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ANESTHESIA FOR TRAUMA (TE GRISSOM, SECTION EDITOR)

The Use of Tranexamic Acid in Trauma

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Abstract

Purpose of Review The role of tranexamic acid (TXA) in hemorrhage control has been extensively studied in non-trauma patients and has been shown to decrease bleeding and improve outcomes. This review aims to discuss the known mechanisms of TXA, previous studies of its use in the surgical setting, and the proposed benefits and drawbacks of its use in trauma patients.

Recent Findings The universal use of TXA in trauma patients at risk for hemorrhage is controversial. Recent studies have shown that TXA may be beneficial and reduces mortality in trauma patients, including for those with traumatic brain injury. However, there is still some uncertainty on the administration and dosing of TXA, as well as its effect on the incidence of thromboembolic events.

Summary This study reviews the role of TXA in trauma patients and the potential risks and benefits TXA administration may have in this patient population.

Keywords TXA · Tranexamic acid · Hemorrhage · Trauma · Coagulopathy · Fibrinolysis · Traumatic brain injury

Introduction

Trauma is a leading cause of death and disability worldwide with 5.8 million people dying each year as a result of traumatic injury [1, 2]. In major trauma, uncontrolled hemorrhage is the most common cause of early mortality and accounts for 30–40% of all trauma deaths [3, 4]. Of these, half occur in the pre-hospital period [5••, 6]. Additionally, every year, there are 60 million new cases of traumatic brain injury (TBI) worldwide. The main causes of these types of traumatic injuries are road traffic accidents and falls, which continue to increase [7, 8]. A common complication associated with TBI is intracranial bleeding, which increases the risk of death and disability [7, 9].

Tranexamic acid (TXA) is an antifibrinolytic drug that has been shown to decrease bleeding. In over 100 trials of non-traumatic surgical patients, TXA has been shown to reduce blood loss without increasing the risk of postoperative complications [10–13]. Since it has been demonstrated to be beneficial in non-trauma patients, an area of great potential benefit is the use of TXA for trauma patients [10].

The Clinical Randomization of an Antifibrinolytic in Significant Hemorrhage (CRASH-2) study was a landmark randomized controlled trial that aimed to identify the potential risks and benefits of administering TXA to adult trauma patients with or at risk of significant bleeding in the initial eight hours of injury. The CRASH-2 study showed that TXA given within 3 h from the time of injury reduced the risk of bleeding and mortality, without an increase in adverse events [10]. This has led to an interest in additional studies of the applicability of TXA use in patients with traumatic injuries.

Search Strategy

A literature review was conducted in May 2021 using the PubMed Search Engine and the search terms "tranexamic acid" and "trauma." Publications were filtered by a publication date within 10 years. Any publications that were not

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in English were excluded. More publications were found beyond this initial search from key studies referenced within the articles. A total yield of 46 publications were included based on their relevancy to the subject matter and publication date.

TXA Mechanism of Action

TXA (trans-4-(aminomethyl) cyclohexane-carboxylic acid) is a synthetic form of the amino acid lysine and works by competitively inhibiting the activation of plasminogen to its active form, plasmin [14]. It exerts this action by occupying the lysine binding sites of plasminogen, thereby preventing plasminogen activation and blocking the interaction between fibrin and plasminogen (Fig. 1) [1]. In this way, TXA stabilizes previously formed clots by inhibiting their breakdown, thus categorizing it as an antifibrinolytic as opposed to an antihemorrhagic agent {Roberts, 2015 #547}[15, 16, 17••].

Plasminogen and plasmin have been found to play a role in inflammation, wound healing, chemotaxis, and many other important physiological processes [17••]. Thus, the inhibition of plasmin production by TXA suggests that TXA may have anti-inflammatory effects. It has been shown that TXA has protective effects on the endothelium, which may explain its beneficial modulation of inflammation. This theorized anti-inflammatory effect has been proposed as a secondary mechanism for reducing mortality in patients with hemorrhage, but additional mechanisms by which TXA exerts beneficial effects in this context have not been wholly elucidated [17••, 18].

The use of TXA in trauma is controversial because trauma-induced coagulopathy (TIC) is a complex, integrated process and the exact mechanism of action of TXA in TIC is not completely understood. A biochemical fibrinolytic pathway that correlates with tissue damage is associated with the clinical spectrum of hemorrhage, which can lead to shock. Patients in hemorrhagic shock and documented hyperfibrinolysis have very high mortality rates. TIC occurs in some patients with a severe traumatic injury where there is an increase in soluble thrombomodulin leading to increased levels of activated Protein C (aPC), which inhibits factors V and VIII. This loss of coagulation factors leads to an inability to initiate more clot formation. These increasing levels of aPC also inhibit plasminogen activator inhibitor-1, which results in increased levels of endogenous tissue plasminogen inhibitor, thereby increasing clot breakdown (i.e., hyperfibrinolysis). Simultaneously, less clot is formed while more clot is broken down. A thorough review of TIC is beyond the scope of this review. This simplified description of the injury-clot interaction has been proposed as one mechanism of TIC and a potential target of action for TXA that deserves further investigation [5••].

