Effectiveness of tranexamic acid for acute traumatic hemorrhage and epistaxis in settings without immediate surgical support: a literature review

Carey Jeanne Rots, BSc, MLT, MPAS (Candidate)
Student number: 6743761
umrotscj@myumanitoba.ca

Supervisor:
Herman Shui-Kee Chow, BSc, MD, CCFP (EM) (COE), FCFP
Assistant Professor, Department of Family Medicine, University of Manitoba
Medical Officer, Canadian Armed Forces
herman.chow@umanitoba.ca

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Abstract

Background: Tranexamic acid has been widely used for the management of acute hemorrhage. Although results remain conflicting on its benefits, several more studies have been produced since the first 2010 publication of the CRASH-2 trial. The purpose of this literature review is to examine available evidence on the efficacy of tranexamic acid for acute hemorrhage due to trauma, isolated traumatic brain injury, and epistaxis. Of particular interest is the utility of tranexamic acid in settings without immediate surgical support, such as in certain rural and remote locations of Canada.

Methods: A literature review was conducted using the PubMed database as a source for trials comparing the efficacy of tranexamic acid as a means to improve morbidity and mortality from acute hemorrhage due to trauma, traumatic brain injury, and epistaxis.

Results: A total of 195 studies were identified from the PubMed database search. After removing duplicates and applying inclusion/exclusion criteria, 18 unique studies were included in the review. There were 5 on trauma, 7 on traumatic brain injury, and 6 on epistaxis. All 18 articles were reviewed in detail, but to keep within the scope of this capstone project, a focus on 2 key studies for each topic (trauma, traumatic brain injury, epistaxis) was performed. Although intravenous tranexamic acid administered within 3 hours of injury appeared to reduce 28-day mortality due to trauma, 28-day mortality due to traumatic brain injury and longer-term neurological outcomes at 6 months were not improved for either. Efficacy of topical tranexamic acid for epistaxis management remains conflicting.

Conclusions: Tranexamic acid can be a medication used to reduce mortality in the context of acute hemorrhage due to trauma when given intravenously within 3 hours of injury. This can be especially relevant in the prehospital setting, and in rural or remote settings of Canada where there is no immediate surgical support. As there is no mortality or morbidity benefit seen when used for isolated traumatic brain injury, tranexamic acid currently has little role in its management. There is still conflicting evidence as to what further benefit tranexamic acid provides within our current armamentarium when given topically for epistaxis management. As a result, its use for this cannot be recommended for or against at this time.

Introduction

Tranexamic acid (TXA) is an antifibrinolytic agent that reversibly displaces plasminogen from fibrin, causing an inhibition of fibrinolysis and plasmin activity.[1] TXA has subsequently been utilized as an adjunct for hemostasis, with increasingly widespread usage in recent years. It has been employed in settings such as the prehospital, Emergency Department, Urgent Care, and office-based clinics for various causes of acute hemorrhage. This includes bleeding due to reasons of trauma, and epistaxis.[1] TXA has been given via the intravenous (IV) route for acute traumatic hemorrhage, and topically to the nasal cavity for epistaxis.[1,2]

The effectiveness of TXA in hemorrhage control has been conflicting, with some studies demonstrating superiority to placebo, while others show no clinically significant benefit.[1,2] The adverse outcomes of TXA use is generally acceptable in comparison to the potential benefits, but balancing the devastating effects of exsanguination to the risks of the medication should be examined for proper patient-oriented care. This will also allow for informed, shared-decision making in cases where time permits. In situations without timely access to surgical intervention such as some rural and remote settings, as well as distant prehospital locations, acute hemorrhage can be a concern that poses an even greater challenge. In these cases, stabilizing the patient for transport to definitive surgical care can thus prove difficult. By reviewing the current literature on the effectiveness of TXA for acute hemorrhage and having an extra focus on settings that lack immediate surgical support, we can decide how to prioritize TXA usage in the treatment plan.

There is uncertainty as to whether TXA use results in clinically significant improvement in outcome, or the degree in which it does so.[1,2] There is also uncertain on whether it affects mortality, morbidity, or if it shortens length of hospital stay. It would be important to know the consequences, such as adverse effects, net harms, and overall cost considerations to the health

care system. The most common known adverse effects include headaches, followed by back pain.[3] Less common but significant reactions include seizures, and thromboembolic events.[1] TXA related costs can include not just the medication itself, but the cost of harms induced, as well as harm related hospital stays.

Purpose of Study

This literature review is being done to understand what the evidence is behind the multiple uses of TXA are in clinical practice that are currently employed. Theoretically, it should work for many situations and it is being widely used for bleeding related treatment.[1,2] However, there is conflicting data on its benefits.[1,2] Particular interest is the use of TXA in areas without immediate surgical support, such as in the prehospital, rural, and remote setting. We can use the results to inform care and guide management. This includes on-site decision making, trauma protocols, and hospital policy. That is, TXA should continue to be considered for use if the evidence supports it. Otherwise, TXA may need to be prioritized lower, focusing more on alternative ways of hemorrhage control. Time and attention can instead be placed on different resuscitative measures such as crystalloids, blood products or other novel treatments. The effects can be widespread, as TXA is used in the prehospital, Emergency Department, Urgent Care, and office settings.

