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Review

Tranexamic acid for trauma: narrative review

Ácido tranexâmico para trauma: revisão narrativa

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ABSTRACT

Trauma is one of the main causes of death and disability worldwide. One of the main treatments for this situation is the infusion of tranexamic acid in patients with trauma-induced coagulopathy or even traumatic brain injury. We discuss the evidence on the use of this drug in trauma patients with the conditions described. Thus, this narrative review aimed to point out the results, divergences and new perspectives of the main studies and new recommendations related to tranexamic acid infusion in patients with trauma-induced coagulopathy and traumatic brain injury.

Keywords: Tranexamic acid; Hemorrhage; Craniocerebral trauma; Wounds and injuries

RESUMO

O trauma constitui uma das principais causas de óbito e incapacidade em todo mundo. Um dos principais tratamentos para essa situação é a infusão de ácido tranexâmico em pacientes com coagulopatia induzida pelo trauma ou mesmo traumatismo craniencefálico. Discutimos as evidências acerca da utilização desse medicamento nos pacientes vítimas de trauma com as condições descritas. Assim, esta revisão narrativa teve o objetivo de apontar os resultados, as divergências e as perspectivas dos principais estudos e das novas recomendações relacionados à infusão de ácido tranexâmico em pacientes com coagulopatia induzida pelo trauma e traumatismo craniencefálico.

Descritores: Ácido tranexâmico; Hemorragia; Traumatismos craniocerebrais; Ferimentos e lesões

INTRODUCTION

Trauma is a disease with major repercussions for public health worldwide, accounting for approximately 8% of all deaths recorded annually.[1] Among the main causes of mortality and morbidity related to trauma, we highlight traumatic brain injury (TBI) and trauma-induced coagulopathy (TIC).[2,3]

Trauma-induced coagulopathy is highly complex, and there is no consensus that precisely defines it.[4,5] However, TIC is present in 25 to 35% of polytrauma patients and contributes to 50% of trauma-related deaths in patients with severe hemorrhage in the pre-hospital environment.[4] Traumatic brain injury affects 27 to 69 million civilians annually, with approximately 39% mortality due to the injury and 60% with some degree of functional neurological damage, causing numerous socioeconomic problems globally.[3,6]

Given the seriousness of both situations, various forms of treatment have been studied, including tranexamic acid (ATX).[7] This drug is a

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fibrinolysis inhibitor that acts by blocking plasmin synthesis, inhibiting the proteolytic activity of plasminogen activators.[8] The infusion of this drug in some studies in patients with CIT or TBI was intended to assess whether there would be a reduction in mortality, and several divergent results were obtained, both in-hospital and out-of-hospital.[9-20]

Therefore, this narrative review aims to point out the results, divergences and new perspectives of the main studies and new recommendations related to the infusion of ATX in patients with CIT and TBI.

TRANEXAMIC ACID IN TRAUMA-INDUCED COAGULOPATHY

The main study of the use of ATX in patients with hemorrhage secondary to trauma was CRASH-2.[9] It was a randomized, double-blind, placebo-controlled clinical trial carried out in 274 hospitals in 40 countries and included 20,207 randomized participants.

The participants included in the study were adults (aged > 18 years) who had suffered trauma within 8 hours of the incident with significant bleeding or considered to be at risk of significant bleeding (heart rate > 110 bpm and/or systolic blood pressure < 90 mmHg). The study assessed, as a primary outcome, whether the infusion of ATX in participants in the intervention group (1g over 10 minutes followed by 1g over 8 hours) would change in-hospital mortality within 4 weeks of the injury. It should be noted that most of the sample in this study was made up predominantly of blunt trauma patients with good physiological reserve (systolic blood pressure > 90 mmHg, heart rate < 100 bpm and Glasgow score > 13).

After analyzing the data, the primary endpoint of the study showed a significant reduction in all-cause mortality in the first 28 days in the group that received the intervention (absolute risk reduction of 1.5%; relative risk [RR] of 0.91; 95% confidence interval 0.85-0.97; p-value = 0.0035). However, the subgroup analysis of this study showed that the benefit of ATX infusion occurred in trauma victims within the first 3 hours of the event, and there was no significant difference in both groups for the need for blood transfusion, surgical intervention or the occurrence of thromboembolic episodes.[9]

The use of ATX in participants with bleeding secondary to trauma was later endorsed by the systematic review published in 2015 in the Cochrane Library, in which the CRASH-2 study contributed 99% of the data.[10] Furthermore, CRASH-2 is the work that supports the recommendation of ATX in the treatment of hemorrhagic shock secondary to trauma.[7]