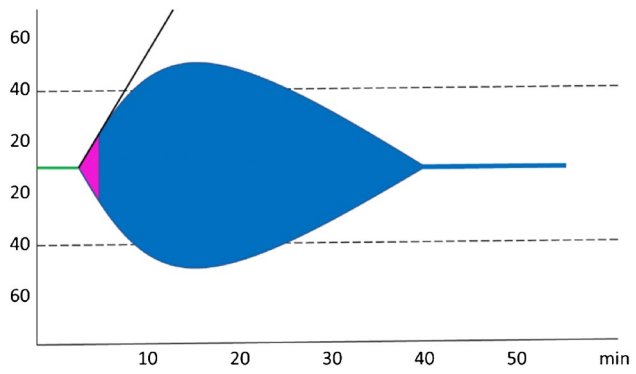

Fig. 1 Viscoelastic testing showing hyperfibrinolysis

Pharmacological antifibrinolysis from TXA could have a significant impact in mitigating TIC, with a potentially significant reduction in mortality. However, it appears that the timing of the administration of TXA is important. Studies show that when TXA is given more than 3 h after injury, there is a significant increase in mortality [5••]. Additionally, recent data from large trauma centers have demonstrated that some patients show viscoelastic evidence of fibrinolytic shutdown, which results in a significant increase in mortality from sepsis and multiple organ failure [19–21]. Currently, it is unclear if TXA administration can lead to fibrinolytic shutdown. The increase in mortality associated with late TXA administration and potential fibrinolytic shutdown has called for increased investigation of its use and timing of administration in injured patients.

Prior Use of TXA

For the last decade, TXA has been one of the most studied pharmaceutical agents [17••]. Several studies have found that the use of TXA reduced blood loss in general, gynecologic, and orthopedic surgeries [10, 12, 13, 15, 18]. A review and meta-analysis of 104 clinical trials found that the administration of TXA reduced blood loss by approximately one-third, regardless of the surgery type [22]. These studies led Roberts et al. to construct the CRASH-2 trial in order to assess whether a similar benefit would exist for trauma patients [10].

Studies of TXA in Trauma Patients

Many of the studies on the use of TXA in injured patients have focused on patients in hemorrhagic shock or those with traumatic brain injury. The results of these studies have led to an increased interest for studies to examine

the potential benefits of TXA administration in the prehospital setting.

TXA in Hemorrhage

One of the largest studies conducted on TXA administration in trauma patients is the landmark CRASH-2 study, a randomized controlled trial conducted across 274 hospitals in 40 countries that enrolled 20,211 adult trauma patients deemed to be at risk for significant bleeding. The CRASH-2 trial reported that administration of TXA was associated with a reduction in all-cause mortality (14.5% vs. 16.0%; RR 0.91, 95% CI 0.85–0.97) and a reduced risk of death due to bleeding (4.9% vs 5.7%; RR 0.85, 95% CI 0.76–0.96) without an increased risk of venous thromboembolism (VTE) or death from all other (non-hemorrhagic) causes. However, contrary to their initial hypothesis, the investigators did not find a substantial reduction in blood transfusions. This led the authors to perform a post hoc analysis to evaluate the risk of death due to bleeding rather than all-cause mortality. Four baseline characteristics were studied: (1) time from injury to treatment ($\leq 1, > 1$ to ≤ 3 and > 3 h), (2) severity of hemorrhage as assessed by systolic blood pressure (≤ 75 mm Hg, 76–89 mmHg and > 90 mmHg), (3) Glasgow Coma Scale (GCS) score (severe 3–8, moderate 9–12, and mild 13–15), and (4) type of injury (penetrating only, blunt only, or blunt plus penetrating). Treatment with TXA within 1 h of injury, and between 1 and 3 h after injury were both proven to be effective (RR 0.68, $p < 0.0001$ vs RR: 0.79, $p = 0.03$, respectively). Conversely, an apparent increase in the risk of death due to bleeding was found in patients treated with TXA more than 3 h after injury (RR 1.44, $p = 0.004$), with the OR estimated to be multiplied by 1.15 for every hour that passed since injury [10].

The conundrum of the increase in mortality with delayed TXA administration (> 3 h from time of injury) has led some to question the utility of widespread administration of TXA in injured patients. Late TXA administration appears to be less effective and has been shown to increase mortality due to fibrinolytic shutdown [7, 23]. This suggests that giving TXA to injured patients is not a straightforward treatment therapy and requires careful consideration of its benefits and risks.