Objectives of Study

This literature review examines evidence-based usages for TXA in acute hemorrhage, with interest of impact on settings without immediate surgical support. This includes prehospital and hospitals without in-house surgical backup such as in certain rural and remote locations of Canada. The effectiveness of TXA in these circumstances will help guide practice, knowing

which clinical scenarios would be the most appropriate for its use. For this review, the focus will be on non-iatrogenic trauma and atraumatic epistaxis, as the current evidence demonstrates less conflict with TXA use for indications such as postpartum hemorrhage, abnormal uterine bleeding, and dental procedures.[1] Additionally, non-iatrogenic trauma and epistaxis tend to be more commonly encountered scenarios, and can be relevant in rural and remote settings. A secondary objective is if TXA does help with hemorrhage control, how effective is it overall from a risk to benefit perspective.

Research Questions

The primary research questions are as follows: Does TXA given IV decrease mortality or morbidity due to acute hemorrhage from trauma or isolated traumatic brain injury (TBI)? Does TXA given topically to the nasal cavity result in increased hemorrhage control for epistaxis?

The secondary research question is as follows: Does the benefit of TXA outweigh the risks when used for acute hemorrhage due to trauma, isolated TBI, or epistaxis?

Methods

Inclusion Criteria

Inclusion criteria included primary research, published in English, with any study methodology. Articles had to involve adults with either acute traumatic hemorrhage (trauma or isolated TBI), or epistaxis. Articles had to primarily assess outcomes of TXA use on mortality or morbidity (trauma, TBI), or on the arrest of epistaxis. Secondary outcomes include serious adverse effects such as thromboembolic events.

Search Strategy

The PubMed database was searched with the "Clinical Trial" filter applied, using the terms "txa" OR "tranexamic", AND with the terms "trauma" OR "epistaxis". This search would be expected to bring up any related clinical trials that included TXA, in the context of trauma or epistaxis.

From the search, 195 results were returned. Looking at the articles, 59 had titles of relevance to our literature review questions. Each article was then examined further to exclude those not meeting the inclusion criteria. There were 38 articles excluded, as they were not actual clinical trials or did not answer the questions of interest for this review. Several of these trials were pertaining to TXA use with surgery. There were also 1 duplicate trial and 2 trials which were otherwise duplicates except for updated economic evaluations. Ultimately, it was narrowed down to 18 unique trials: 5 on trauma, 7 on TBI, and 6 on epistaxis (Appendix Figure 1).

Literature Review and Discussion

Unless further specified in the individual trials, the definition of acute hemorrhage due to trauma, TBI, and epistaxis will be clarified as it pertains to this literature review. Hemorrhage due to trauma may include bleeding from an extracranial source, but may also be present together with an intracranial hemorrhage (ICH). Hemorrhage due to TBI includes isolated ICH as seen on computed tomography (CT) brain, but without significant extracranial bleeding. Epistaxis includes hemorrhage due to atraumatic causes only.

After reviewing the 18 trials, 2 trials for each subject of trauma, TBI, and epistaxis were chosen for critical analysis. This was done to fall within the scope of the capstone project instructions, reviewing 6 key journal articles in this case.

Literature Review

For TXA use in trauma, the CRASH-2[4] and PATCH-Trauma[5] trials were selected. CRASH-2 is the landmark trial published in 2010 that was the first to examined TXA use for hemorrhage in trauma.[4] It also contains by far the largest study population size for this topic (Appendix Table 1). PATCH-Trauma is the most recent trial, published in 2023, and has the second largest study population size (Appendix Table 1). It was also partly conducted in Canada, and its prehospital relation adds even more understanding to answering our literature review questions of interest.[5]

The CRASH-2 trial is a double-blind randomized control trial (RCT) published 2010 in the Lancet.[4] It took place in 274 hospitals across 40 countries and enrolled 20211 adult trauma patients. There were 10096 patients randomized to TXA given within 8 hours of injury, and 10115 randomized to placebo (saline). TXA (1g) or placebo were administered IV as a 10ml bolus over 10 minutes, then 1g TXA or 10ml placebo IV over 8 hours. Patients required a clinical inclusion criteria of systolic blood pressure <90mmHg, heart rate >110bpm, significant hemorrhage or considered at risk of significant hemorrhage as determined by the treating physician. Primary outcome of 28-day all-cause mortality was significantly reduced when TXA within 3 hours, 14.5% vs placebo 16%, risk ratio (RR) 0.91 [95% confidence interval (CI) 0.85 to 0.97], p=0.0035. Risk of death due to bleeding was significantly reduced with TXA 4.9% vs placebo 5.7%, RR 0.85 (95% CI 0.76 to 0.96), p=0.0077. Secondary outcome of vascular

occlusive events including myocardial infarction (MI), stroke (CVA), pulmonary embolism (PE), and deep vein thrombosis (DVT) were not increased with TXA.[4]

