplementary File 3 (https://turkjemergmed.com/pages/2024-4-issue-supplementary-files).

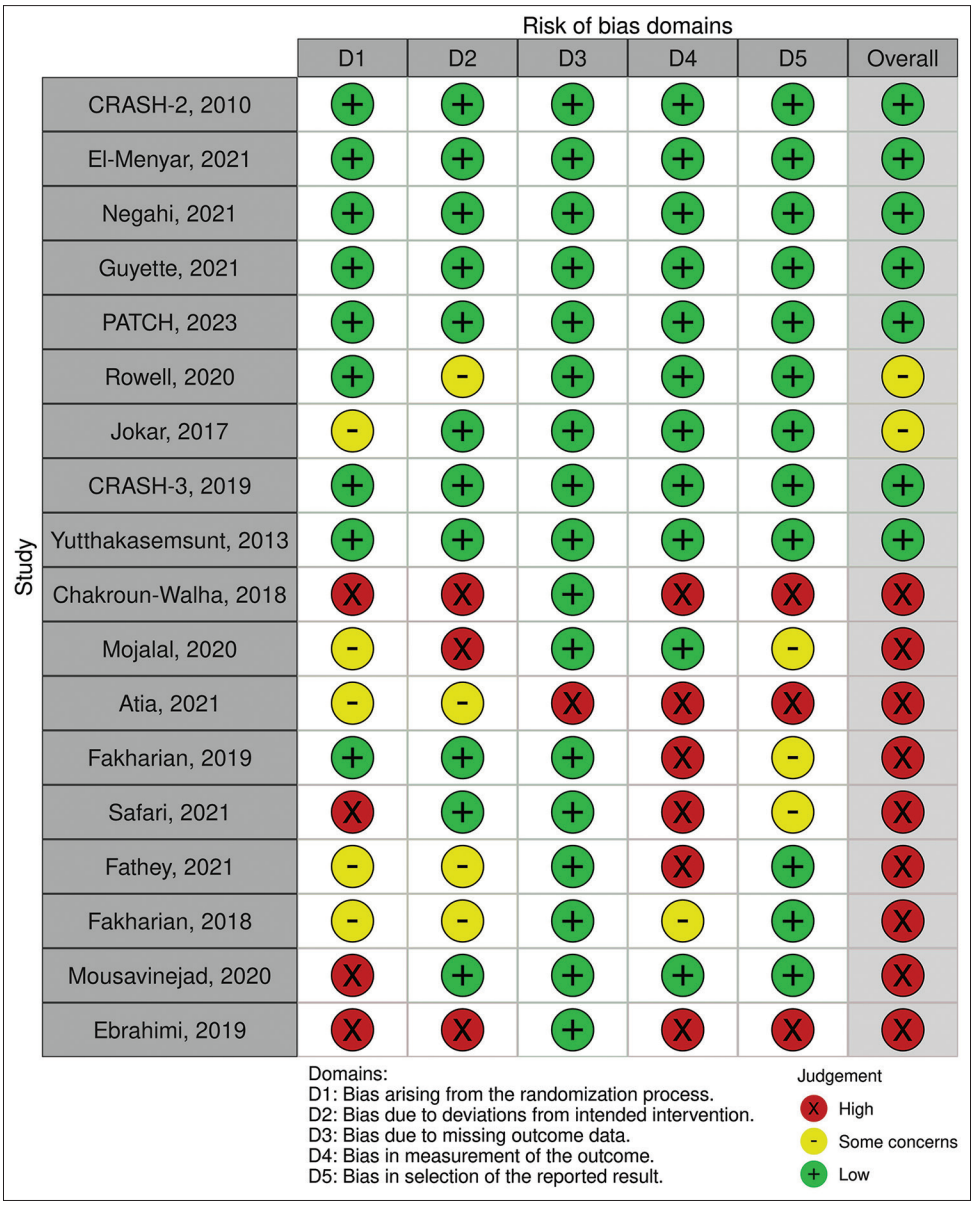

Figure 2: Traffic light charts for studies on the use of tranexamic acid in patients with trauma (RoB-2 bias assessment)

In conclusion, the 18 RCTs were discussed separately under the headings of general trauma (5 studies) and head trauma (13 studies).

Scenario 2a: Is tranexamic acid, in addition to standard care, an effective and safe treatment option in patients with general major trauma who are bleeding or at high risk of bleeding?

Overview of studies and measures of outcome

Five RCTs from the literature focused directly on general trauma patients, all of which had low risk of bias.[23-27] While these studies did not explicitly exclude head trauma as a criterion, they generally excluded severe head injuries, such as penetrating head trauma, exposed brain tissue, or patients whose most significant area of trauma was the head. The treatment protocols in these studies typically involved comparing TXA to a placebo, with El-Menyar *et al*.'s study investigating the effect of continuing a hospital infusion dose of 1 g TXA following a prehospital routine dose of 1 g TXA IV bolus.[23-27] All five studies reported 28-day mortality, blood product transfusion requirements, and thromboembolic event rates as outcome measures.

The largest study reporting 28-day mortality in the general trauma population is the CRASH-2 trial, published in 2010, which analyzed data from a total of 20,127 patients.[23] The results showed that 14.5% of patients in the TXA group and 16% in the placebo group had all-cause mortality, with a statistically significant difference favoring TXA (RR: 0.91; 95% CI: 0.85–0.97; $P = 0.0035$). Importantly, mortality due to bleeding was

significantly lower in the TXA group (RR: 0.85; 95% CI: 0.76–0.96; $P = 0.0077$).

When comparing the need for blood product transfusion and the median number of blood product units transfused, the CRASH-2 study found no significant differences between the groups (RR: 0.98; 95% CI: 0.96–1.01; $P = 0.21$ and $P = 0.59$, respectively).

In terms of fatal and nonfatal vascular occlusive adverse events, 1.7% of patients in the TXA group and 2% in the placebo group experienced such events in the CRASH-2 study, with the difference not being statistically significant (RR: 0.84; 95% CI: 0.68–1.02; $P = 0.084$).