There are a few shortcomings of the CRASH-2 study including generalizability of the data beyond the military setting where the injury profile favors penetrating injury rather than blunt injury, failure to stratify injury severity, and low transfusion rate. This prompted the design of the Military Application of Tranexamic Acid in Trauma Emergency Resuscitation (MATTERs) study. This large, retrospective observational study was designed to assess the use of TXA in the combat setting [24]. A total of 896 consecutive admissions to a level 1 trauma hospital in southern Afghanistan were identified, with 293 patients receiving TXA, 125 of whom also received a massive transfusion (MT) protocol (i.e., > 10 units of packed red blood cells within 24 h). The study reported that the TXA cohort, despite being more severely injured, had a lower mortality (17.4% vs. 23.9%). The survival benefit of TXA was most significant among patients with MT, demonstrated by an odds ratio of 7.228 ($p < 0.01$). In the study cohort, the group treated with TXA had a lower absolute reduction in in-hospital mortality rate at 6.5% versus 13.7% in the group treated with MT and TXA (relative reduction of 49%) [24]. Venous thrombotic events (VTE) were also examined in this study and were greater in the TXA cohort (PE rate: 2.7% vs. 0.3%, DVT rate 2.4% vs. 0.2%) as well as the massive transfusion subgroup (PE rate: 3.2% vs. 0%, DVT rate 1.6% vs. 0.5%). However, a separate analysis found no association between any clinical parameter, including TXA administration and DVT/PE. The authors postulate this is because increased injury burden is independently associated with increased thrombotic events. Furthermore, the total number of VTEs in this study was small and therefore it is difficult to draw accurate conclusions. Additionally, these results might be the result of a survivorship phenomenon (i.e., analyzing only those that survived the intervention, while failing to factor in those that did not) since more patients remained alive in the TXA group [24]. The study team also notes that the introduction of practice guidelines to include TXA administration was introduced halfway through this study, whereas previously the administration of TXA was left to the discretion of the surgeon or anesthesiologist. In addition, inclusion of civilians' limited longitudinal data collection after these patients were stabilized and discharged, making 30-day outcome information difficult to assess. Finally, like the CRASH-2 trial, this study failed to quantify, with thromboelastography or serum coagulation makers, the degree of hyperfibrinolysis, and the response to treatment [25].

In the MATTERs study, it was observed that the TXA cohort received a greater volume of cryoprecipitate, prompting the design of the MATTERs II study [26]. The MATTERs II study is a retrospective observational study evaluating the impact of fibrinogen-containing cryoprecipitate in addition to the use of TXA on survival in combat injuries. A total of 1334 patients receiving at least one unit of PRCs were identified and subdivided into the following groups: TXA alone ($n = 148$), cryoprecipitate alone ($n = 168$), TXA + cryoprecipitate ($n = 258$), and no TXA or cryoprecipitate ($n = 758$). Of note, the ISS was higher in the cryoprecipitate (mean [SD], 28.3 [15.7]) and TXA + cryoprecipitate groups (mean [SD], 26 [14.9]) ($P < 0.001$). Despite the greater ISS, mortality was lower in the cryoprecipitate

groups (TXA + cryoprecipitate [11.6%] and TXA alone [18.2%] vs. cryoprecipitate alone [21.4%] and no TXA or cryoprecipitate [23.6%]) [26]. TXA and cryoprecipitate were independently associated with a reduced mortality (odds ratio, 0.61; 95% CI, 0.42–0.89; $P = 0.01$ and odds ratio, 0.61; 95% CI, 0.40–0.94; $P = 0.02$), respectively. Some of the strengths in the findings of this study compared to its predecessor is the longer study period and greater number of patients, making the analysis of the subgroups receiving cryoprecipitate alone and in combination with TXA feasible. Overall, the benefit of TXA in trauma patients seen in the CRASH-2 and MATTERs studies was confirmed [26]. Some limitations noted by the authors are similar to those discussed in the MATTERs study, namely changes in the protocol for the administration of TXA and blood products during the study period, as well as a nonuniform study population that included military personnel, patients, and civilians. Additionally, limited pre-hospital data is available to identify which patients had physician-led teams and therefore may have received interventions prior to hospital arrival. It is also important to note that an assumption was made regarding the benefit of cryoprecipitate administration being attributable to its fibrinogen content. Cryoprecipitate also contains von Willebrand factor and factor VIII, which could have played a role in the decreased mortality. Finally, recombinant factor VIIa was administered more frequently in the cryoprecipitate and TXA/cryoprecipitate group, which may have confounded the study's results.

TXA in Traumatic Brain Injury

One of the first studies examining the effect of TXA use on neurologic outcomes in patients with TBI was conducted as a retrospective review of the Joint Theatre Trauma Registry. The study found that early administration of TXA in combat-related head injuries was associated with reduced mortality (0% vs. 10.1%, $p = 0.02$) and improved neurologic outcomes measured by GCS scores at discharge. Specifically, patients who were treated with TXA showed an improvement in the GCS score to 14–15 regardless of their GCS upon admission (100% vs 87%, $p = 0.01$). There were limitations to this retrospective study such as possible medical documentation errors, small cohort size, and a lack of information about the timing and dose of TXA administration [27].

