

Mortality due to coagulopathy in victims of hemorrhagic shock resulting from trauma attended by pre-hospital service

RESUMO | Objetivo: identificar a mortalidade por coagulopatia nos pacientes vítimas de choque hemorrágico decorrente de trauma atendidos pelo serviço pré-hospitalar. Método: foi realizada revisão da literatura no período de maio até dezembro de 2021. A estratégia de busca baseou-se na pesquisa de artigos nas bases de dados PubMed/MedLine, Biblioteca Virtual de Saúde, Cochrane Library e SciELO englobando estudos publicados em 2017 até julho de 2021 e usou como descritores os termos “Pacientes OU trauma OU choque hemorrágico OU Atendimento pré-hospitalar E ácido tranexâmico E choque hipovolêmico OU coagulopatia OU mortalidade”. Em português, inglês e espanhol, o que resultou em 06 artigos após análise final. Resultados: os estudos analisados mostraram redução da taxa de mortalidade quando o ácido tranexâmico foi administrado em até 3 horas após o trauma. Conclusão: os resultados das pesquisas analisadas corroboram o uso do ácido tranexâmico em pacientes traumatizados, sendo um adjuvante eficaz no manejo do trauma.

Descritores: Trauma; Atendimento pré-hospitalar; Ácido tranexâmico; Coagulopatia; Mortalidade.

ABSTRACT | Objective: to identify mortality from coagulopathy in patients with hemorrhagic shock due to trauma treated at the pre-hospital service. Method: a literature review was carried out from May to December 2021. The search strategy was based on the search for articles in the PubMed/MedLine, Virtual Health Library, Cochrane Library and SciELO databases, encompassing studies published from 2017 to July 2021 and used as descriptors the terms “Patients OR Injury OR hemorrhagic shock OR Pre-hospital care AND tranexamic acid AND hypovolemic shock OR coagulopathy OR mortality”. In Portuguese, English and Spanish, which resulted in 06 articles after final analysis. Results: the analyzed studies showed a reduction in the mortality rate when tranexamic acid was administered within 3 hours after the trauma. Conclusion: the results of the analyzed studies support the use of tranexamic acid in trauma patients, being an effective adjuvant in the management of trauma.

Keywords: Injury; Pre-hospital care; Tranexamic acid; Coagulopathy; Mortality

RESUMEN | Objetivo: identificar la mortalidad por coagulopatía en pacientes con shock hemorrágico por trauma atendidos en el servicio prehospitalario. Método: se realizó una revisión bibliográfica de mayo a diciembre de 2021. La estrategia de búsqueda se basó en la búsqueda de artículos en las bases de datos PubMed/MedLine, Virtual Health Library, Cochrane Library y SciELO, abarcando estudios publicados desde 2017 hasta julio de 2021 y utilizados como descriptores los términos “Pacientes O traumatismo O shock hemorrágico O Atención prehospitalaria Y ácido tranexámico Y shock hipovolémico O coagulopatía O mortalidad”. En portugués, inglés y español, lo que resultó en 06 artículos después del análisis final. Resultados: los estudios analizados mostraron una reducción en la tasa de mortalidad cuando se administró ácido tranexámico dentro de las 3 horas posteriores al trauma. Conclusión: los resultados de los estudios analizados apoyan el uso del ácido tranexámico en pacientes traumatizados, siendo un coadyuvante eficaz en el manejo del trauma.

Palabras claves: Trauma; Atención prehospitalaria; Ácido tranexámico; Coagulopatía; Mortalidad.

Jhonata Rocha de Sá Simões

Nurse. Student of the Multiprofessional Residency Program in Urgency and Trauma at the Escola Superior de Ciências da Saúde (ESCS). Foundation for Teaching and Research in Health Sciences (FEPECS). Health Department of the Federal District (SES-DF). Brasília, DF, Brazil.
ORCID: 0000-0002-9847-9640

Lilyan Paula de Sousa Teixeira Lima

MSN, RN, Mobile Emergency Care Service: Mobile Emergency Care Service – SAMU. Brasília, DF, Brazil.
ORCID: 0000-0001-5334-9968

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Moises Wesley de Macedo Pereira

Nurse. Master in Medical Sciences from the University of Brasília (UnB). Professor at the Higher School of Health Sciences (ESCS), Nurse at the State Health Department of the Federal District. Brasília, DF, Brazil.
ORCID: 0000-0002-8666-5702