TRANEXAMIC ACID IN TRAUMATIC BRAIN INJURY

The first major evidence for the use of ATX in participants with TBI was published in 2014, in which a meta-analysis evaluated two randomized clinical trials involving 3 countries and 497 participants.[11] The primary outcome analyzed was not in-hospital mortality, but the progression of intracranial hemorrhage 24 to 48 hours after ATX infusion. Despite a significant reduction in the spread of intracranial hemorrhage (RR 0.76; 95%CI 0.58-0.98; p-value = 0.45; I^2 = 0.0%), there was no benefit in reducing in-hospital mortality (RR 0.64; 95%CI 0.41-1.02; p-value = 0.77; I^2 = 0.0%).[11]

The study that evaluated mortality after ATX infusion in participants with TBI was CRASH-3.[12] This study was a multicenter, randomized, placebo-controlled clinical trial that evaluated the effect of intravenous administration of ATX at the same dose as the CRASH-2 study, on mortality in adult TBI victims within 3 hours of the injury, without hemorrhagic shock, who had a Glasgow Coma Scale score of 12 or less or the presence of any intracranial bleeding demonstrated on computed tomography.[12]

A total of 9,127 participants from 175 hospitals in 29 countries were randomized. The primary outcome analyzed was TBI-related death in the in-hospital setting within 28 days. The results

were similar and with no statistically significant difference, both in the intervention group and the placebo group (18.5% *versus* 19.8%; RR of 0.94; 95%CI 0.86-1.02). However, the subgroup analysis, after excluding participants who scored 3 on the Glasgow coma scale or bilaterally mydriatic pupils, showed a benefit in the population with mild to moderate TBI (Glasgow coma scale 9 to 15; RR 0.78; 95%CI 0.64-0.95), but not in severe TBI (Glasgow coma scale < 9; RR 0.99; 95%CI 0.91-1.07). [12] Despite showing benefit in the subgroup with mild to moderate TBI, the hypothesis of ATX infusion in this population still needs to be confirmed in further studies for better scientific validation.

TRANEXAMIC ACID IN THE PRE-HOSPITAL ENVIRONMENT

The first randomized study in the pre-hospital setting that evaluated ATX infusion in participants at risk of hemorrhagic shock secondary to trauma was STAAMP.[13] This study was a randomized, double-blind, placebo-controlled clinical trial and included 927 participants who were randomized to receive 1g of ATX intravenously in the out-of-hospital setting (via ground or air transport) or placebo, with the primary objective of assessing mortality within 30 days.[13]

Participants included in this study were adults (age > 18 years) and those who had at least one episode of hypotension (systolic blood pressure < 90 mmHg) or one episode of tachycardia (heart rate > 110 bpm) within 2 hours of a trauma were eligible. In addition, participants randomized to receive ATX in the out-of-hospital setting were also randomized in the in-hospital setting to receive the abbreviated dose (only 1 g of ATX in the out-of-hospital setting), the standard dose (2 g of ATX in total, in the same infusion schedule as CRASH-2) or the repeated dose (3 g of ATX in total, two boluses of 1 g and an 8-hour infusion of 1 g).[13]

The primary endpoint showed that there was no significant change in mortality within 30 days in the participants who received the ATX infusion in the out-of-hospital setting (hazard ratio 0.81; 95%CI 0.59-1.11; p-value 0.18), however the subgroup analysis showed that the participants who received a total of 3g of ATX resulted in lower mortality within 30 days (RR 0.73; 95%CI 0.54-0.99; p-value 0.04), which was also repeated in the subgroup that received the infusion less than 1 hour after the trauma (RR 0.60; 95%CI 0.44-0.83; p-value 0.002) and in those with systolic blood pressure < 70 mmHg (RR 0.52; 95%CI 0.52-0.80; p-value 0.003). [13]

Another study that evaluated the benefit of ATX infusion in participants with CIT in an out-of-hospital setting was PATCH-Trauma.[14] This study was a double-blind, randomized, placebo-controlled clinical trial that evaluated 1,307 participants in 15 out-of-hospital emergency services in Australia, New Zealand and Germany.

The primary objective was to evaluate the efficacy and safety of ATX therapy at a dose of 1g intravenously started within 3 hours of the traumatic event and before hospital admission in participants aged ≥ 18 years with severe trauma and at risk of induced coagulopathy using the COAgulopathy in Severe Trauma (COAST) score > 3 (**Table 1**).[14]

Participants were randomized into two groups: 661 participants received 1 g of ATX pre-hospital, followed by 1 g within 8 hours of hospital admission. In the other arm, 646 participants received placebo instead of the drug. The primary endpoint was the assessment of functionality after 6 months using the Glasgow Outcome Scale-Extended (GOS-E) tool, a functional outcome score that