The CRASH-3 trial focused specifically on the effects of TXA administration in patients with acute TBI. Previously, two smaller trials showed decreased mortality with TXA administration in TBI, but failed to elucidate its effect on disability or adverse complications [10, 28••, 29, 30]. Thus, the CRASH-3 trial aimed to not only quantify the effects of TXA on mortality but also on several adverse events including pneumonia, cardiac arrest, and seizures. The CRASH-3 trial is a randomized, placebo-controlled trial performed in 175 hospitals in 29 countries that measured the mortality of early administration of TXA in patients with a TBI. The final analysis included 4613 patients who received TXA within 3 h and 4514 who received placebo. The primary outcome of 28-day in-hospital head injury associated mortality showed no significant difference between the two groups [TXA: 12.5% vs. placebo: 14.0%; RR 0.94 (95% CI, 0.86–1.02)]. However, in patients with mild to moderate TBI (GCS 9–15), mortality was significantly reduced [TXA: 5.8% vs. placebo: 7.5%; RR: 0.78 ((95% CI, 0.64–0.95)]. The investigators postulated that patients with severe TBI had sustained such extensive intracerebral hemorrhage (ICH) and brain herniation that TXA would unlikely improve the outcomes. The results of the CRASH-3 trial indicate that administration of TXA to patients with mild to moderate TBI within 3 h of injury reduces head injury-related mortality without evidence of adverse effects or complications [28••].

The Resuscitation Outcomes Consortium-Tranexamic Acid for Traumatic Brain Injury (ROC-TXA) study sought to determine the effects of TXA given pre-hospital to patients with TBI. This trial enrolled 966 participants with a mean GCS of 8. There was no statistically significant difference in 28-day mortality between the TXA groups vs the placebo group (14% vs 17%; difference, − 2.9% [95% CI, − 7.9 to 2.1%]; $P = 0.26$), 6-month Disability Rating Scale score (6.8 vs 7.6; difference, − 0.9 [95% CI, − 2.5 to 0.7]; $P = 0.29$), or progression of intracranial hemorrhage (16% vs 20%; difference, − 5.4% [95% CI, − 12.8 to 2.1%]; $P = 0.16$). The authors concluded that among patients with moderate to severe TBI, out-of-hospital TXA administration within 2 h of injury did not significantly improve 6-month neurological outcomes [31••].

TXA Use in Pre-hospital Settings

In most studies involving injured patients, the greatest benefit of TXA administration appears to be in those who received it within 1 h of injury [12]. Furthermore, it has also been noted that the risk of mortality increases with administration after the 1-h mark [12]. The mechanism behind this time-dependent effect of TXA administration has not been elucidated. However, these effects do not appear to be explained by the type of injury, presence of head injury, or systolic blood pressure (SBP) [32]. The effect may be due to PA-1 levels increasing after 3 h and causing fibrinolytic shutdown. Thus, it is recommended that all trauma patients with potentially life-threatening bleeding be treated within 3 h of injury with TXA regardless of the physiological parameters or type of injury [32].

Since the effect of TXA administration is time dependent, many researchers have sought to understand the benefits and risks of TXA administration in the pre-hospital setting. It has been shown that ambulance service personnel and emergency departments can effectively administer TXA [33]. The German Air Rescue Service

registry found that the use of TXA during pre-hospital treatment of injured civilians was associated with a significantly improved early survival [34, 35]. Another study performed in the USA found that injured civilians who were treated with pre-hospital TXA had a statistically significant decrease in 28-day mortality and fewer units of total blood products transfused with no difference in the incidence of thromboembolic complications when compared with the control groups. These studies have led to the integration of pre-hospital TXA in some institutional algorithms as this allows for TXA to administered within less time after the injury [36].

Use of TXA in Trauma Patients

During the design of the CRASH-2 trial, research into the optimal dosing of TXA revealed that dosing regimens of TXA vary widely [10, 11]. After consideration of the current literature, the investigators decided on a fixed dosing schedule of a 1 g loading dose over 10 min, followed by and additional 1 g given over 8 h [10].

As noted previously, the main consideration for the use of TXA is the time after injury, since it has been shown to be most effective when given early [14]. For this reason, experts advocate for the *empiric* use of TXA within 3 h in all trauma patients at risk of death due to bleeding, especially for patients requiring a blood transfusion. Additionally, the increasing use of viscoelastic analyzers allows the detection of hyperfibrinolysis, for which TXA can be used as a *therapeutic* agent (Fig. 1). Since the use of viscoelastic analyzers is not widespread, investigators suggest that TXA should be given to all injured patients, not only those who show evidence of hyperfibrinolysis [15, 37, 38]. Currently, in both the European and North American guidelines, the use of TXA for injured patients, either empirically (within three hours of injury) or therapeutically based on viscoelastic demonstration of hyperfibrinolysis, is recommended [5••]. However, because TXA administration after 3 h from the time of injury increases the risk of death, it is generally contraindicated outside of this window.

Potential Risks of TXA Administration in Trauma Patients

Despite the potential benefits of TXA use in trauma patients, there are some potential risks that should be considered. As noted in the CRASH-2 trial, the therapeutic window seems to be limited to administration within 3 h of injury. The CRASH-2 collaborators speculated that the adverse effects of TXA administration past 3 h may be attributed to the development of disseminated intravascular coagulation (DIC) in the later phases of trauma, wherein antifibrinolytics would be contraindicated [10, 39]. The findings of the CRASH-3 trial also noted that a delay in treatment could decrease the benefit of TXA administration. The CRASH-3 collaborators postulated this decreased benefit may be due to the hemorrhage expansion that occurs in the time immediately after head injury and thus a time delay in treatment would reduce the ability of TXA to prevent intracranial bleeding [28••, 40••].