Kate Winslet Siqueira dos Santos

Nurse. Student of the Multiprofessional Residency Program in Urgency and Trauma at the Escola Superior de Ciências da Saúde (ESCS). Foundation for Teaching and Research in Health Sciences (FEPECS). Health Department of the Federal District (SES-DF). Brasília, DF, Brazil.
ORCID: 0000-0002-4288-978X

Samara Silva de Queiroz

Nurse. Student of the Multiprofessional Residency Program in Urgency and Trauma at the Escola Superior de Ciências da Saúde (ESCS). Foundation for Teaching and Research in Health Sciences (FEPECS). Health Department of the Federal District (SES-DF). Brasília, DF, Brazil.
ORCID: 0000-0001-6874-6202

Francimar Sousa Marques

Nurse. Student of the Multiprofessional Residency Program in Urgency and Trauma at the Escola Superior de Ciências da Saúde (ESCS). Foundation for Teaching and Research in Health Sciences (FEPECS). Health Department of the Federal District (SES-DF). Brasília, DF, Brazil.
ORCID: 0000-0002-6267-4559

INTRODUCTION

According to the World Health Organization (WHO), in the last decade, there were 5.8 million deaths from trauma per year (9% of all deaths in the world). In addition, trauma is also responsible for the largest number of permanent disabilities, affecting more people between 1 and 44 years of age. (1-2)

The increase in mortality in trauma is directly linked to the process of shock and coagulopathy. Among the acute situations related to trauma, it is worth mentioning the process of trauma-induced coagulopathy (TIC) in victims of hemorrhagic shock, occurring in 10 to 34% of cases, depending on the severity of the trauma, being an independent cause of mortality. TIC occurs after the traumatic injury and shock is already installed, accompanied by inflammatory events, dysfunction in the coagulation, anticoagulation and fibrinolysis processes. (3-4)

TIC can be classified into acute traumatic coagulopathy (ATC) and iatrogenic coagulopathy (IC). CAT is triggered soon after trauma, it is an endogenous phenomenon, associated with inflammation, hypoperfusion, tissue trauma, sympathetic activation and fibrinolysis. Acidosis exacerbates fibrinolysis when the pH drops from 7.4 to 7.2, with the activity of each clotting protease reduced by more than half. IC, on the other hand, is caused by exogenous phenomena and is caused by inadequate volume replacement, leading to hemodilution and depletion of clotting factors. (1,5)

An adjunct in the management of coagulopathy is tranexamic acid (TXA). However, research has focused on its in-hospital use in trauma victims. Due to the lack of randomized controlled studies on TXA in pre-hospital care (PHC), the evidence for its use in PHC is still insufficient. (1)

This study is justified by identifying

the importance of TXA in pre-hospital care in trauma victims who developed hemorrhagic shock. Therefore, the objective of this study was to identify mortality from coagulopathy in patients with hemorrhagic shock resulting from trauma treated at the pre-hospital service.

METHOD

It is an integrative review, being defined as "a method that aims to synthesize results obtained in research on a topic or issue, in a systematic, orderly and comprehensive way". (6)

Primary studies with different methodologies were approached. There were six steps: 1) Identification of the theme and elaboration of the guiding question; 2) Establishment of criteria for inclusion and exclusion; 3) Definition of information to be extracted from

studies and categorization of studies; 4) Critical analysis of included studies; 5) Interpretation of results; 6) Presentation of the integrative review and the synthesis of the obtained content. (7)

The elaboration of the research question was guided by the PICO strategy (8) in a modified form, as shown in table 1. Thus, the guiding question was "Is the use of TXA capable of reducing the coagulopathy state and mortality in trauma patients who have progressed to severe hemorrhagic shock associated with early pre-hospital care?".

The search took place in July 2021, by two researchers independently in the Latin American and Caribbean Literature on Health Sciences (LILACS), through the Virtual Health Library (BVS) portal; Medical Literature Analysis and Retrieval System Online (MEDLINE), through the PubMed portal, Scientific Electronic Library Online (SciELO) and

Table 1 - Description of the PICO strategy for the elaboration of the research question, selection of descriptors and non-controlled terms used in the search. Brasília, Federal District, Brazil, 2021.