Another study, considered to have a low risk of bias, is the PATCH study conducted by the PATCH study group in 2023 with 1300 patients. The primary endpoint was the comparison of the 6-month Glasgow Outcome Scale-Extended (GOSE) score. No difference was found in the primary outcome between the placebo group and the treatment group who received a prehospital 1-g IV bolus of TXA and in-hospital 1-g maintenance dose (RR, 1.00; 95% CI, 0.90–1.12; $P = 0.95$). When secondary outcomes were examined, a 28-day mortality rate of 17.3% was observed in the TXA group compared to 21.8% in the placebo group, and the difference between the groups was found to be statistically significant (RR: 0.79, 95% CI: 0.63–0.99). When adverse effects were examined, vascular occlusive events were observed in 23.6% of the TXA group and 19.7% of the placebo group, and the difference was not significant (RR: 1.20, 95% CI: 0.97–1.48).[27]

In Guyett's 2021 STAAMP study, conducted with 894 general trauma patients, four treatment arms were compared: three different TXA protocols in the intervention group and a placebo group. Patients underwent separate randomization at three different times: A 1-g TXA bolus or placebo bolus pre-hospital, a 1-g bolus or placebo bolus in-hospital, and a 1-g TXA or placebo infusion over 8 h in-hospital. Accordingly, four distinct treatment arms were established: the control arm, which received a placebo at all three phases; the reduced TXA arm, which received only a prehospital bolus of TXA; the standard TXA arm, which received a prehospital bolus followed by an 8-hour in-hospital infusion of TXA; and the repeat-dose TXA arm, which received a total of 3 g of TXA administered across all three phases.[25] When comparing patients who received TXA regardless of dose with those who did not, no difference was reported in the 30-day mortality outcome between the TXA and the placebo groups (8.1% vs. 9.9%, respectively; difference, −1.8; 95% CI, −5.6% to 1.9%; $P = 0.17$). Similarly, when subgroups receiving 1 g and 2 g of TXA were compared with the placebo, no difference in mortality was observed. However, in the 30-day mortality outcome, a significant difference was observed in the group receiving a total of 3 g of TXA compared to the placebo group (7.3% vs. 10.0%, respectively; difference, −2.7%; 95% CI, −5.0% to −0.4%; $P = 0.04$). No significant difference was observed between the groups in terms of pulmonary embolism, deep vein thrombosis, and blood product requirements ($P = 0.78$, $P = 0.83$, and $P = 0.97$, respectively).

In contemporary practice, the TXA protocol involves a 1-g bolus followed by a 1-g infusion over 8 h. A meta-analysis was performed, evaluating mortality outcomes using the main results of the CRASH-2 and PATCH studies, along with data from the STAAMP study's standard TXA dose treatment arm and control group, and it indicates that early administration of TXA reduces 30-day mortality (RR: 0.90, 95% CI: 0.84–0.95). Due to differences in dosage and administration of TXA, mortality data from the other two studies were included as a subgroup in the meta-analysis to assess their impact on the main outcomes.[24,26] When the data of these two studies were included, it was found that they did not significantly alter the primary results, confirming that TXA treatment reduces 30-day mortality (RR: 0.90, 95% CI: 0.84–0.95) [Figure 3]. Similarly, a meta-analysis using data from the PATCH and CRASH-2 studies shows that TXA treatment did not lead to an increased frequency of vascular occlusive events compared to placebo [Figure 4].

The results of these five RCTs demonstrate that the administration of TXA in the acute phase can significantly contribute to reducing mortality in general trauma patients. In addition, it can be inferred that TXA is a safe drug in terms of its adverse effect profile. However, as a panel, we particularly want to emphasize that the patient populations in these studies were those with hemorrhagic shock or at risk of hemorrhagic shock. Therefore, we recommend TXA treatment not for all multitrauma patients but specifically for those where mortality is particularly feared to be due to hemorrhage, with a moderate level of recommendation (Panel note: The recommendation level is set to moderate due to the relatively small effect size of the benefit [RR: 0.90, 95% CI: 0.85–0.96]).

Scenario 2b: Is tranexamic acid, in addition to standard care, an effective and safe treatment option in patients with traumatic brain injury?

Overview of studies and measures of outcome

In the literature review conducted to address this clinical question, 4 out of 13 RCTs were found to have a low or moderate risk of bias. Therefore, these four studies were given more weight in answering the clinical question. Studies are summarized in Supplementary File 3 (https://turkjemergmed.com/

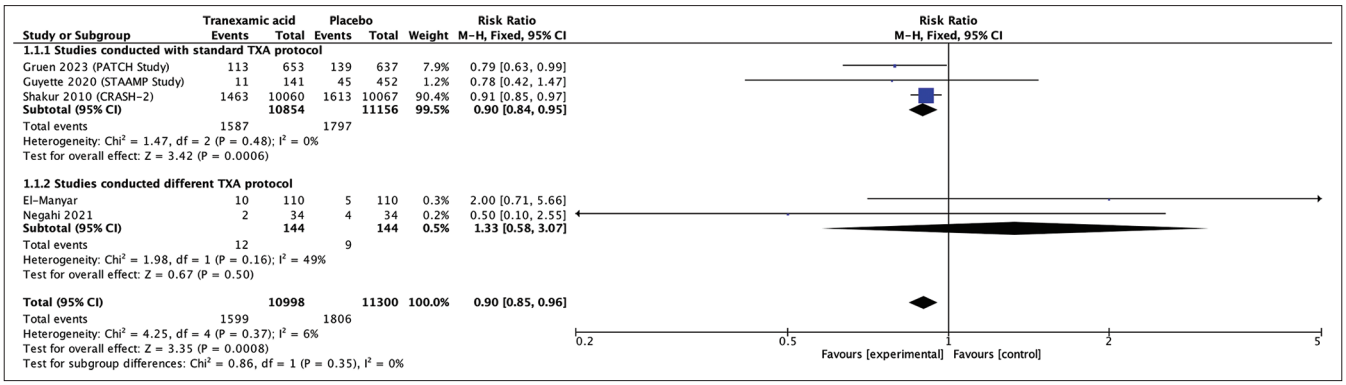

Figure 3: Forest plot illustrating the effectiveness of tranexamic acid treatment in 1-month mortality outcomes in general multitrauma patients with bleeding or high risk of bleeding. *Standard tranexamic acid (TXA) Protocol: 1-g TXA bolus followed by a 1-g TXA infusion over 8 h

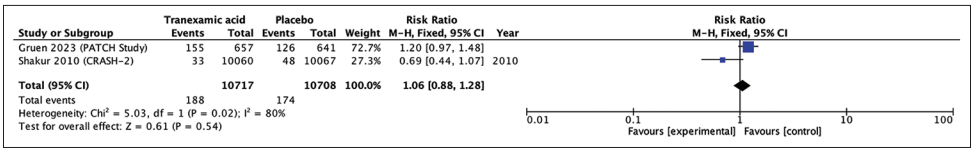

Figure 4: Forest plot illustrating the frequency of vascular occlusive events with tranexamic acid treatment in general multitrauma patients with bleeding or high risk of bleeding

pages/2024-4-issue-supplementary-files). Except for one, all studies with a low or moderate risk of bias were designed with patients suffering from moderate-to-severe head trauma.[3,28,29] Only one study had the inclusion criterion of detecting intracranial bleeding after head trauma.[30] Most studies reported 28-day mortality, 6-month favorable neurological outcomes, and thromboembolic complications.

The largest study on this topic is the CRASH-3 trial, published in 2019, which compared a protocol of a 1-g bolus of TXA followed by a 1-g infusion over 8 h with a placebo.[3] In this study, 12,639 patients were randomized, and treatment was started within the first 3 h for 9,127 of these patients. No significant difference was reported between the groups in terms of the primary outcome of 28-day mortality (TXA: 18.5%, placebo: 19.8%, RR: 0.94, 95% CI: 0.86–1.02). When the analysis excluded patients with a GCS of 3 and no pupillary response, the difference between the groups increased slightly but did not reach statistical significance (TXA 12.5% vs. placebo 14%, RR: 0.89, 95% CI: 0.80–1.00). When this analysis was repeated with only mild to moderate TBI patients (GCS 9–15), the authors reported a statistically significant reduction in mortality in favor of TXA (TXA 5.8% vs. placebo 7.5%, RR: 0.78, 95% CI: 0.64–0.95).

