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The Role of Tranexamic Acid in Managing Traumatic Hemorrhage: A Review of Current Evidence

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ABSTRACT

Introduction. Traumatic hemorrhage is one of the leading causes of death among patients with severe injuries. Tranexamic acid (TXA), a synthetic antifibrinolytic agent, has shown potential to reduce massive blood loss and decrease mortality.

Aim. The aim of this study was to analyze current evidence regarding the efficacy and safety of tranexamic acid in the treatment of traumatic hemorrhage and to assess the factors influencing its therapeutic effect**.**

Methods. A literature review was conducted covering publications (2010-2026), including clinical studies, randomized controlled trials, systematic reviews, and meta-analyses concerning the use of TXA in trauma patients. Data on the timing and route of administration, dosing, efficacy, and safety of therapy were analyzed.

Results. TXA reduces blood loss and may lower mortality, especially when administered early after injury. Intravenous use is standard, while intraosseous or intramuscular routes may be used prehospital. TXA is generally safe, but monitoring for thromboembolic events and dose-related adverse effects is recommended in patients with multiple injuries.

Conclusions. TXA is an effective and safe option in traumatic hemorrhage management. Its efficacy depends on timing, dosing, and patient factors. Early use improves outcomes, but further research is needed to optimize treatment and assess alternative administration routes.

Keywords: tranexamic acid, traumatic hemorrhage, antifibrinolytic therapy, trauma, timing of administration, route of administration

INTRODUCTION

Severe trauma constitutes a major global public health burden. Each year, injuries account for 4.4 million deaths worldwide.(1) Traumatic hemorrhage and trauma-induced coagulopathy remain leading causes of potentially preventable multiorgan failure and death when not promptly recognized and appropriately managed.(2,3,4) Early diagnosis and rapid initiation of treatment are therefore crucial for improving patient outcomes.(3)

Trauma-induced coagulopathy is a complex hemostatic disorder that develops in the early phase of severe injury. It results, among other factors, from shock, tissue damage, and activation of inflammatory pathways. This process leads to excessive activation of fibrinolysis, resulting in clot breakdown and increased blood loss. Consequently, growing attention has been directed

toward the use of antifibrinolytic agents as part of the management of patients with severe trauma.(4,5)

Tranexamic acid (TXA) is a synthetic lysine analogue with antifibrinolytic properties. It is used in the management of critical bleeding states, including traumatic hemorrhage, as well as in surgical settings, particularly cardiac surgery and orthopedics, (5) in order to reduce blood loss and transfusion requirements.

A major contribution to research on the use of tranexamic acid came from the multicenter CRASH-2 clinical trial, which demonstrated a reduction in the risk of death in patients with traumatic bleeding treated with TXA. (6) Subsequently, the CRASH-3 trial suggested that tranexamic acid may reduce the risk of death due to traumatic brain injury, with the timing of administration being a key determinant of therapeutic benefit. (7)

Despite numerous studies, the efficacy of tranexamic acid in the treatment of traumatic hemorrhage remains a matter of some debate. Ongoing analyses aim to determine the optimal dose and timing of administration, as well as to assess potential adverse effects. Therefore, a systematic summary of the current scientific evidence regarding its use in the treatment of traumatic hemorrhage is warranted.

The aim of this study is to analyze current scientific reports published between 2010 and 2026 regarding the efficacy and safety of tranexamic acid in the treatment of traumatic hemorrhage.

METHODS

A literature review was conducted using the PubMed database. The search included publications published between 2010 and 2026. Keywords related to tranexamic acid and traumatic hemorrhage were applied, including, but not limited to, “tranexamic acid,” “trauma,” “traumatic hemorrhage,” “bleeding,” “traumatic brain injury,” “mortality,” and “tranexamic mechanism.”

English-language publications involving human subjects were included in the analysis. Eligible study types comprised clinical studies, randomized controlled trials, systematic reviews, and meta-analyses. Publications not directly related to traumatic hemorrhage were excluded, particularly articles concerning the use of tranexamic acid in dermatology and gynecology, as well as single case reports.

The selection of publications was performed in two stages. In the first stage, article titles and abstracts were analyzed in order to exclude studies that did not meet the inclusion criteria. In the second stage, full-text assessment of the eligible publications was conducted. Ultimately,

articles presenting current data on the efficacy and safety of tranexamic acid in the treatment of traumatic hemorrhage were included in the analysis.