There are multiple limitations of the CRASH-2 trial that should be discussed. Specifically, the participating centers were in areas without mature trauma networks, calling into question the applicability of the results to countries with more advanced trauma systems. Furthermore, patient enrollment into the trial was based on the "uncertainty principle" of randomization. This means that if the physician clearly thought the patient would benefit from TXA or that TXA was contraindicated, the patient was excluded. Patients were enrolled only if the enrolling physician was uncertain if there would be a benefit of TXA administration [1, 34]. Due to this method of inclusion in the study, most of the patients in shock were thought to benefit from TXA administration and therefore were not enrolled in the study. This may be the reason that about half of the patients enrolled in the trial did not receive a transfusion. Also, there was no protocolized approach in the CRASH-2 trial for detection or diagnosis for the incidence of VTE [1, 16]. This has led some to question the outcome that TXA administration did not increase the incidence of VTE. Finally, the overall reduction of all-cause mortality and deaths due to bleeding in the TXA group was small (1.5% and 0.8%, respectively). While these results are statistically significant due to the large enrollment, there may not be a significant *clinical* benefit.

Subsequently, several smaller cohort studies on the use of TXA in advanced trauma systems within the USA did not produce the same results as the CRASH-2 trial, finding instead that TXA was *not* associated with a reduction in mortality [1, 41, 42]. Furthermore, a retrospective study showed a threefold increase in the risk of VTE in patients treated with TXA and another study of patients at US military combat support hospitals likewise found that TXA administration was an independent risk factor for VTE [43, 44]. Thus, the frequency of thrombotic events among trauma patients receiving TXA is unclear and deserves more investigation [16, 38].

Many questions regarding the benefit of early TXA administration remain and as a result, trauma systems have been slow to adopt its widespread use within their treatment algorithms for hemorrhagic shock. Following the publication of the CRASH-2 trial results, Coats et al. reported low proportions of patients treated with TXA in a longitudinal and cross-sectional study. These results persisted in groups with early physiological

Table 1 Summary of major tranexamic acid studies

	Patient population	TXA dosing	Outcomes (mortality)
CRASH-2	Adult trauma patients deemed to be at risk for significant bleeding	**Loading dose:** 1 g at an infusion rate of 100 mL over 10 min **Maintenance dose:** 1 g at an infusion rate of 60 ml/h for 8 h	**Reduction in all-cause mortality** TXA group (treated within 1 h and between 1 and 3 h after injury): 14.5% No TXA group: 16.0% (RR 0.91, 95% CI 0.85–0.97)
MATTERs	Patients admitted to a level 1 trauma hospital in southern Afghanistan	Mean [SD] dose: IV administration of 2.3 [1.3] g within 1 h of injury	**Lower mortality** TXA group: 17.4% No TXA group: 23.9%
MATTERs II	Patients admitted to a level 1 trauma hospital in southern Afghanistan	Bolus of 1 g intravenous, followed by further doses at clinician's discretion *Cryoprecipitate pooled from 10 donors with a fibrinogen concentration around 15 g/L	**Mortality lower** in the cryoprecipitate groups TXA + cryoprecipitate: 11.6% TXA alone: 18.2% cryoprecipitate alone: 21.4% no TXA or cryoprecipitate: [23.6%)]
CRASH-3	Patients with acute TBI	**Loading dose:** 1 g over 10 min **Maintenance dose**: infusion of 1 g over 8 h	in patients with mild to moderate TBI (GCS 9–15), **mortality significantly reduced** TXA group: 5.8% No TXA group: 7.5% RR: 0.78 (95% CI, 0.64–0.95)

abnormalities indicating a serious risk of hemorrhage [45]. Pre-hospital administration of TXA might prove to be an effective strategy since the effects of TXA are time dependent, but more studies are needed to conclude whether pre-hospital TXA administration improves overall trauma outcomes [46].

The limitations of this review include the possibility that not all relevant recent publications were included due to the constraints of the literature search. Also, since the literature search was limited to publications written in English (or those that had a form that was translated into English), the findings may be biased towards English-speaking countries.

Conclusion

The implementation of TXA in trauma care remains a prominent topic of interest. Its use has the potential to improve survival in patients at risk of hemorrhage or TBI-associated mortality, as shown in numerous studies (Table 1). The exact mechanism of action of TXA remains unclear, as do the potential for thrombotic and fibrinolytic shutdown-related complications. Caution must be used when the timing of injury is unknown, as outcomes have been shown to be worse when TXA is administered more than 3 h after injury. Although further research must be conducted to fully elucidate the clinical utility and guidelines for administering TXA in trauma patients, recent studies show that TXA provides a clear benefit in hemorrhage control when given within 3 h of injury.