When evaluating the secondary outcomes of the CRASH-3 study, specifically 28-day functional survival, the mean Disability Rating Scale (DRS) score for the TXA group was calculated as 4.99 (±7.6), compared to 5.03 (±7.6) for the placebo group, with no significant difference found between the groups. Similarly, when comparing all vascular occlusive events, no difference was reported between the groups (RR: 0.98, 95% CI: 0.74–1.28).

Another RCT with a low risk of bias is the study by Yutthakasemsunt *et al*., conducted in 2013, which randomized a total of 238 head trauma patients and compared the rates of progressive intracranial hemorrhage as the primary outcome.[29] This study reported no significant difference between the groups for the primary outcome (RR: 0.65, 95% CI: 0.4–1.05). The secondary outcomes of this study included unfavorable GOS outcome and mortality, and no significant differences were found between the groups for these outcomes either (RR: 0.76, 95% CI: 0.46–1.27, and RR: 0.69, 95% CI: 0.35–1.39, respectively).

In the 2020 study by Rowell *et al*., which has a moderate risk of bias, a total of 966 patients with moderate-to-severe TBI were randomized, and two different TXA treatment protocols were compared with each other and with a placebo.[28] The first treatment protocol involved a 1-g IV bolus of TXA followed by a 1-g IV infusion over 8 h, whereas the second protocol involved the total dose of 2 g of TXA given as an IV bolus, and the last protocol was a placebo. The primary outcome was defined as having a GOSE score >4 at 6 months, and the two TXA intervention arms were combined for analysis. According to the results, there was no significant difference between the combined TXA group and the placebo group in terms of GOSE >4 at 6 months, 28-day mortality, 6-month DRS, and intracranial hemorrhage expansion ($P = 0.16$, $P = 0.26$, $P = 0.29$, and $P = 0.16$, respectively). Although

the study compared adverse effects among the three arms, no statistical analysis was performed. Accordingly, thromboembolic adverse effects were observed in 4% of the bolus + maintenance group, 9% of the bolus-only group, and 10% of the placebo group.

The data from the placebo arm of Rowell *et al*.'s study, along with the mortality and vascular occlusive data from the arm using the 1-g TXA bolus followed by an 8-h infusion protocol commonly used in daily practice, were included in a meta-analysis of 28-day mortality and vascular occlusive outcomes, together with the main results of the CRASH-3 and Yutthakasemsunt *et al*.'s studies. When evaluating the meta-analysis results, it was found that routine TXA treatment had no effect on 28-day mortality for all TBI patients (RR: 0.85, 95% CI: 0.62-1.17). Regarding the frequency of vascular occlusive events, TXA treatment did not result in an additional increased risk (RR: 0.63, 95% CI: 0.25–1.58) [Figures 5 and 6].

Another study with a moderate risk of bias that differs from other studies in terms of patient population and outcomes is the 2017 study by Jokar *et al.*, which randomized a total of 80 patients.[30] This study included only patients with intracranial hemorrhage and analyzed the effect of a 1-g IV bolus followed by a 1-g IV maintenance dose of TXA on hemorrhage volume expansion. The results showed significantly less hemorrhage expansion in patients treated with TXA ($P < 0.001$).

The other nine RCTs with a high risk of bias had primary outcomes that differed from the aforementioned studies and generally investigated the effects of TXA treatment on the expansion of detected hemorrhagic lesions. In addition, there is significant heterogeneity in the patient populations. Finally, there is heterogeneity in the reported effectiveness of TXA treatment on primary outcomes; three studies reported significant differences in the investigated primary outcomes, whereas the remaining studies reported no differences in primary outcomes [Supplementary File 3] (https://turkjemergmed.com/pages/2024-4-issue-supplementary-files).

Scenario 3: Is intravenous tranexamic acid, used in addition to standard care, an effective and safe treatment option in patients with nontraumatic acute intracranial hemorrhage?

Strong recommendation: None.

Moderate recommendation: In patients with acute nontraumatic intracerebral hemorrhage (ICH), early administration of IV TXA treatment does not lead to a significant increase in the frequency of adverse effects. However, it also does not have a positive effect on outcomes such as hematoma expansion, mortality, and neurological sequelae. Therefore, as panel members, we do not recommend the routine use of IV TXA treatment in patients with acute nontraumatic ICH (moderate level of evidence).

Weak recommendation: In patients with acute nontraumatic subarachnoid hemorrhage (SAH), early administration of IV TXA treatment does not lead to a significant increase in the frequency of adverse effects; however, it does not appear to have an improving effect on neurological outcomes. Therefore, we do not recommend the routine use of early TXA in the management of SAH patients (low level of evidence).

Rationale and background for the recommendations

Although acute intracranial hemorrhages are not as frequently encountered as ischemic stroke, they have similar mortality rates and a higher risk of developing permanent disability.[40] Various studies have investigated the efficacy of antifibrinolytic treatments, particularly early administration of TXA, alongside standard treatments to reduce these adverse effects. However, these studies exhibit differences in their primary outcome measures, main results, and

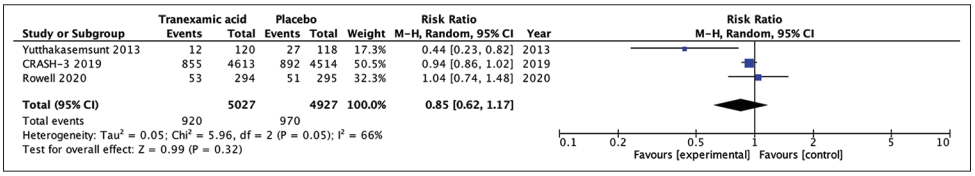

Figure 5: Forest plot illustrating the effectiveness of tranexamic acid treatment in 1-month mortality outcomes in traumatic brain injury patients

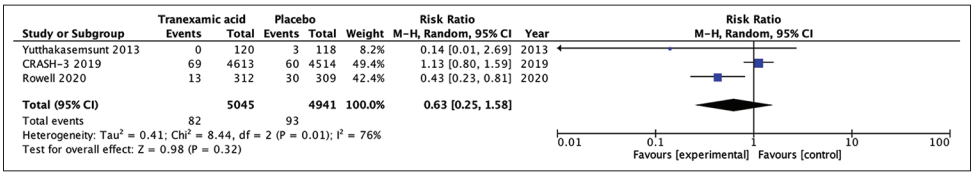

Figure 6: Forest plot illustrating the frequency of vascular occlusive events with tranexamic acid treatment in traumatic brain injury patients

methodologies. In this guideline, ICH, SAH, and postthrombolytic hemorrhage in ischemic stroke patients are examined under separate headings. The aim is to provide evidence-based recommendations on the use of TXA for emergency physicians managing these patient groups in the early period.