Table 1. Score *COAgulopathy in Severe Trauma*

Variable	Presentation	Score
Vehicle entrapment	Positive	1
Systolic blood pressure	< 100 mmHg < 90 mmHg	1 2
Temperature	< 35°C < 32°C	1 2
Suspected thorax trauma	Positive	1
Suspected intra-abdominal or pelvic trauma	Positive	1

ranges from 1 (death) to 8 (excellent recovery without functional impairment); in the study, a favorable functional outcome was defined as GOS-E ≥ 5 points. There was no significant difference in functional outcomes between participants who used ATX and those who used placebo (RR 1.00; 95%CI 0.90-1.12; p-value 0.95). However, the study found a trend towards lower overall mortality in the first 24 hours (RR of 0.69; 95%CI 0.51-0.94) and at 28 days (RR of 0.79; 95%CI 0.0-0.94) after the injury in the group that received the intervention.[14]

Another study carried out in a pre-hospital setting also evaluated the infusion of ATX in participants with TBI.[15] It was a randomized, multicenter, double-blind, placebo-controlled clinical trial in 39 emergency medical services and 20 trauma centers in the United States and Canada. The participants included in this study were aged ≥ 15 years, had suffered a TBI (blunt or penetrating) within 2 hours of the injury, had a Glasgow Coma Scale score of 3 to 12, had at least one reactive pupil and systolic blood pressure of at least 90 mmHg.[15]

The 963 selected participants were randomized to receive one of the following treatments: a single intravenous bolus of 2 g of ATX in the pre-hospital setting or a bolus of 1 g of ATX in the pre-hospital setting followed by 1 g infused over 8 hours in the in-hospital setting or a placebo infusion. The primary outcome analyzed was neurological outcome at 6 months using the GOS-E (considered favorable if > 4 points), and the secondary outcome was 28-day mortality and progression of intracranial hemorrhage.[15]

There was no significant difference in neurological outcome at 6 months (adjusted difference 3.5%; 95%CI -0.9%-10.2%; p-value 0.16), and no reduction in 28-day mortality in all ATX infusion regimens (adjusted difference -2.9%; 95% CI -7.9%-2.1%; p-value 0.26) or progression of intracranial hemorrhage (adjusted difference -5.4%; 95% CI -12.8%-2.1%; p-value 0.16). [15]

Finally, 4 months after the PATCH-Trauma study, a systematic review with meta-analysis was published which analyzed the three randomized clinical studies mentioned above.16 The results of this meta-analysis showed that there is a benefit of ATX infusion in these participants in the pre-hospital environment with a reduction in all-cause mortality at 30 days (RR of 0.82; 95%CI 0.69-0.97; p-value of 0.02; I^2 of 0%), but no effect on favorable neurological status after 6 months (RR of 1.00; 95%CI 0.93-1.09; p-value of 0.94; I^2 of 0%).[16]

PERSPECTIVES

The tenth edition of Prehospital Trauma Life Support (PHTLS), a guide widely used as a basis for the management of trauma victims in the pre-hospital environment, updated the dose of ATX in participants with hemorrhage secondary to trauma, changing the previous dose of 1 g intravenously to 2 g in a single dose intravenously or intraosseously, both for participants with a possible need for blood transfusion (hemorrhagic shock, significant amputations, penetrating trauma to the torso, etc.) and for participants with signs of TBI (altered level of consciousness associated with shock wave or blunt trauma) within 3 days of the injury.), and for participants with signs of significant TBI (altered level of consciousness associated with shock wave injury or blunt trauma) within 3 hours of the injury.[17]

Most of these recommendations were based on studies of tactical pre-hospital settings and combat situations.[18] However, the use of ATX in participants with TBI remains of uncertain benefit; moreover, the use of 2 g of ATX in these participants showed an increase in the incidence of seizures without altering major adverse events.[15] Furthermore, the MATTERs study, a retrospective analysis carried out in a tactical combat environment, demonstrated that the use of 1 g of ATX reduced mortality in severely injured participants with penetrating trauma or requiring more than ten units of packed red blood cells when compared to participants who did not receive ATX (mortality of 14.4% *versus* 28.1%; p-value of 0.004).[19]

Despite the discussion, the right dose of ATX in participants with CIT remains uncertain. A recent study published in October 2023 analyzed a cohort from a UK trauma center in adult participants who received ATX after triggering the bleeding protocol.[20] Over the 11-year period of this study, 525 participants were analyzed and three groups were identified: those who received only 1 g of ATX, those who received 1 g in bolus plus 1 g in continuous infusion for 8 hours and those who received a single bolus of 2 g of ATX. The outcome analyzed was 28-day mortality, which showed no significant difference in these three groups.[20]

CLOSING REMARKS

The use of ATX is safe and has been shown to reduce mortality in patients with CIT and, with a certain degree of uncertainty, in those with mild to moderate TBI, as long as it is infused as early as possible in both situations. Despite this, further studies are needed to assess the appropriate dose of this drug for reducing trauma mortality.

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