GCS Glasgow Coma Scale, *TBI* traumatic brain injury, *TXA* tranexamic acid.

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Declarations

Conflict of Interest The authors do not have any potential conflicts of interest to disclose.

Human and Animal Rights and Informed Consent This article does not contain any studies with humans or animals as the subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
• Of importance
•• Of major importance

1. Ramirez RJ, Spinella PC, Bochicchio GV. Tranexamic acid update in trauma. Crit Care Clin. 2017;33(1):85–99. https://doi.org/10.1016/j.ccc.2016.08.004.
2. Ker K, Kiriya J, Perel P, Edwards P, Shakur H, Roberts I. Avoidable mortality from giving tranexamic acid to bleeding

trauma patients: an estimation based on WHO mortality data, a systematic literature review and data from the CRASH-2 trial. BMC Emerg Med. 2012;12:3. https://doi.org/10.1186/1471-227X-12-3.

3. Pabinger I, Fries D, Schochl H, Streif W, Toller W. Tranexamic acid for treatment and prophylaxis of bleeding and hyperfibrinolysis. Wien Klin Wochenschr. 2017;129(9–10):303–16. https://doi.org/10.1007/s00508-017-1194-y.
4. Rossaint R, Bouillon B, Cerny V, Coats TJ, Duranteau J, Fernandez-Mondejar E, et al. The European guideline on management of major bleeding and coagulopathy following trauma: fourth edition. Crit Care. 2016;20:100. https://doi.org/10.1186/s13054-016-1265-x.
5.•• Hanley C, Callum J, Jerath A. Tranexamic acid and trauma coagulopathy: where are we now? Br J Anaesth. 2021;126(1):12–7. https://doi.org/10.1016/j.bja.2020.09.014. (**This review proposed the mechanism of TXA in controlling bleeding and thus made hypotheses about the time-dependent effect of TXA administration in trauma patients.**)
6. Callcut RA, Kornblith LZ, Conroy AS, Robles AJ, Meizoso JP, Namias N, et al. The why and how our trauma patients die: a prospective Multicenter Western Trauma Association study. J Trauma Acute Care Surg. 2019;86(5):864–70. https://doi.org/10.1097/TA.0000000000002205.
7. CRASH-2 Collaborators, Roberts I, Shakur H, Afolabi A, Brohi K, Coats T, et al. The importance of early treatment with tranexamic acid in bleeding trauma patients: an exploratory analysis of the CRASH-2 randomised controlled trial. Lancet. 2011;377(9771):1096–101, 101 e1–2. https://doi.org/10.1016/S0140-6736(11)60278-X.
8. Dewan MC, Rattani A, Gupta S, Baticulon RE, Hung YC, Punchak M, et al. Estimating the global incidence of traumatic brain injury. J Neurosurg. 2018:1–18. https://doi.org/10.3171/2017.10.JNS17352.
9. Perel P, Roberts I, Bouamra O, Woodford M, Mooney J, Lecky F. Intracranial bleeding in patients with traumatic brain injury: a prognostic study. BMC Emerg Med. 2009;9:15. https://doi.org/10.1186/1471-227X-9-15.
10. Roberts I, Shakur H, Coats T, Hunt B, Balogun E, Barnetson L, et al. The CRASH-2 trial: a randomised controlled trial and economic evaluation of the effects of tranexamic acid on death, vascular occlusive events and transfusion requirement in bleeding trauma patients. Health Technol Assess. 2013;17(10):1–79. https://doi.org/10.3310/hta17100.
11. Henry DA, Carless PA, Moxey AJ, O'Connell D, Stokes BJ, Fergusson DA, et al. Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion. Cochrane Database Syst Rev. 2011(1):CD001886. https://doi.org/10.1002/14651858.CD001886.pub3.
12. McCormack PL. Tranexamic acid: a review of its use in the treatment of hyperfibrinolysis. Drugs. 2012;72(5):585–617. https://doi.org/10.2165/11209070-000000000-00000.
13. Hu M, Liu ZB, Bi G. Efficacy and safety of tranexamic acid in orthopaedic trauma surgery: a meta-analysis. Eur Rev Med Pharmacol Sci. 2019;23(24):11025–31. https://doi.org/10.26355/eurrev_201912_19810.
14. Hunt BJ. The current place of tranexamic acid in the management of bleeding. Anaesthesia. 2015;70 Suppl 1:50–3, e18. https://doi.org/10.1111/anae.12910.