Selection of studies

A systematic literature review was conducted using the relevant keywords for all nontraumatic intracranial hemorrhages (SAH and ICH) [Supplementary File 1] (https://turkjemergmed.com/pages/2024-4-issue-supplementary-files), resulting in 14 studies. Due to the sufficient number of RCTs among the articles related to ICH, only the eight articles designed as RCTs were included for further evaluation [Supplementary File 2] (https://turkjemergmed.com/pages/2024-4-issue-supplementary-files).[41-48] Bias assessment using the Cochrane RoB-2 tool revealed that seven articles had a low or moderate risk of bias, whereas one article had high risk of bias [Figure 7]. Due to the sufficient number of RCTs related to SAH, a total of six studies were considered for the evaluation.[49-54] In the bias assessment of these six studies using the RoB-2 tool, four articles were found to have high risk of bias, whereas two studies had a low or moderate risk of bias [Figure 8]. Summaries of the studies' populations, treatment protocols, primary and secondary endpoints, and main findings are presented in Supplementary File 3 (https://turkjemergmed.com/pages/2024-4-issue-supplementary-files).

Scenario 3a: Is intravenous tranexamic acid, used in addition to standard care, an effective and safe treatment option in patients with nontraumatic acute intracerebral hemorrhage?

Overview of studies and measures of outcome

In the current studies, the efficacy of the TXA protocol, consisting of a 1-g IV bolus followed by a 1-g IV infusion over 8 h, has been primarily investigated in patients with acute ICH. Only in the 2023 study by Arumugam *et al*.,[45] in addition to the standard 2-g TXA protocol, a third group was included using a protocol of a 1-g IV bolus followed by a 2-g IV infusion over 8 h. However, in this guideline, only the data from the 2-g protocol of the relevant study are used. Considering the study populations, all studies, except for the one by Polymeris *et al*., have defined patients with acute ICH as the primary inclusion population and excluded those using anticoagulation. In contrast, the study by Polymeris *et al*. targeted the patients with acute ICH associated with new oral anticoagulants (NOACs).[46] Therefore, the data from this study have been discussed separately throughout the guideline. There are differences in the endpoints of the current studies. Thus, mortality, neuroclinical outcomes (modified Rankin Scale [mRS]), hematoma growth, and safety endpoints reported in the studies have been analyzed under separate headings with common studies reporting the relevant outcomes.

90-day modified Rankin Scale

There are four studies suitable for meta-analysis that compared the neuroclinical outcomes of TXA

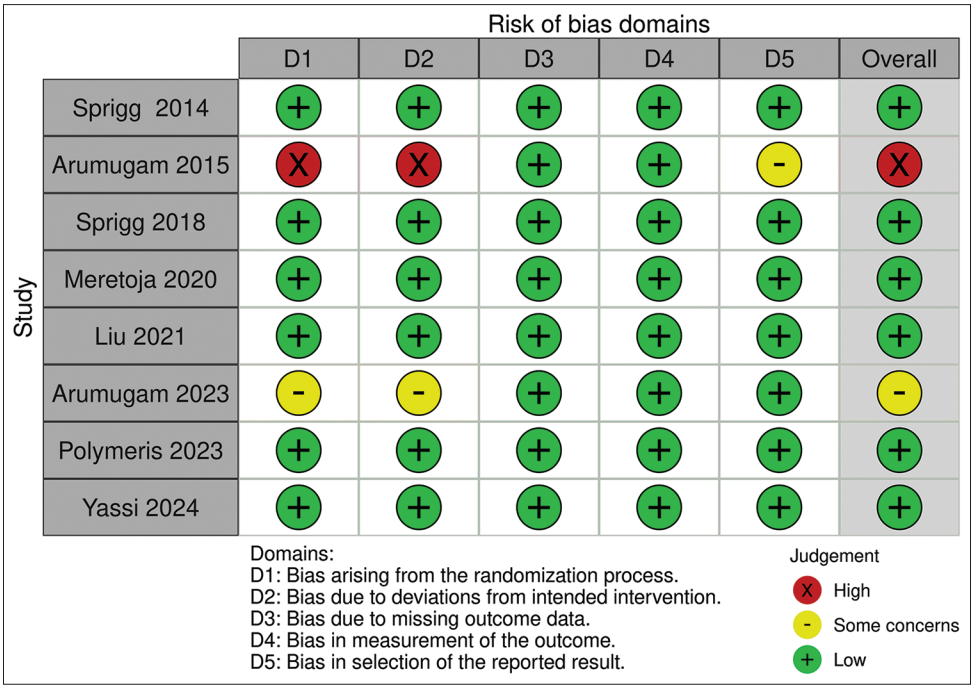

Figure 7: Traffic light charts of articles on the use of tranexamic acid in patients with nontraumatic intracerebral hemorrhage (RoB-2 bias assessment)

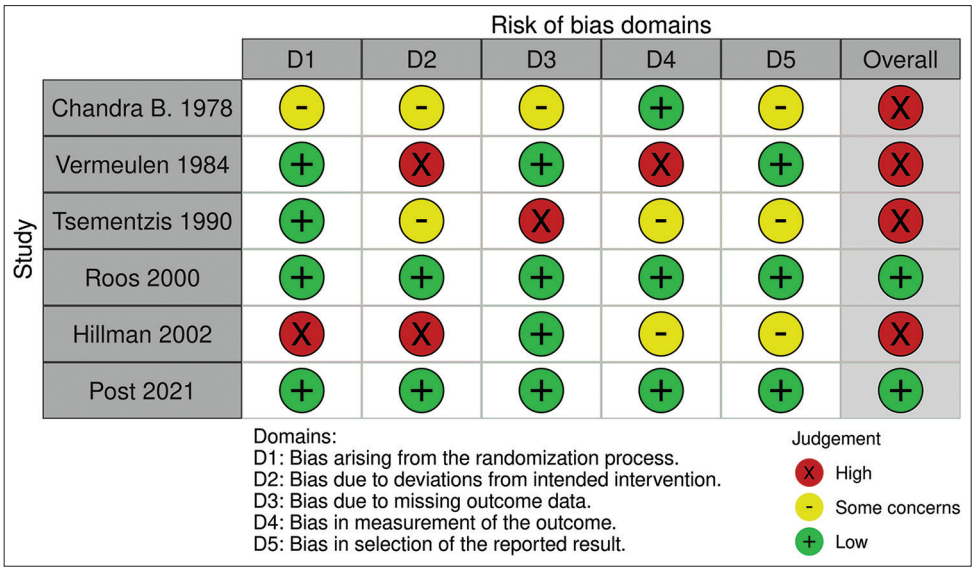

Figure 8: Traffic light charts of articles on the use of tranexamic acid in patients with nontraumatic subarachnoid hemorrhage (RoB-2 bias assessment)