The PATCH-Trauma trial is a double-blind RCT published in 2023 in the New England Journal.[5] It took place in 15 emergency medical services and 21 hospitals in Australia, New Zealand, and Germany. They enrolled 1310 adult trauma patients, with 661 patients randomized to TXA, and 646 patients to placebo (saline). Either TXA or placebo were administered prehospital within 3 hours of injury as a 10ml IV bolus (1g TXA), then another 10ml TXA or placebo IV over 8 hours on hospital arrival. Inclusion criteria required patients to be at high risk for trauma-induced coagulopathy using the Coagulopathy of Severe Trauma (COAST) score. COAST scores range from 0 to 7, with 1 point given for certain risk factors, and the authors considered a score of 3 to 7 as high risk. Primary outcome of survival with favourable outcome at 6 months after injury as assessed by the Glasgow outcome scale-extended (GOS-E) was not improved with TXA 53.7% vs placebo 53.5%, RR 1.00 (95% CI 0.90 to 1.12), p=0.95. The GOS-E ranges from 1 (death) to 8 (upper good recovery), in which the authors used 5 to 8 as a favourable outcome. Secondary outcomes of 28-day all-cause mortality and 6-month all-cause mortality were 17.3% TXA vs 21.8% placebo, RR 0.79 (95% CI 0.63 to 0.99) and 19.0% TXA vs 22.9% placebo, RR 0.83 (95% CI 0.67 to 1.03) respectively. There was no difference in serious adverse events.[5]

For TXA use in TBI, the CRASH-3[6] trial contains the largest study population size (Appendix Table 2), and delves even further into information partly studied and nested in CRASH-2[4]. The other trial selected is similar to the PATCH-Trauma trial in that it contains the second largest study population size for TBI (Appendix Table 2), was conducted partly in

Canada, had a prehospital TXA administration relevant to the questions of interest, and has the same primary outcome.[5,7]

The CRASH-3 trial is a double-blind RCT published 2019 in the Lancet by some of the same authors as CRASH-2.[6] It took place at 175 hospitals across 29 countries and enrolled 12737 adult TBI patients. There were 6406 patients randomized to TXA given within 3 hours of injury, and 6331 randomized to placebo (saline). TXA (1g) or placebo were administered IV as a 10ml bolus over 10 minutes, then 1g TXA or 10ml placebo IV over 8 hours. Patients required a clinical inclusion criteria of Glasgow coma score (GCS) ≤12 or ICH on CT brain, and no major extracranial bleed. Primary outcome of 28-day head injury related mortality was not reduced with TXA 18.5% vs placebo 19.8%, RR 0.94 (95% CI 0.86 to 1.02). There was also a prespecified subgroup analysis which excluded GCS 3 or bilateral unreactive pupils at baseline. This was done due to the thought that this group would be a poor prognosis. Head injury mortality was also not reduced with TXA 12.5% vs placebo 14.0%, RR 0.89 (95% CI 0.80 to 1.00). A subgroup analysis that was not prespecified included those suffering from mild to moderate head injury (GCS 9 to 15), and was found to have statistically significant head injury mortality benefit with TXA 5.8% vs placebo 7.5%, RR 0.78 (95% CI 0.64 to 0.95). Secondary outcomes of 24-hour head injury mortality, all-cause and cause-specific mortality, disability, vascular occlusive events (MI, CVA, PE, DVT), seizures, complications, neurosurgery needed, days in intensive care unit, adverse events within 28 days of randomization were all similar.[6]

The second TBI trial titled, Effect of Out-of-Hospital Tranexamic Acid vs Placebo on 6-Month Functional Neurologic Outcomes in Patients With Moderate or Severe Traumatic Brain Injury, is a double blind RCT published 2020, more recently than the CRASH-3 trial, in the Journal of the American Medical Association.[7] It took place in 39 emergency medical services

and 20 trauma centers across the United States and Canada, and enrolled 966 adult TBI patients. There were 312 patients randomized to 1g TXA bolus followed by 1g over 8 hours (bolus-maintenance group), 340 patients to 2g TXA bolus (bolus only group), and 309 randomized to placebo (saline). The treatment was given within 2 hours of injury, with inclusion criteria requiring moderate to severe TBI (GCS ≤12) and systolic blood pressure ≥90mmHg. Primary outcome of favourable neurologic function at 6 months was based on the GOS-E of 5 to 8. Both TXA groups were combined for analysis against placebo, and showed no improvement with TXA 65% vs 62% placebo (90% 1-sided confidence limit for benefit -0.9%), p=0.16. Secondary outcome did not show statistically significant difference in 28-day mortality between both TXA groups 14% vs 17% placebo (95% CI -7.9% to 2.1%), p=0.26, nor for 6-month disability rating scale (DRS) score with TXA 6.8 vs 7.6 (95% CI -2.5 to 0.7), p=0.29.[7]