MECHANISM OF ACTION OF TRANEXAMIC ACID

Tranexamic acid (TXA) is a synthetic lysine analogue that acts as an effective inhibitor of fibrinolysis. Its primary mechanism of action is the competitive blockade of lysine-binding sites on plasminogen molecules, thereby preventing their interaction with fibrin and their activation to plasmin, the enzyme responsible for fibrin degradation. Inhibition of this process stabilizes the fibrin clot and prevents excessive blood loss.(8)

In addition to its antifibrinolytic effect, tranexamic acid may also influence the cellular and inflammatory response following trauma. Experimental studies have shown that TXA may reduce the release of mitochondrial DNA (mtDNA) from granulocytes and endothelial cells, thereby attenuating the systemic inflammatory response that occurs after injury. It has also been reported to improve cellular energy metabolism by enhancing mitochondrial respiration and ATP production, thereby increasing cellular survival under conditions of hypoxia and post-traumatic stress. Another proposed effect of TXA is the stimulation of mitochondrial biogenesis together with inhibition of mitochondrial elimination. Through these pleiotropic effects, tranexamic acid may help preserve endothelial integrity and reduce endothelial disruption associated with hemorrhagic shock.(9)

Tranexamic acid may also affect fibrin structure. Experimental data suggest that high doses of TXA can alter fibrin network density, which may initially appear beneficial, particularly in the context of more rapid hemorrhage control. However, higher TXA concentrations may lead to the formation of abnormally dense fibrin networks that, although seemingly more stable at first, may ultimately compromise clot stability over time. Such structural alterations may impair the mechanical properties of fibrin and consequently increase the risk of forming less stable clots that may subsequently undergo breakdown.(10) This may adversely affect tissue healing; however, this issue requires further investigation.

EFFICACY OF TRANEXAMIC ACID IN THE TREATMENT OF TRAUMATIC HEMORRHAGE

Tranexamic acid is widely used in the treatment of traumatic hemorrhage. Its efficacy has been demonstrated in numerous clinical studies showing benefits in terms of improved survival among trauma patients. In recent years, however, several studies have also introduced some controversy regarding its effect on survival and long-term functional outcomes.

The randomized CRASH-2 trial, which included more than 20,000 patients with traumatic bleeding, demonstrated that the use of TXA significantly reduced the risk of death within 28 days of injury.(6) The international CRASH-3 trial evaluated the efficacy of TXA in patients with acute traumatic brain injury. According to its findings, the authors concluded that TXA is safe and may reduce the number of deaths related to head injury, provided that it is administered within an appropriate time frame after trauma.(7)

By contrast, the 2023 PATCH-Trauma trial, which analyzed the effect of prehospital administration of tranexamic acid, showed that this treatment did not increase the likelihood of survival with a favorable functional outcome at six months compared with placebo. (11)These findings suggest that the efficacy of TXA may depend not only on the use of the drug itself, but also on the timing of administration, the patient population, and the selected study endpoints.

TIMING OF ADMINISTRATION

The timing of drug administration is a key determinant of therapeutic efficacy. Available evidence indicates that the effectiveness of TXA is closely associated with the earliest possible initiation of treatment after injury.(12)

In the CRASH-2 and CRASH-3 trials, administration of TXA within the first 3 hours after trauma was found to be most beneficial in terms of reducing bleeding and improving patient outcomes.(6 ,7) In particular, CRASH-3 demonstrated that treatment initiated within 3 hours of injury reduced the risk of death due to traumatic brain injury.(7)

A more detailed analysis of the relationship between treatment timing and therapeutic effect was provided by Gayet-Ageron et al. in an individual patient-level data meta-analysis including 40,138 patients with acute severe bleeding. The authors showed that immediate treatment increased survival from bleeding by more than 70%, while the therapeutic benefit decreased by approximately 10% for every 15-minute delay, up to 3 hours, after which no significant benefit was observed. Moreover, most deaths due to bleeding occurred within the first 12 hours after the onset of hemorrhage, and many patients died within the first hours after injury.(12)

More recent studies suggest that the optimal therapeutic window may be even shorter, potentially within approximately 90 minutes after injury, whereas administration beyond this period may be of uncertain benefit.(13) However, this issue still requires further investigation.