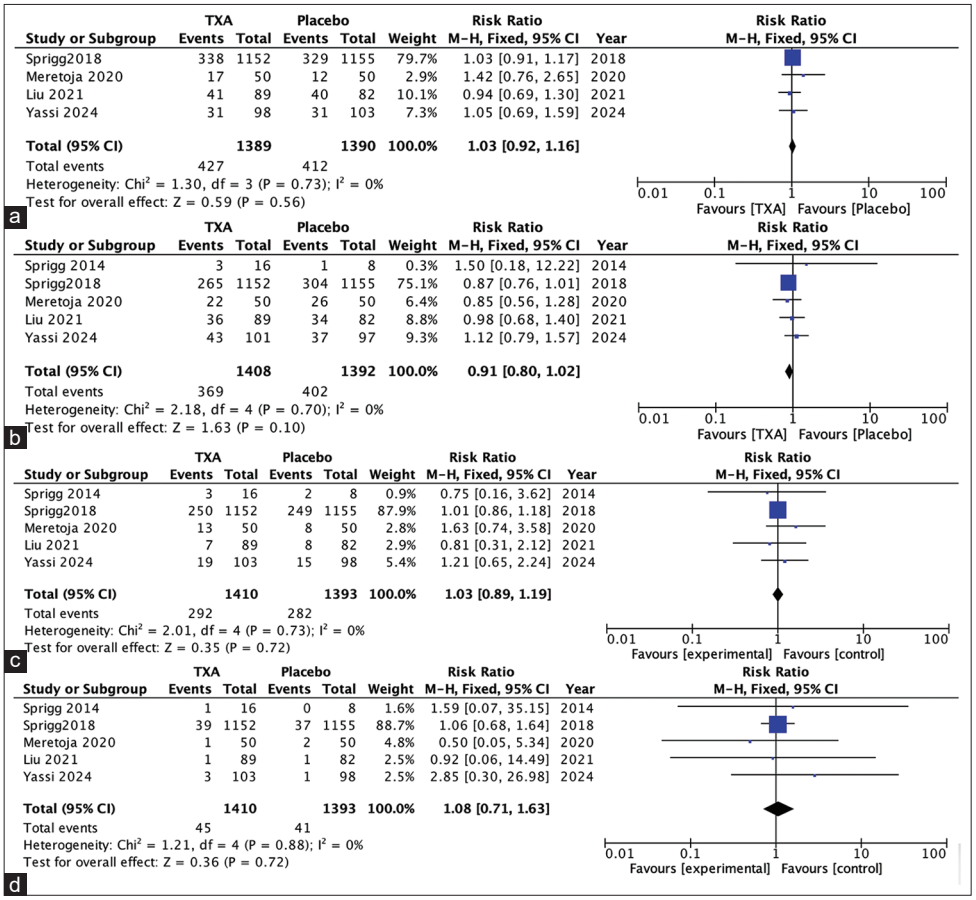

Figure 9: (a-d) Forest plots demonstrating the efficacy of tranexamic acid treatment in nontraumatic intracerebral hemorrhage patients for outcomes including mRS, hematoma growth, 90-day mortality, and thromboembolic events

versus placebo in patients with acute ICH, reporting mRS scores at day 90.[42-44,48] According to these studies, TXA treatment in acute ICH patients did not exhibit a significant difference in terms of patients with mRS scores below 3 or those returning to their baseline mRS scores by day 90 (RR: 1.03, 95% CI: 0.92–1.16) [Figure 9a]. Among the studies not included in the meta-analysis due to differences in outcome measures or population differences, Arumugam *et al*.'s TANICH-II study reported mRS values at day 30 and

found no statistically significant difference between the TXA and the placebo groups.[45] In Sprigg *et al*.'s 2014 pilot study, day 90 mRS values were reported as mean and standard deviation, showing no difference between the groups (mRS: 3.6 ± 1.9 vs. 3.4 ± 2.1; P = 0.82).[41] Finally, in the TICH-NOAC study involving acute ICH patients associated with NOAC, Polymeris *et al*. also demonstrated no significant difference in day 90 mRS values between the TXA and the placebo groups.[46]

Hematoma growth

In most studies, the expansion of the initially identified hematoma on follow-up CT at approximately 24 h was reported as a significant outcome. Hematoma expansion was defined as a 33% increase in hematoma volume or a net growth of 6 ml on the follow-up CT compared to the initial CT. A meta-analysis of studies reporting the proportion of cases with hematoma expansion between the treatment groups indicates that TXA treatment did not result in a significant difference compared to placebo in terms of hematoma expansion (RR: 0.91, 95% CI: 0.80–1.02) [Figure 9b].[41-44,48] Among the studies not included in the meta-analysis due to the differences in outcome measures or population differences, Arumugam *et al*.'s 2023 TANICH-II study also showed no statistically significant difference in hematoma growth on follow-up CT between the TXA and the placebo groups.[45] Similarly, in the TICH-NOAC study involving acute ICH patients associated with NOAC, Polymeris *et al*. found no superiority of TXA over placebo in terms of the proportion of patients with hematoma expansion.[46]

90-day mortality

Among the eight studies examining the efficacy of TXA treatment in patients with acute ICH, five studies clearly reported 90-day mortality data.[41-44,48] When the pooled mortality data from these five studies were analyzed, it was evident that TXA treatment did not reduce mortality in acute ICH patients compared to placebo (RR: 1.03, 95% CI: 0.89-1.19) [Figure 9c]. Similarly, in the TICH-NOAC study involving acute ICH patients associated with NOAC, Polymeris *et al*. demonstrated that TXA treatment did not reduce mortality in this patient group either.[46]

Thromboembolic events

The most concerning safety outcome of IV TXA treatment is the increased risk of thromboembolic events. Five of the previous studies clearly reported this adverse effect.[41-44,48] According to the results of the meta-analysis of these five studies, IV TXA did not increase the risk of thromboembolic events compared to placebo [Figure 9d]. Similarly, in the TICH-NOAC study where acute ICH patients associated with NOAC were investigated, Polymeris *et al*. found that TXA treatment did not increase the frequency of thromboembolic events in this patient group either.[48]

Scenario 3b: Is intravenous tranexamic acid, used in addition to standard care, an effective and safe treatment option in patients with subarachnoid hemorrhage?

Overview of studies and measures of outcome

The majority of the RCTs found in the literature review was conducted in 1990 or earlier and have a high risk of bias. Moreover, the TXA treatment protocols used in these studies, such as 6-g or 9-g doses, differ from the 2-g treatment protocols used today (1-g bolus followed by 1-g infusion over 8 h). In addition to differences in TXA treatment protocols, the diagnostic methods and standard care treatments in studies from approximately 30 years ago differ from those used today, making direct comparisons with current studies challenging. Therefore, a meta-analysis of existing studies was not preferred in this guideline. Instead, a review of the literature focusing on recent studies with a low risk of bias was preferred.