For TXA use in epistaxis, the NoPAC[8] trial contains the largest study population size (Appendix Table 3), and was published recently in 2021. The other selected trial contains the second largest study population size (Appendix Table 3), and has the same primary outcome as NoPAC.[8,9]

The NoPAC trial is a double blind RCT published 2021 in the Annals of Emergency Medicine.[8] It took place in 26 emergency departments across the United Kingdom, and enrolled 496 adult patients with spontaneous atraumatic epistaxis, despite at least 10 minutes of pressure and/or ice application. There were 254 patients randomized to 400mg topical TXA and 242 patients randomized to placebo. The treatment was used after a 10-minute application of a topical vasoconstrictor soaked on a cotton wool dental roll with external pressure. The exclusion criteria included hemodynamic instability, out-of-hospital packing, allergy to TXA, nasopharyngeal malignancy, pregnancy, and hemophilia. Primary outcome was the need for anterior packing,

which was not improved with TXA 43.7% vs 41.3% placebo, OR 1.11 (95% CI 0.77 to 1.59). Secondary outcomes of hospital admission, need for blood transfusion, recurrent epistaxis, and thrombotic events within 1 week were similar.[8]

The second epistaxis trial titled, Intranasal Topical Application of TXA in Atraumatic Anterior Epistaxis: A Double-Blind Randomized Clinical Trial, is a double blind RCT published 2022 in the Annals of Emergency Medicine.[9] It took place in an ear, nose, throat (ENT) emergency clinic in Iran, and enrolled 240 adult patients with atraumatic anterior epistaxis. There were 120 patients randomized to 500mg TXA with 10ml phenylephrine, and 120 patients randomized to the control group of 50mg lidocaine with 10ml phenylephrine. The treatment was soaked in cotton pledgets and applied for 15 minutes. Exclusion criteria included hemodynamic instability, out-of-hospital packing, allergy to TXA, nasopharyngeal malignancy, pregnancy, bleeding disorders, trauma, recent use of anticoagulants, clopidogrel, and suspected posterior epistaxis. Primary outcome was the need for anterior packing, which was reduced using TXA with phenylephrine 50% vs 64.2% control, OR 0.56 (95% CI 0.33 to 0.94). Secondary outcomes which improved with TXA include stay in the ENT clinic for more than 24 hours [9.2% vs 20.8 % control, OR 0.38 (95% CI 0.18 to 0.82)[and 24-hour rebleed [OR 0.41, (95% CI 0.22 to 0.78)]. There were no significant adverse events.[9]

Discussion

Tranexamic Acid Use in Trauma

Evidence for TXA superiority in 28-day all-cause mortality can be seen from the CRASH-2 trial. There is an absolute risk reduction of 1.5% (14.5% TXA vs 16.0% placebo) when TXA is administered IV within 3 hours of injury, with the authors concluding the earlier is

more effective.[4] The 1.5% reduction in mortality is small, but from an epidemiological view, this translates to a number needed to treat (NNT) of 67. If implemented on a widescale across the world, this would translate into a significant number of lives saved. Though it has been shown that TXA within 3 hours can reduce mortality, there was also a signal of harm when given beyond 3 hours.[4] Looking at the all-cause mortality subgroup for TXA given beyond 3 hours, there is a small non-statistically significant trend to harm with TXA 15.0% vs 14.9% placebo, RR 1.00 (95% CI 0.86-1.17).[4] Therefore, cautious use of this medication in relation to being under the 3-hour window has been made in subsequent trials.[5,6,7]

CRASH-2 is the first of its kind, setting the stage for TXA use in acute hemorrhagic trauma.[4] It is a very large trial by absolute number (n=20211)[4] and relative to all the other trials (Appendix Table 1). It can be reasoned that if a meta-analysis were to be performed, the data used from this study will likely have a strong influence on results. Another strength is that most patients were followed up on, reducing attrition bias.[4]

There are several limitations identified in the CRASH-2 trial. Though there is decreased 28-day all-cause mortality, the 28-day bleeding mortality which is also significant showed only approximately 5% of the groups actually died from hemorrhage.[4] This leads one to think what the mechanism could be, or if there is bias, given TXA's role should be to decrease death due to hemorrhage control. The absolute risk reduction is 0.8% (5.7% TXA vs 4.9% placebo)[4], resulting in a NNT of 125 for bleeding mortality. Another potential limitation of this study is that although multicentered and large, most of the study population resides in Europe, Africa, and India.[4] Can we extrapolate the findings to a North American population or system of health care? The 28-day mortality reduction with TXA is encouraging, but it would be prudent to consider patient-oriented outcomes such as morbidity in the form of functional disability in the longer term.