ROUTE OF ADMINISTRATION

In the treatment of traumatic hemorrhage, the primary and best-studied route of tranexamic acid administration is the intravenous route. This was the route used in the largest clinical trials

evaluating TXA in trauma patients, including the CRASH-2 and PATCH-Trauma studies.(6,11) Intravenous administration enables the rapid achievement of therapeutic drug concentrations, which is of particular importance in acute bleeding, where efficacy is highly dependent on the timing of administration.(12)

The drug is most commonly administered initially as an intravenous bolus, followed by continuous infusion over 8 hours. This regimen allows for a rapid onset of antifibrinolytic activity and subsequent maintenance of the therapeutic effect.(6,11) For this reason, the intravenous route remains the standard of care in the management of patients with severe traumatic hemorrhage.

Recent studies have also drawn attention to the potential role of alternative routes of administration, particularly in the prehospital setting, where rapid intravenous access may be difficult or impossible to obtain. One such option is the intraosseous route, which may serve as a practical alternative, especially in critically ill patients. Available data suggest that intraosseous administration may provide effects comparable to those of intravenous administration; however, the number of clinical studies in this area remains limited.(14,15)

The intramuscular route has also been considered, particularly in the context of prehospital use, including by personnel who are not authorized to establish intravenous access. Pharmacokinetic studies suggest that intramuscular administration may allow therapeutic concentrations of tranexamic acid to be achieved; however, its actual clinical relevance in the treatment of severe traumatic hemorrhage requires further investigation. A potential advantage of this route is that it may facilitate broader use of the drug in trauma patients and in other bleeding conditions, particularly in situations where rapid intravenous access is difficult to obtain, as well as in low- and middle-income healthcare systems.(16)

The literature also describes non-standard routes of tranexamic acid administration, such as inhalational or endotracheal delivery,(17) but these apply mainly to selected clinical situations, such as pulmonary hemorrhage, rather than typical traumatic bleeding. Therefore, their role in trauma management remains limited.

In summary, the intravenous route remains the route of choice in the treatment of traumatic hemorrhage, whereas alternative routes, such as intraosseous or intramuscular administration, may have a role in selected clinical situations, particularly when intravenous access is delayed or impossible.

DOSING

The best-documented dosing regimen of tranexamic acid in the treatment of traumatic hemorrhage consists of 1 g administered intravenously over 10 minutes, followed by 1 g by intravenous infusion over 8 hours. This regimen was established in the CRASH-2 trial and subsequently became the foundation for recommendations regarding the use of tranexamic acid in trauma patients.(6) It is also recommended in current European guidelines for the management of major bleeding and coagulopathy following trauma.(3)

Alternative dosing regimens, including higher doses such as 2–3 g, are currently under investigation. In the STAAMP analysis, a regimen involving administration of 3 g of TXA (two bolus doses plus infusion) was associated with lower mortality compared with placebo, which may suggest a potential dose–response relationship; however, this finding requires further confirmation.(18) At present, the available evidence is insufficient to replace the conventional 1 g + 1 g regimen with an alternative dosing strategy.

SAFETY OF TRANEXAMIC ACID USE

Available evidence indicates that tranexamic acid has a favorable safety profile in the treatment of traumatic hemorrhage. One of the key arguments supporting this conclusion was provided by the CRASH-2 trial, which did not demonstrate an increased risk of thromboembolic events.(6)

Subsequent meta-analyses likewise did not show a statistically significant increase in the incidence of thromboembolic complications, including deep vein thrombosis, pulmonary embolism, or stroke.(19,20) This is of particular importance in the trauma population, in whom severe tissue injury, immobilization, and coexisting hemostatic disturbances already confer an inherently increased thrombotic risk.

At the same time, it should be noted that the safety data are not entirely unequivocal. Some more recent studies have suggested a possible higher incidence of thromboembolic events in patients with multiple injuries receiving tranexamic acid.(20) These findings, however, should be interpreted with caution, as they generally involve more severely injured patients who are already at higher baseline risk. The authors of these studies do not recommend withholding the drug, but rather advise screening for thromboembolic complications and initiating thromboprophylaxis as soon as possible after hemostatic disturbances have been controlled.(21)

In recent years, attention has also been drawn to the possibility of seizures, particularly with higher doses of tranexamic acid. In an analysis involving patients with moderate to severe traumatic brain injury, prehospital administration of a 2 g TXA bolus was not associated with

an increased incidence of seizures, although the authors emphasized the need for further research.(22)

IMPACT OF TRANEXAMIC ACID ON MORTALITY

The effect of tranexamic acid on mortality is one of the key components in assessing its efficacy. The most important evidence was provided by the CRASH-2 trial, which demonstrated a reduction in the risk of death, particularly death due to exsanguination.(6)

In patients with traumatic brain injury, the effect of tranexamic acid is less clear-cut. The CRASH-3 trial showed that the drug may reduce the risk of death related to head injury.(7) However, the PATCH-Trauma trial did not demonstrate an increased rate of survival with a favorable functional outcome at 6 months compared with placebo.(11) These findings suggest that the impact of TXA on mortality and long-term outcomes may depend on the type of injury, the characteristics of the study population, and the endpoints adopted in a given trial.