15. Roberts I. Tranexamic acid in trauma: how should we use it? J Thromb Haemost. 2015;13(Suppl 1):S195–9. https://doi.org/10.1111/jth.12878.
16. Cai J, Ribkoff J, Olson S, Raghunathan V, Al-Samkari H, DeLoughery TG, et al. The many roles of tranexamic acid: an overview of the clinical indications for TXA in medical and surgical patients. Eur J Haematol. 2020;104(2):79–87. https://doi.org/10.1111/ejh.13348.
17.•• Lier H, Maegele M, Shander A. Tranexamic Acid for acute hemorrhage: a narrative review of landmark studies and a critical reappraisal of its use over the last decade. Anesth Analg. 2019;129(6):1574–84. https://doi.org/10.1213/ANE.0000000000004389. (**This review discussed the general mechanism of action of TXA and analyzed the findings of major studies examining the use of TXA in trauma. By analyzing the landmark CRASH-2 trials and the MATTERs studies, this review gave a comprehensive understanding of the known benefits and risks of TXA use in trauma.**)
18. Jennings JD, Solarz MK, Haydel C. Application of tranexamic acid in trauma and orthopedic surgery. Orthop Clin North Am. 2016;47(1):137–43. https://doi.org/10.1016/j.ocl.2015.08.014.
19. Moore HB, Moore EE, Liras IN, Gonzalez E, Harvin JA, Holcomb JB, et al. Acute Fibrinolysis shutdown after injury occurs frequently and increases mortality: a multicenter evaluation of 2,540 severely injured patients. J Am Coll Surg. 2016;222(4):347–55. https://doi.org/10.1016/j.jamcollsurg.2016.01.006.
20. Moore HB, Moore EE, Gonzalez E, Chapman MP, Chin TL, Silliman CC, et al. Hyperfibrinolysis, physiologic fibrinolysis, and fibrinolysis shutdown: the spectrum of postinjury fibrinolysis and relevance to antifibrinolytic therapy. J Trauma Acute Care Surg. 2014;77(6):811–7; discussion 7. https://doi.org/10.1097/TA.0000000000000341.
21. Meizoso JP, Karcutskie CA, Ray JJ, Namias N, Schulman CI, Proctor KG. Persistent fibrinolysis shutdown is associated with increased mortality in severely injured trauma patients. J Am Coll Surg. 2017;224(4):575–82. https://doi.org/10.1016/j.jamcollsurg.2016.12.018.
22. Ker K, Prieto-Merino D, Roberts I. Systematic review, meta-analysis and meta-regression of the effect of tranexamic acid on surgical blood loss. Br J Surg. 2013;100(10):1271–9. https://doi.org/10.1002/bjs.9193.
23. Moore HB, Moore EE, Neal MD, Sheppard FR, Kornblith LZ, Draxler DF, et al. Fibrinolysis Shutdown in trauma: historical review and clinical implications. Anesth Analg. 2019;129(3):762–73. https://doi.org/10.1213/ANE.0000000000004234.
24. Morrison JJ, Dubose JJ, Rasmussen TE, Midwinter MJ. Military Application of Tranexamic Acid in Trauma Emergency Resuscitation (MATTERs) Study. Arch Surg. 2012;147(2):113–9. https://doi.org/10.1001/archsurg.2011.287.
25. Inaba K. Antifibrinolytics in trauma patients: does it MATTER? Arch Surg. 2012;147(2):119. https://doi.org/10.1001/archsurg.2011.286.
26. Morrison JJ, Ross JD, Dubose JJ, Jansen JO, Midwinter MJ, Rasmussen TE. Association of cryoprecipitate and tranexamic acid with improved survival following wartime injury: findings from the MATTERs II Study. JAMA Surg. 2013;148(3):218–25. https://doi.org/10.1001/jamasurg.2013.764.
27. Morte D, Lammers D, Bingham J, Kuckelman J, Eckert M, Martin M. Tranexamic acid administration following head trauma in a combat setting: does tranexamic acid result in improved neurologic outcomes? J Trauma Acute Care Surg. 2019;87(1):125–9. https://doi.org/10.1097/TA.0000000000002269.
28.•• Collaborators C-t. Effects of tranexamic acid on death, disability, vascular occlusive events and other morbidities in patients with acute traumatic brain injury (CRASH-3): a randomised, placebo-controlled trial. Lancet. 2019;394(10210):1713–23. https://doi.org/10.1016/S0140-6736(19)32233-0. (**This was a subsequent study conducted by the CRASH-2 investigators that examined the effects of TXA administration on patients with acute**