Unlike the CRASH-2 trial, the PATCH-Trauma trial examines the patient-oriented outcome of longer 6-month survival, with favourable outcomes.[5] This study is more recent, being published in 2023, and is more generalizable to this literature review focus of Canadians in settings without immediate surgical support. Initial TXA dose was given prehospital, which can provide results on effect when given in rural or remote settings of Canada where patients need to be transferred. Unfortunately, the results did not demonstrate improvement in 6-month favourable outcomes.[5] One limitation of this study was that the primary outcome data was missing for 13% of patients to do lost to follow-up.[5] This could have affected the results due to attrition bias. Further research with regard to longer term TXA influence on function outcomes may provide more insight on this matter.

Tranexamic Acid Use in Traumatic Brain Injury

The CRASH-3 trial is another very large trial (n=12737), with some of the authors returning from the CRASH-2 trial.[6] This time, the trial does incorporate morbidity as a secondary outcome, along with the primary 28-day head injury-related mortality outcome in TBI. There is an absolute risk reduction of 1.3% (18.5% TXA vs 19.8% placebo) for the primary outcome, but it was not significant.[6] The authors prespecified a subgroup for analysis that excluded those with a GCS of 3, or with bilateral unreactive pupils, as they thought these patients may be too severely injured for benefit.[6] The absolute risk reduction was 1.5% (12.5% TXA vs 14% placebo). As with the primary outcome, this comes very close to statistical significance, but does not.[6] Additionally, there was a subgroup analyzed that was not preplanned. This group was those with mild to moderate TBI (GCS 9-15). In this case, a statistically significant absolute risk reduction of 1.7% (5.8% TXA vs 7.5% placebo) was found.[6] Unfortunately, the authors conclusion of TXA being effective is too strong. TXA did not improve the primary outcome of

28-day mortality. The unplanned subgroup analysis may lead to potential bias, but is hypothesis generating. Therefore, further studies into the effects of TXA given within 3 hours on mortality due to mild to moderate TBI is needed.

One strength is that there was a large population size, and almost no lost to follow-up.[6] This reduces attrition bias. They also examined disability at 6 months, though there was no benefit with TXA. A weakness of this trial was that the did not examine mortality beyond 28 days, which would be possible in patients who suffered from TBI.

The trial, Effect of Out-of-Hospital Tranexamic Acid vs Placebo on 6-Month Functional Neurologic Outcomes in Patients With Moderate or Severe Traumatic Brain Injury, is similar to the PATCH-Trauma trial in that it examined the prehospital use of TXA and 6-month survival with favourable neurologic function.[7] This is also a multi-center North America study that included Canada. As such, it has the same strengths in relevance to our literature review. The conclusion is similar to the CRASH-3 trial in that no benefit was seen with TXA on TBI.[7]

Limitations identified include almost all TBI being from blunt trauma.7 This would thus not be a good study to extrapolate to penetrating trauma. The authors also planned to examine the 2 TXA groups (bolus-maintenance, bolus only) separately, but due to power concerns, they were ultimately combined together and compared with the placebo group.[7]

Tranexamic Acid Use in Epistaxis

The NoPAC trial was a trial that showed no superiority of TXA compared to placebo. Prior to this, trials were small and possibly underpowered (Appendix Table 3).[8] This trial included posterior epistaxis as the authors believe it hard to differential in the real world, and that it only represents <5% of epistaxis.[8] Limitations include a sample size though larger, may still be

underpowered to detect a difference. Initial predictions on the rate of anterior packing needed was incorrect, and this led to adjustment of sufficient sample size needed.[8] Additionally, prior studies used 500mg of TXA where as this study differed in its protocol (400mg used).[8] Finally, a convivence sample was used, as patients presented to the Emergency Department rather that being randomly selected.[8]

The trial, Intranasal Topical Application of TXA in Atraumatic Anterior Epistaxis: A Double-Blind Randomized Clinical Trial, had the same primary outcome as the NoPAC trial.[9] This leads to interesting dilemma, as the conclusion is instead one of TXA superiority. Some differences in the study itself however, is that it is from a single center in Iran.[9] Moreover, it is a specialized ENT clinic, leading to selection bias. NoPAC collected patients from Emergency Departments in the United Kingdom.[8] The exclusion criteria also included patients that were on anticoagulants, which the NoPAC trial included.[8,9] TXA in this case had lower rates of anterior packing needed (50% TXA + phenylephrine vs 64.2% control, OR 0.56).[9] The absolute risk reduction would be 14.2%, yielding a NNT of 7. It is important to note that 50% or more patients still required anterior packing despite TXA.[9] Regardless, we come to the crossroads of whether to implement TXA or not for epistaxis. From a negative study in the NoPAC trial,[8] to one with an NNT of 7.[9]

Literature Review Limitations

Overall, a limitation for this literature review is that a search was done of the PubMed database only. There are several additional databases such as SCOPUS, and CINAHL that could have been used. The PubMed database did provide ample records, and even narrowing down studies yielded 18 trials.