The strongest evidence supports a reduction in deaths due to hemorrhage, whereas the effect of TXA on overall mortality and long-term outcomes remains more complex.

DISCUSSION

Analysis of the available evidence confirms that tranexamic acid is an effective antifibrinolytic agent in the treatment of traumatic hemorrhage, although its efficacy depends on multiple clinical factors.(23,24) The timing of administration is of particular importance, as early initiation of therapy, ideally within the first hours after injury, significantly increases the likelihood of limiting massive blood loss. (6,7,12) Delayed administration reduces the therapeutic benefit, suggesting the existence of a limited time window during which TXA can exert its maximum effect on hemostatic processes.(12,13)

The route of administration represents another important determinant of treatment efficacy.(14,15,16,25) Intravenous administration ensures rapid attainment of therapeutic drug concentrations, which is crucial in the acute phase of hemorrhage.(12,26) In the prehospital setting or in cases of difficult intravenous access, alternative routes such as intraosseous or intramuscular administration have been considered.(14,16) Although clinical data in this area remain limited, these approaches may improve treatment accessibility and enable earlier drug administration in critical situations.(15,16)

The safety profile of TXA is generally favorable, and the incidence of thromboembolic complications remains low with standard doses and administration regimens.(20,27,28,29,30) Nevertheless, it should be recognized that patients with severe trauma already belong to a

population at increased risk of thrombotic events, which warrants careful monitoring and individualized management.(21,29,31) Higher doses of the drug may be associated with adverse effects such as seizures, highlighting the need for caution and for further research in this area.(22)

The efficacy of TXA may vary depending on the type of injury and the characteristics of the patient population. Factors such as the severity of bleeding, the presence of traumatic brain injury, and coexisting comorbidities may all influence the therapeutic response. In addition, heterogeneity in study endpoints and dosing regimens across available trials makes direct comparison difficult and limits the ability to draw definitive conclusions regarding the optimal treatment strategy.(32,33)

Despite promising findings from some studies, the efficacy of tranexamic acid has not been confirmed uniformly across all trauma populations. In particular, with respect to patients with traumatic brain injury, prehospital treatment, and alternative dosing regimens, the currently available evidence remains inconclusive, making it difficult to formulate fully definitive clinical conclusions. It should also be emphasized that the benefits attributed to tranexamic acid are derived largely from analyses of selected endpoints, whereas its effect on overall mortality and long-term outcomes is not equally consistent across all studies.(34)

The variability of study findings underscores the need for individualized therapy and for consideration of patient-specific clinical factors. At the same time, it highlights the necessity for further research aimed at precisely defining the optimal time window for TXA administration, appropriate dosing regimens, and the potential role of alternative routes of administration, particularly in the prehospital setting.(35,36)

CONCLUSIONS

Tranexamic acid is an important component of the treatment of traumatic hemorrhage and is widely recommended in the management of patients with severe trauma. Its use may reduce hemorrhage-related mortality, particularly when administered early after injury.(3, 6,37,38)

The timing of administration remains a key determinant of therapeutic efficacy. The greatest benefit is observed when TXA is given within the first hours after trauma, highlighting the importance of rapid identification of patients at risk of severe hemorrhage and immediate initiation of treatment.(6,7,12,39,40)

The standard dosing regimen remains 1 g of tranexamic acid administered intravenously as a bolus, followed by 1 g by continuous infusion over 8 hours. The intravenous route is the best-documented method of administration; however, alternative routes, such as intramuscular or

intraosseous administration, may represent useful options in selected clinical situations, particularly in the prehospital setting.(6,14,15,39)

Available studies indicate that TXA has a favorable safety profile in the trauma population. At the same time, further research is required to more precisely define the optimal timing of administration, dosing regimens, and the identification of patients who may derive the greatest benefit from this therapy. In light of current evidence, TXA remains an important component of trauma management protocols, particularly in the setting of early intervention.(20)

Disclosure

Authors do not report any disclosures.

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