One of the two studies with a low risk of bias is by Post *et al*. in 2021, and the other is by Roos *et al*. in 2000.[49,50] In the study by Post *et al*., the intervention arm, which involved administering 1-g of TXA as a bolus followed by 1-g every 8 h until endovascular treatment (up to a maximum of 24 h), was compared with placebo in patients diagnosed with aneurysmal SAH. The primary outcome of the study was favorable clinical outcome (mRS score of 0–3 at 6 months). Rebleeding was determined as the secondary outcome. No significant difference was found in both the outcomes. However, a difference was observed in favor of TXA treatment in the outcome of excellent clinical outcome (mRS score of 0–2 at 6 months [OR: 0.74, 95% CI: 0.57–0.96]).[49] The second study with a low risk of bias by Roos *et al*. involved the patients with aneurysmal SAH and compared the administration of 1-g IV bolus every 4 h for the 1st week (total daily dose of 6 g) followed by 1.5-g per oral every 6 h (total daily dose of 6 g) during the 2nd and 3rd weeks with placebo in terms of various outcomes. The primary outcome was the Glasgow Outcome Scale (GOS) at the end of 3 months, where no significant difference was found. However, a difference was reported in favor of TXA in terms of rebleeding (19% vs. 33%, OR: 0.58, 95% CI: 0.42–0.80). No difference was observed in adverse outcomes, including thromboembolic events, in both the studies.

However, when considering studies with a high risk of bias, although no differences were observed in outcomes such as mRS or GOS, the risk of rebleeding was reported to be reduced in favor of TXA. In addition, these studies indicate that there is no increase in the frequency of adverse effects with TXA treatment.

Scenario 4: Is tranexamic acid, used in addition to standard care, an effective and safe treatment option in emergency department management of hemoptysis patients?

Strong recommendation: None.

Moderate recommendation: None.

Weak recommendation:

1. TXA treatment may be considered for patients with nonmassive hemoptysis requiring hospitalization or procedures such as bronchoscopy in the ED, as no significant adverse effects have been reported (very low evidence level)
2. Studies evaluating the efficacy of nebulized TXA suggest that the nebulized route appears superior to other methods of delivery. However, due to the small sample sizes and the IV TXA doses being well below standard, the panel does not make a recommendation on which treatment route to prefer (very low evidence level)
3. Despite encountering varying doses in studies and daily practice for IV TXA administration, the panel considers it more reasonable to follow the protocol of 1-g IV bolus followed by 1-g IV infusion over 8 h, as we have more information on the safety profile of this regimen (very low evidence level)
4. There is insufficient evidence regarding the efficacy of TXA treatment in the management of patients with massive hemoptysis. However, considering the indirect evidence provided by low-level studies in patients with nonmassive hemoptysis, the use of TXA may be considered in cases where interventions such as embolization or bronchoscopy are likely to be delayed (very low evidence level).

Rationale and background for the recommendations

Hemoptysis, often caused by malignancy, infection, or bronchiectasis, is classified as massive or nonmassive. In the literature, there are various definitions for massive hemoptysis, ranging from 100 ml/24 h to 1000 ml/24 h.[55] Particularly in cases exceeding 300 ml/24 h, the mortality rate can reach up to 80%.[56] Certain medications are frequently used to stop or reduce bleeding before interventional treatments such as interventional bronchoscopy. TXA, an antifibrinolytic drug, is commonly used for this purpose. However, the role of TXA in the treatment of nonmassive hemoptysis remains a topic of debate. Although various studies focus on the efficacy of TXA in the management of patients with hemoptysis, a significant portion of these studies consist of observational studies or RCTs with differing outcome measures and significant methodological variations.[57,58] Therefore, this guideline aims to provide evidence-based recommendations for the early management of patients with hemoptysis, particularly for ED physicians.

Selection of studies

A systematic literature review using all the relevant keywords related to hemoptysis [Supplementary File 1] (https://turkjemergmed.com/pages/2024-4-issue-supplementary-files) resulted in 621 studies. Due to the sufficient number of RCTs among the articles related to hemoptysis, only five RCTs were selected for further evaluation [Supplementary File 2] (https://turkjemergmed.com/pages/2024-4-issue-supplementary-files). Bias assessment using the Cochrane RoB-2 tool identified two studies with moderate risk of bias and three studies with high risk of bias [Figure 10]. Summaries of the studies, including populations, treatment protocols, primary and secondary outcome measures, and main results, are presented in Supplementary File 3 (https://turkjemergmed.com/pages/2024-4-issue-supplementary-files).

Overview of studies and measures of outcome

Three of the five existing studies have a high risk of bias, with significant methodological differences in the methods used to measure outcomes, the preparations used in interventions, and their methods of application. Therefore, a meta-analysis of the existing studies was not preferred in this guideline. Instead, a review of the literature focusing on recent studies with a low risk of bias was preferred.

The five RCTs that included patients with nonmassive hemoptysis were generally designed with the outcomes targeting the cessation of bleeding or the amount of bleeding, but no standard exists in this regard. There were differences in the timeframes for cessation of bleeding, such as 30 min and 5 days, as well as varying definitions, including observing the cessation of bleeding through bronchoscopy or external observation, evaluating daily bleeding frequency, or assessing the amount of bleeding using a visual analog scale (VAS).

In the study conducted by Tscheikuna *et al*. in 2002 investigating patients with nonmassive hemoptysis, a total of 46 patients were included. The intervention group received oral TXA capsules, two capsules three times a day (n = 21) and was compared with a placebo control group (n = 25). It was stated that patients with massive hemoptysis who might require intervention were excluded from this RCT, and massive hemoptysis was defined as >500 mL/day. It should be noted that this threshold is higher than that used in many other studies. At the end of the study (day 7), four patients (19%) in the TXA group and seven patients (28%) in the placebo group still had hemoptysis, with no statistically significant difference reported (P = 0.514). The sample was divided into three groups based on the amount of hemoptysis and analyzed separately, with results similar to the main analysis. However, it was noted that the sample size was very small for subgroup analysis.[59]

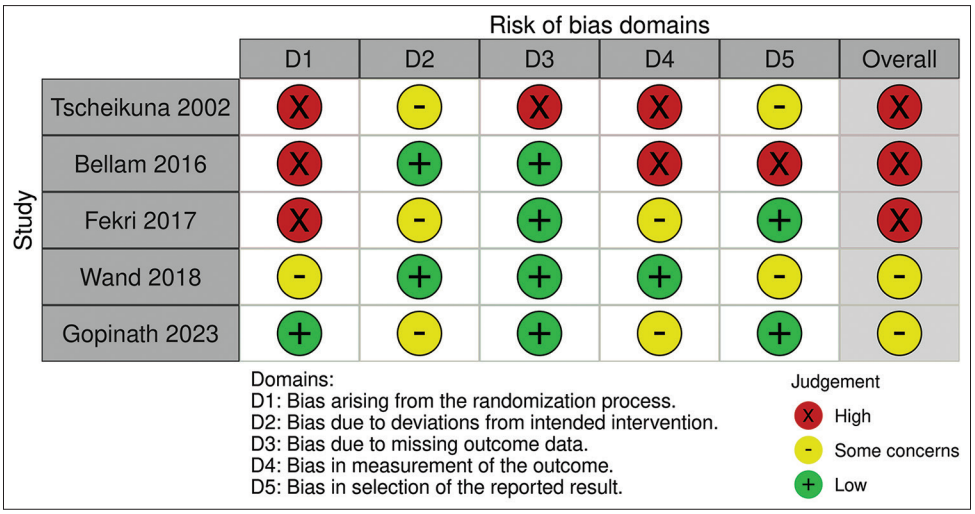

Figure 10: Traffic light charts of studies on the use of tranexamic acid in patients with hemoptysis (RoB-2 bias assessment)