Conclusions and Recommendations

Conclusions

TXA given IV within 3 hours of injury has been shown to reduce 28-day bleeding and all-cause mortality due to acute trauma,[4,5] but not longer term 6-month functional outcomes.[5] The risks of serious adverse events associated with TXA are minimal, thus the benefits outweigh the risks in this case.[4,5]

TXA given IV within 3 hours of injury has not been shown to reduce 28-day bleeding mortality due to TBI, nor disability at 28 days.[6,7] Disability and functional outcomes at 6 months are not improved either.[7] Given there was a signal for reduced 28-day mortality in patients with mild to moderate TBI,[6] and that the risks of serious adverse events are minimal,[6,7] there may be a role for TXA in these select patients. Benefits may outweigh the risks in this case. However, TXA cannot be recommended otherwise.

Though possible, TXA used topically has not convincingly been shown to be effective for arrest of epistaxis.[8] As such, it does not provide any significant advantages over other currently established treatments. Risks are minimal,[8,9] but further research is needed before TXA can be recommended for epistaxis management.

Recommendations

Given the potential transfer time delays to centers with surgical support, TXA given IV can be an adjunct in hemorrhage management when given within 3 hours of trauma. This may be at the initial point of contact in rural or remote hospital settings. As it has been shown to be cost-effective,[22,23] adverse events were not higher than placebo[4,5] and the alternative potential is increased mortality if not treated, patients could be given TXA empirically if the provider is

unsure whether exact criteria are met. Although TXA can also be considered for TBI that is mild to moderate, it cannot currently be recommended for this or epistaxis.

Further Research

Further research is needed on the topic of TXA for trauma use regarding its relevance to a North Americans. Multi-center trials with more participants originating from Canadian and United States locations would allow for conclusions that may better reflect Canadian populations. Further research for TXA use specifically enrolling patients with mild to moderate TBI may help add strength to the CRASH-3 trial authors conclusion, as this subgroup was not prespecified and there was no overall 28-day mortality benefit.[6] More research considering patient-oriented outcomes for TXA use in trauma and TBI could help justify its use beyond that of 28-mortality, as the short- and long-term morbidity for trauma and TBI were not improved.[5,6,7] Further research on TXA for epistaxis use should include larger multicenter double-blind RCTs in the Emergency Department and Urgent Care, so that they are sufficiently powered and generalizable. Interventions could also compare TXA with placebo, and with other topical treatments such as phenylephrine, oxymetazoline, lidocaine with epinephrine.

In terms of further research related to answering our questions on TXA, a systematic review and meta-analysis using a more exhaustive search of several databases could provide further details and potentially better recommendations. To noted however, many of the trials from our search contained small sample sizes, were single centered, and single-blinded or unblinded (Appendix Tables 1-3). Thus, there may still be flaws in the resultant meta-analysis, so further double-blind randomized control trials of sufficient power would be ideal.