traumatic brain injury. Thus, this study further broadened the scope of understanding TXA use in trauma.)

29. Yutthakasemsunt S, Kittiwatanagul W, Piyavechvirat P, Thinkamrop B, Phuenpathom N, Lumbiganon P. Tranexamic acid for patients with traumatic brain injury: a randomized, double-blinded, placebo-controlled trial. BMC Emerg Med. 2013;13:20. https://doi.org/10.1186/1471-227X-13-20.
30. Perel P, Al-Shahi Salman R, Kawahara T, Morris Z, Prieto-Merino D, Roberts I, et al. CRASH-2 (Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage) intracranial bleeding study: the effect of tranexamic acid in traumatic brain injury--a nested randomised, placebo-controlled trial. Health Technol Assess. 2012;16(13):iii-xii, 1–54. https://doi.org/10.3310/hta16130.
31. •• Rowell SE, Meier EN, McKnight B, Kannas D, May S, Sheehan K, et al. Effect of out-of-hospital tranexamic acid vs placebo on 6-month functional neurologic outcomes in patients with moderate or severe traumatic brain injury. JAMA. 2020;324(10):961–74. https://doi.org/10.1001/jama.2020.8958. (**This was a multicenter, double-blinded, randomized clinical trial aimed at examining TXA administration in patients with TBI, concluding that in patients with moderate to severe TBI, TXA administration within 2 h compared with the placebo did not significantly improve 6-month neurologic outcome. This is a more recent application of TXA in trauma and ongoing area of research.**)
32. Roberts I, Edwards P, Prieto D, Joshi M, Mahmood A, Ker K, et al. Tranexamic acid in bleeding trauma patients: an exploration of benefits and harms. Trials. 2017;18(1):48. https://doi.org/10.1186/s13063-016-1750-1.
33. Paudyal P, Smith J, Robinson M, South A, Higginson I, Reuben A, et al. Tranexamic acid in major trauma: implementation and evaluation across South West England. Eur J Emerg Med. 2017;24(1):44–8. https://doi.org/10.1097/MEJ.0000000000000323.
34. Huebner BR, Dorlac WC, Cribari C. Tranexamic acid use in prehospital uncontrolled hemorrhage. Wilderness Environ Med. 2017;28(2S):S50–60. https://doi.org/10.1016/j.wem.2016.12.006.
35. Wafaisade A, Lefering R, Bouillon B, Bohmer AB, Gassler M, Ruppert M, et al. Prehospital administration of tranexamic acid in trauma patients. Crit Care. 2016;20(1):143. https://doi.org/10.1186/s13054-016-1322-5.
36. Neeki MM, Dong F, Toy J, Vaezazizi R, Powell J, Wong D, et al. Tranexamic acid in civilian trauma care in the California Prehospital Antifibrinolytic Therapy Study. West J Emerg Med. 2018;19(6):977–86. https://doi.org/10.5811/westjem.2018.8.39336.
37. Chapman MP, Moore EE, Ramos CR, Ghasabyan A, Harr JN, Chin TL, et al. Fibrinolysis greater than 3% is the critical value for initiation of antifibrinolytic therapy. J Trauma Acute Care Surg. 2013;75(6):961–7; discussion 7. https://doi.org/10.1097/TA.0b013e3182aa9c9f.
38. Napolitano LM, Cohen MJ, Cotton BA, Schreiber MA, Moore EE. Tranexamic acid in trauma: how should we use it? J Trauma Acute Care Surg. 2013;74(6):1575–86. https://doi.org/10.1097/TA.0b013e318292cc54.
39. Sawamura A, Hayakawa M, Gando S, Kubota N, Sugano M, Wada T, et al. Disseminated intravascular coagulation with a fibrinolytic phenotype at an early phase of trauma predicts mortality. Thromb Res. 2009;124(5):608–13. https://doi.org/10.1016/j.thromres.2009.06.034.
40. •• Gayet-Ageron A, Prieto-Merino D, Ker K, Shakur H, Ageron FX, Roberts I, et al. Effect of treatment delay on the effectiveness and safety of antifibrinolytics in acute severe haemorrhage: a meta-analysis of individual patient-level data from 40 138 bleeding patients. Lancet. 2018;391(10116):125–32. https://doi.org/10.1016/S0140-6736(17)32455-8. (**This was a meta-analysis conducted to understand the effect of treatment delay in the use of antifibrinolytics like TXA. Importantly, this study found that even a short delay in treatment reduces the benefit of TXA administration.**)
41. Harvin JA, Peirce CA, Mims MM, Hudson JA, Podbielski JM, Wade CE, et al. The impact of tranexamic acid on mortality in injured patients with hyperfibrinolysis. J Trauma Acute Care Surg. 2015;78(5):905–9; discussion 9–11. https://doi.org/10.1097/TA.0000000000000612.
42. Valle EJ, Allen CJ, Van Haren RM, Jouria JM, Li H, Livingstone AS, et al. Do all trauma patients benefit from tranexamic acid? J Trauma Acute Care Surg. 2014;76(6):1373–8. https://doi.org/10.1097/TA.0000000000000242.
43. Myers SP, Kutcher ME, Rosengart MR, Sperry JL, Peitzman AB, Brown JB, et al. Tranexamic acid administration is associated with an increased risk of posttraumatic venous thromboembolism. J Trauma Acute Care Surg. 2019;86(1):20–7. https://doi.org/10.1097/TA.0000000000002061.
44. Johnston LR, Rodriguez CJ, Elster EA, Bradley MJ. Evaluation of military use of tranexamic acid and associated thromboembolic events. JAMA Surg. 2018;153(2):169–75. https://doi.org/10.1001/jamasurg.2017.3821.
45. Coats TJ, Fragoso-Iniguez M, Roberts I. Implementation of tranexamic acid for bleeding trauma patients: a longitudinal and cross-sectional study. Emerg Med J. 2019;36(2):78–81. https://doi.org/10.1136/emermed-2018-207693.
46. Briggs GD, Balogh ZJ. Tranexamic acid and inflammation in trauma. ANZ J Surg. 2020;90(4):426–8. https://doi.org/10.1111/ans.15755.