In the RCT by Bellam *et al*. in 2016, which included a total of 66 patients, TXA treatment was applied intravenously. The study included ongoing acute hemoptysis cases. The intervention arm used a loading dose of 1-g IV TXA diluted with 10 mL of 0.9% normal saline, followed by an 8-h IV infusion of 1-g TXA in 500 mL of 0.9% normal saline. The placebo arm used the same protocol without TXA. The study analyzed the frequency and amount of hemoptysis as the outcome. The severity of hemoptysis measured by VAS score was 14.7 ± 15.5 mm in the treatment group and 31.3 ± 22.1 mm in the placebo group, exhibiting a statistically significant difference ($P < 0.001$). However, no differences were found between the two groups in terms of daily number of hemoptysis and volume of hemoptysis assessed on the first and second days. Although the TXA group was found superior in terms of VAS score, the study was considered high-risk for bias.[60]

In the 2017 study by Fekri *et al*., TXA (500 mg diluted in 20 mL normal saline) was directly applied to the bleeding site under bronchoscopy in the intervention group, whereas adrenaline (1 mg diluted in 20 mL normal saline) was applied in the control group. This RCT included a total of 50 patients, and the bleeding cessation time was noted by directly observing clot formation through bronchoscopy. It was reported that TXA (133.9 ± 77.9 s) was as effective as adrenaline (136.7 ± 83.5 s), ($P = 0.908$). In addition, no difference was found in the number of applications required to stop the bleeding.[61]

In the 2018 RCT by Wand *et al*., the efficacy of nebulized TXA was investigated. A total of 47 patients admitted to the department of pulmonology were included, with the intervention group receiving 500 mg/5 mL of nebulized TXA three times a day and the control group receiving the same volume and frequency of normal saline. It was reported that on the 5th day, bleeding had stopped in 96% of the TXA group compared to 50% of the placebo group ($P < 0.0005$). In addition, the volume of hemoptysis was lower in the TXA group on the 2nd and 5th days ($P < 0.01$). Regarding the secondary outcomes, there was no difference in 30-day mortality and hemoptysis recurrence. However, TXA was superior in terms of 1-year mortality (4.0% vs. 22.7%; $P < 0.01$) and recurrence of hemoptysis (16% vs. 18%; $P < 0.01$).[62]

The most recent study is the 2023 RCT conducted by Gopinath *et al*., which is ED-focused and compares different pharmaceutical forms of TXA. This study included a total of 110 patients, with one group receiving 500 mg nebulized TXA (diluted in 5 mL distilled water) three times a day, and the other group receiving 500 mg IV TXA. The outcome was defined as the cessation of bleeding at 30 min. It was reported that at the 30-minute evaluation, bleeding had stopped in 72.7% of the nebulized drug group and 50.9% of the IV drug group ($P = 0.002$). The reduction in the bleeding volume was significantly higher in the nebulization group compared to the IV group at all observation periods (30 min; 6, 12, and 24 h) ($P < 0.05$).[63]

Adverse effects

In the literature, none of the reviews evaluating the use of TXA in patients with hemoptysis have reported serious thromboembolic adverse effects, such as acute myocardial infarction, stroke, acute renal failure, or death.[57,58,64] In the study by Gopinath *et al*., two patients with COPD in the nebulization group experienced bronchospasm that resolved with standard inhaler beta-agonist treatment.[63] In the study by Tscheikuna *et al*., minor symptoms such as mild headache, slight chest discomfort, and nausea were reported in the TXA group. In addition, a minor skin rash believed to be an allergic reaction to antituberculosis drugs was reported in one patient in the placebo group. It was also noted that these adverse effects did not lead to discontinuation of

the study medications.[59] No adverse effects related to the drug groups were reported in the other three studies included in this guideline.[60-62]

Scenario 5: Is the application of local tranexamic acid plus compression, as an alternative to standard interventions, an effective and safe treatment option in patients with epistaxis?

Strong recommendation: None.

Moderate recommendation: None.

Weak recommendation:

1. After the application of local TXA and external nasal compression, although there are conflicting results between anterior nasal packing and placebo applications, no result indicates that TXA treatment is inferior. Considering the discomfort associated with anterior nasal packing application and studies showing no serious adverse effects, we believe that local application of TXA could be a potential alternative for emergency physicians in the management of epistaxis in EDs (low level of evidence)
2. Due to conflicting and insufficient evidence regarding the method of delivery for TXA application and the optimal drug dose, we do not make any specific recommendations and suggest adhering to local protocols.

Rationale and background for the recommendations

In the management of patients with epistaxis in EDs, there are various treatment options. While simple external compression is sufficient in most cases, other options include the application of anterior packing that may contain lidocaine or epinephrine, plain packing, or commercially available packing products. Due to the discomfort associated with the routine use of anterior nasal packing for up to 3 days, short-term local application of TXA has recently become more popular among emergency physicians as an alternative, particularly for epistaxis that cannot be controlled with simple external compression. Despite the increasing number of studies on the bleeding control effect of TXA in epistaxis patients, there are significant differences in both the results and methodological quality of these studies. Therefore, this guide aims to provide evidence-based summary recommendations for ED physicians in the management of epistaxis.

Selection of studies

A systematic literature review conducted with the relevant keywords [Supplementary File 1] (https://turkjemergmed.com/pages/2024-4-issue-supplementary-files) resulted in 104 studies. Due to the sufficient number of RCTs related to the clinical question, only 11 studies with an RCT design were included for further evaluation [Supplementary File 2] (https://turkjemergmed.com/pages/2024-4-issue-supplementary-files).[65-75] Using the Cochrane RoB-2 tool for bias assessment, it was determined that one article had a low risk, four articles had moderate risk, and six articles had high risk of bias [Figure 11]. Summaries of the studies are presented in Supplementary File 3 (https://turkjemergmed.com/pages/2024-4-issue-supplementary-files).

Overview of studies and measures of outcome

In the existing studies, the efficacy of TXA was primarily investigated; however, there were differences in the outcomes and the choice of comparison groups. Similarly, although TXA was applied locally in the studies, different application methods were used, such as simple external pressure after spraying, anterior packing application with TXA-soaked tampons, and TXA-containing gels. Considering the outcomes, the primary endpoint was generally the cessation of bleeding; however, there were differences in the time points of this evaluation. Due to these methodological differences among the studies, a meta-analysis was not preferred. Instead, a review of the literature focusing on studies with low and moderate risks of bias was conducted.