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Appendix

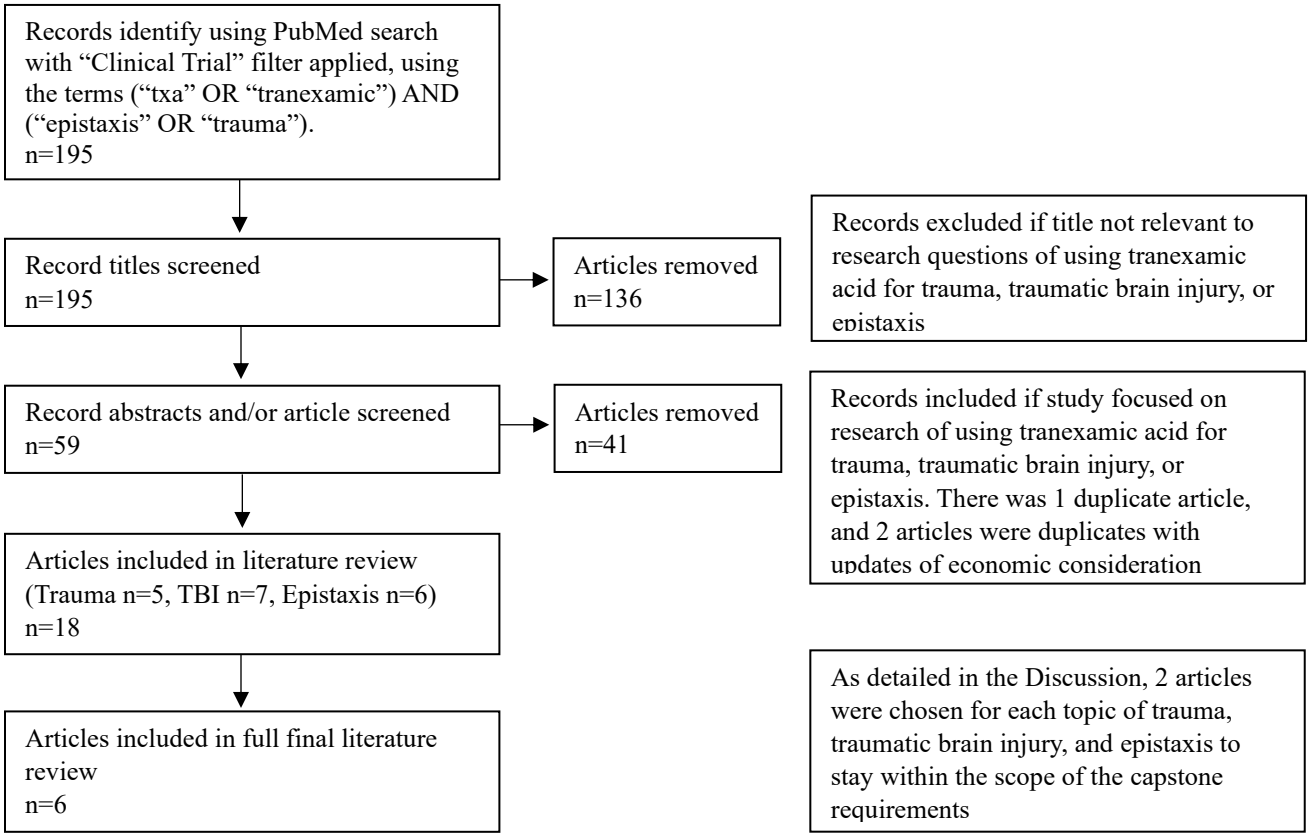

Figure 1. Study selection flow diagram.

Table 1. Summary of trauma studies using tranexamic acid compared.

Year Published	Trial	Comparison	Location	Trial Type	Blinding	Number of Patients	Primary Outcome	Secondary Outcome	Primary Outcome TXA Superiority
2010	Effects of TXA on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial[4]	TXA vs placebo	Multi-center	Randomized Control Trial	Double	20211	Death in hospital within 4 wks due to: 1. Bleeding 2. Vascular occlusion (MI, CVA, PE) 3. Multiorgan failure 4. Head injury 5. Other	1. Vascular occlusive events (MI, CVA, PE, DVT) 2. Surgical intervention 3. Blood transfusion 4. Units of blood products	1. Yes 2. No difference 3. No difference 4. No difference 5. No difference
2015	TXA use in severely injured civilian patients and the effects on outcomes: a prospective cohort study[10]	TXA vs no TXA	UK (single center)	Prospective Cohort Study	Open label	385	TXA effect on: 1. Early mortality 2. Late mortality 3. Organ failure 4. Infection 5. VTE 6. CVA 7. MI 8. Ventilator free days 9. Critical care LOS 10. Total Hospital LOS	Differential TXA effects in patients with vs without shock	1. No 2. No 3. No 4. No 5. No 6. No 7. No 8. No 9. No 10. No
2021	Efficacy and safety of the second in-hospital dose of TXA after receiving the prehospital dose: double-blind randomized controlled clinical trial in a level 1 trauma center[11]	TXA vs placebo	Qatar (single center)	Randomized Control Trial	Double	220	Mortality at: 1. 24 hrs 2. 48 hrs	1. Vascular occlusive events 2. Blood transfusion 3. Hospital LOS 4. Organ failure	1. No 2. No
2021	The effect of early TXA on bleeding, blood product consumption, mortality and length of hospital stay in trauma cases with hemorrhagic shock: a randomized clinical trial[12]	TXA vs placebo	Tehran, Iran (single center)	Randomized Control Trial	Double	68	1. Mortality 2. Hospital LOS 3. Blood transfusion		1. No 2. Yes 3. Yes
2023	Prehospital TXA for severe trauma (PATCH-Trauma)[5]	TXA vs placebo	Multi-center	Randomized Control Trial	Double	1310	Survival with favourable outcomes at 6 months	All cause mortality: 1. 28-day 2. 6-months	No

TXA- tranexamic acid, MI- myocardial infarction, CVA- cerebrovascular accident, PE- pulmonary embolism, VTE- venous thromboembolism, LOS- length of stay, DVT- deep venous thrombosis

Table 2. Summary of traumatic brain injury studies using tranexamic acid compared.

Year Published	Trial	Comparison	Location	Trial Type	Blinding	Number of Patients	Primary Outcome	Secondary Outcome	Primary Outcome TXA Superiority
2012	CRASH-2 (Clinical randomisation of an antifibrinolytic in significant haemorrhage) intracranial bleeding study: the effect of TXA in TBI - a nested, randomised, placebo-controlled trial[13]	TXA vs placebo	Multi-center	Nested Randomized Control Trial	Double	270	Change in total ICH growth from first to follow-up CT brain	1. Occurrence of significant ICH growth 2. New ICH 3. Change in subarachnoid haemorrhage grade 4. Mass effect 5. Occurrence of new focal cerebral ischaemic lesions	No
2013	TXA for patients with TBI: a randomized, double-blinded, placebo-controlled trial[14]	TXA vs placebo	Khon Kaen, Thailand (single center)	Randomized Control Trial	Double	238	Progressive ICH on second CT brain		No
2017	The effect of TXA in TBI: a randomized controlled trial[15]	TXA vs placebo	Arak, Iran (single center)	Randomized Control Trial	Single	80	ICH growth on 48 hr CT brain		Yes
2019	Benefits of the TXA in head trauma with no extracranial bleeding: a prospective follow-up of 180 patients[16]	TXA vs no TXA	Sfax, Tunisia (single center)	Prospective Randomized follow-up	Open label	180	TXA effect on: 1. Mortality (28-day) 2. Blood transfusion 3. Neurosurgery	Thromboembolic events (PE, DVT)	1. No 2. No 3. No
2019	Effects of TXA on death, disability, vascular occlusive events and other morbidities in patients with acute TBI (CRASH-3): a randomised, placebo-controlled trial[6]	TXA vs placebo	Multi-center	Randomized Control Trial	Double	12737	Mortality (28-day)	1. Mortality (24 hr) 2. All cause mortality 3. Cause specific mortality 4. Disability 5. Vascular occlusive events (MI, PE, DVT, CVA) 6. Seizures 7. Complications 8. Neurosurgery 9. Intensive care unit length of stay 10. Adverse events (28-day)	No
2020	Effect of out-of-hospital TXA vs placebo on 6-month functional neurologic outcomes in patients with moderate or severe TBI[7]	TXA vs placebo	US and Canada Multi-center	Randomized Control Trial	Double	966	Favorable neurological function at 6 months	1. Mortality (28-day) 2. 6-month disability 3. Progression of ICH 4. Incident of seizures 5. Thromboembolic events	No
2021	Effect of intravenous TXA on intracerebral brain hemorrhage in TBI[17]	TXA vs placebo	Jundishapur, Iran	Randomized Control Trial	Double	94	1. CT growth in hematoma size 2. Midline shift	Decrease in level of consciousness	1. Yes 2. No

TXA- tranexamic acid, TBI- traumatic brain injury, ICH- intracranial hemorrhage, CT- computed tomography, MI- myocardial infarction, PE- pulmonary embolism, DVT- deep venous thrombosis, CVA- cerebrovascular accident

Table 3. Summary of epistaxis studies using tranexamic acid compared.

Year Published	Trial	Comparison	Location	Trial Type	Blinding	Number of Patients	Primary Outcome	Secondary Outcome	Primary Outcome TXA Superiority
2013	A new and rapid method for epistaxis treatment using injectable form of TXA and topically: a randomized controlled trial[18]	TXA vs epinephrine + lidocaine + tetracycline ointment packing	Tehran, Iran (single center)	Randomized Control Trial	Open label	216	1. Time needed to stop epistaxis 2. Hospital LOS 3. Rebleeding (24 hrs) 4. Rebleeding (1 wk) 5. Patient satisfaction		1. Yes 2. Yes 3. No 4. No 5. Yes
2017	Topical TXA compared with anterior nasal packing for treatment of epistaxis in patients taking antiplatelet drugs: randomized controlled trial[19]	TXA vs compression vs packing	Tehran, Iran (2 centers)	Randomized Control Trial	Open label	124	Proportion of patients whose epistaxis stopped at 10 mins	1. Rebleeding (24 hrs) 2. Rebleeding (1 wk) 3. LOS 4. Patient satisfaction	Yes
2019	Evaluating effectiveness of nasal compression with TXA compared with simple nasal compression and Merocel packing: a randomized controlled trial[20]	TXA + external compression vs Merocel packing vs external compression	Ankara, Turkey (single center)	Randomized Control Trial	Double	135	Effectiveness to stop anterior epistaxis within 15 mins	Rebleeding (24 hrs)	Yes (vs external compression) Non-inferior (vs Merocel packing)
2021	The use of TXA to reduce the need for nasal packing in epistaxis (NoPAC): randomized controlled trial[8]	TXA vs placebo	United Kingdom (multi-center)	Randomized Control Trial	Double	496	Need for anterior packing	1. Hospital admission 2. Blood transfusion 3. Rebleeding 4. Thrombotic event (1 wk)	No
2022	Intranasal topical application of TXA in atraumatic anterior epistaxis: a double-blind randomized clinical trial[9]	TXA + phenylephrine vs lidocaine + phenylephrine	Shiraz, Iran (single center)	Randomized Control Trial	Double	240	Need for anterior packing	1. LOS > 2 hrs 2. Need for electrocautery 3. Rebleeding (24 hrs) 4. Rebleeding (1 wk)	Yes
2022	Comparison of the therapeutic efficacy of topical TXA, epinephrine, and lidocaine in stopping bleeding in non-traumatic epistaxis: a prospective, randomized, double-blind study[21]	TXA vs epinephrine vs lidocaine	Turkey (single center)	Randomized Control Trial	Double	108	Time needed to stop epistaxis		No

TXA- tranexamic acid, LOS- Length of stay