The initial studies on this topic were conducted by Zahed *et al*., who, in their 2013 randomized controlled trial (RCT), included nontraumatic adult patients with active anterior epistaxis, while excluding those with bleeding diathesis or an international normalized ratio (INR) greater than 1.5. They compared the rates of bleeding cessation within 10 min using TXA-soaked cotton tampons versus anterior nasal packing containing epinephrine + lidocaine (2%). In this study, which included a total of 217 patients, the bleeding cessation rate was 71% in the TXA group compared to 31% in the control group, indicating the superiority of TXA in stopping the bleeding (OR, 2.28; 95% CI, 1.68–3.09; $P < 0.001$).[65]

In another RCT conducted by Zahed *et al*. in 2018, adult patients using antiplatelet drugs were evaluated for eligibility; however, only those whose bleeding did not stop despite 20 min of external pressure were included in the study. Patients using anticoagulants, those with INR >1.5, those with trauma, and those with renal disease were excluded, resulting in a total of 124 patients being included. The study compared the rates of bleeding cessation within 10 min between topical TXA and anterior nasal packing applications. In the TXA group, 73% of patients achieved bleeding cessation within the first 10 min, compared to 44% in the control group, with results statistically significantly favoring TXA (difference: 44%, 95% CI: 25%–57%).[66]

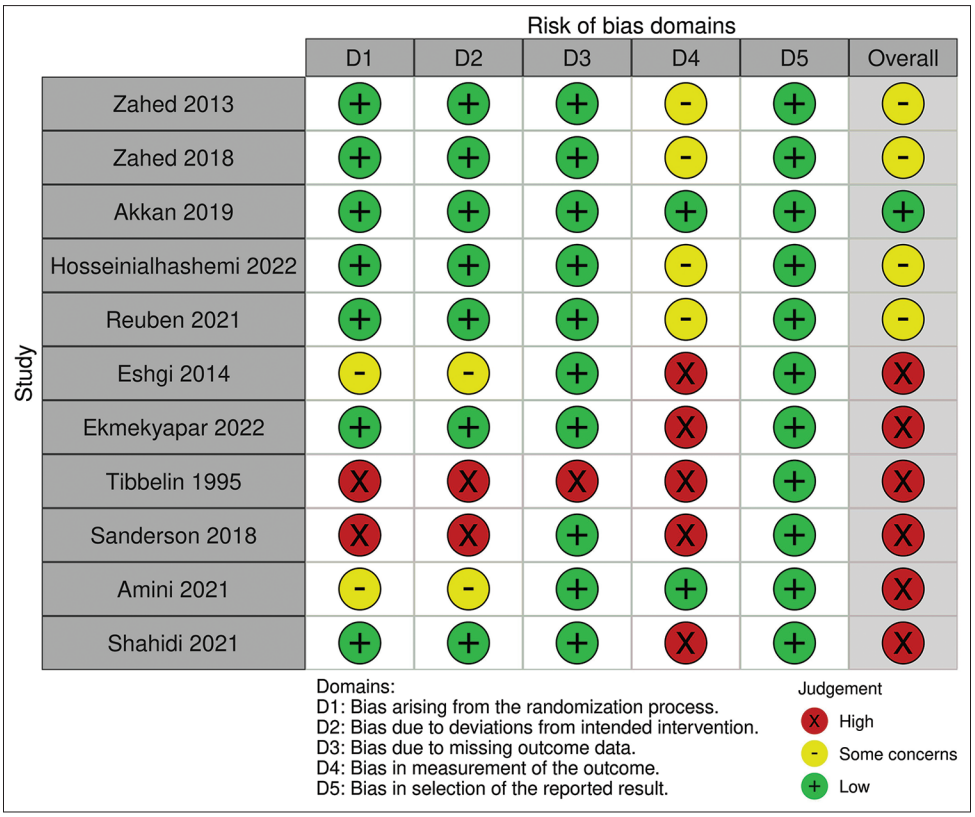

Figure 11: Traffic light charts of articles on the use of tranexamic acid in patients with epistaxis (RoB-2 bias assessment)

In a 2019 RCT by Akkan *et al.*, which included adult patients with epistaxis, three different treatment groups were compared in a total of 135 patients: (1) nasal compression with TXA, (2) simple nasal compression with saline, and (3) nasal tampon using Merocel (Merocel 2000; Medtronic Xomed, Heerlen, Netherlands). The primary outcome was the cessation of bleeding within 15 min. The success rate was found to be 91.1% in the TXA group, 93.3% in the Merocel group, and 71.1% in the simple compression group. While there was no statistically significant difference between the TXA and Merocel groups, a statistically significant difference was reported between the placebo group and the other two groups, favoring the TXA and Merocel over the placebo.[67]

In a study published by Reuben *et al*. in 2021, 496 adult patients with epistaxis that did not stop with 10 min of simple external pressure were included. This study compared the need for anterior nasal packing between the topical application of TXA and a placebo (sterile saline) group. This multicenter study, conducted across 26 centers and the largest study on this topic, found no statistically significant difference between the two groups. The need for nasal packing was 43.7% in the TXA group compared to 41.3% in the placebo group (OR: 1.11, 95% CI: 0.77–1.59).[69]

In a 2022 study by Hosseinialhashemi *et al*., adult patients with anterior nosebleeds were first evaluated by an ear–nose–throat resident physician. Patients underwent procedures such as nasal compression, ice application, and cold water mouth rinse, and those whose bleeding continued despite these measures were included in the study. The study compared the application of TXA-soaked cotton versus phenylephrine-soaked cotton, focusing on the continuation of bleeding after 15 min. Bleeding continued in 50% of patients in the TXA group, whereas it continued in 64% of patients in the control group. The study reported that bleeding was significantly less in the TXA group (OR: 0.56, 95% CI: 0.33–0.94).[68]

When the overall results of the six studies with a high risk of bias were evaluated, three studies reported that the local application of TXA was superior to standard treatment.[70-75] In two studies, TXA was found to be at least as effective as standard treatment. Only in the study conducted by Eshghi *et al*. in 2014, TXA was reported to be less effective when compared to a commercial anterior packing product.[70]

Because of the local application of TXA, most studies did not report any adverse effects. In the studies that did report adverse effects, no increase in the frequency of adverse events attributable to TXA was observed.

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Author contributions statement

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- Methodology: GA (lead), ŞKÇ (equal), AŞ (support), HA (support), and AŞ (support)
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- Writing – Original draft: GA (equal), ŞKÇ (equal), MMİ (support), FNK (support), RÇ (support), and AŞ (support)
- Writing – Review and editing: GA (lead), ŞKÇ (lead), FSD (support), MMİ (support), and AŞ (support).

Conflicts of interest

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Supplementary Files

Supplementary files are available at (https://turkjemergmed.com/pages/2024-4-issue-supplementary-files)

Supplementary File 1: Search hedges used in the systematic literature review for the relevant clinical question (https://turkjemergmed.com/pages/2024-4-issue-supplementary-files)

Supplementary File 2: Flowcharts (5 flowcharts) of studies identified through the systematic literature review and included in the clinical policy (https://turkjemergmed.com/pages/2024-4-issue-supplementary-files)

Supplementary File 3: Tables (5 tables) containing summaries of studies related to the clinical question (https://turkjemergmed.com/pages/2024-4-issue-supplementary-files)

Supplementary File 4: GRADE evidence level classification tables (https://turkjemergmed.com/pages/2024-4-issue-supplementary-files)