P	Trauma patients who progressed to severe hemorrhagic shock in pre-hospital care. (Population)	("Patients" OR "Patient" OR "Customers" OR "Sick" OR "enfermo" OR "Sick" OR "Person Sick" OR "Person with Illness" OR "People Sick" OR "people disease" OR "Injuries" OR "Trauma" OR "Traumas" OR "Wounds" OR "Multiple Trauma" OR "Multiple Traumas" OR "Multiple Wound" OR "Multiple Wounds" OR "Polytrauma" OR "Polytraumas" OR "Multiple Injury" OR "Multiple Injuries" OR "Injuries And Wounds" OR "Wounds And Injury" OR "Injury Wounds" OR "Trauma" OR "Traumas" OR "Wounds Injuries" OR "Research-Related Injuries" OR "Research-Related Injury" OR "Injuries" OR "Injury" OR "wound" OR "Wounds" OR "First Aid" OR "First Aids" OR "Medical Emergency Service" OR "Medical Emergency Services" OR "Emergency Medical Service" OR "Prehospital Emergency Care" OR "Emergencers" OR "Emergicenter" OR "Emergency Care" OR "Emergency Health Services" OR "Emergency Health Service") AND
I	Early use of tranexamic acid. (Intervention)	("tranexamic acid" OR "amcha" OR "trans-4-(aminomethyl) cyclohexanecarboxylic acid" OR "t-amcha" OR "amca" OR "anvitoff" OR "cyklokapron" OR "ugurel" OR "kabi 2161" OR "spot of" OR "transamin" OR "alphafibrin" OR "n acyl") AND
C	Comparison	Not applicable
O	Regression of shock, coagulopathy and mortality	("Shock" OR "Circulatory Failure" OR "Circulatory Collapse" OR "Hypovolemic Shock" OR "hemorrhagic shock" OR "traumatic shock" OR "traumatic hemorrhagic shock" OR "Blood Coagulation Disorders" OR "Blood Coagulation Disorder" OR "Coagulopathy Traumatic" OR "Coagulopathies Traumatic" OR "Fatal Outcomes" OR "Fatal Outcome").

Source: the authors, 2021.

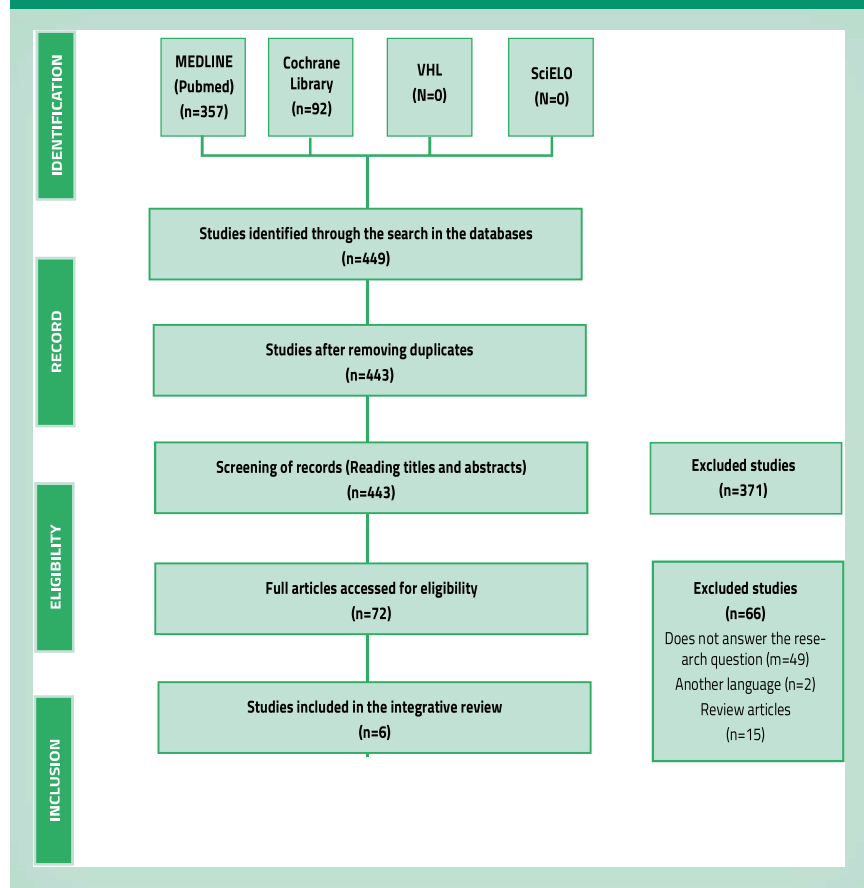
Cochrane Library. To systematize the search in the databases, Health Sciences Descriptors (DeCS) were listed, as well as the equivalents in Spanish and English (Medical Subject Headings - MeSH) presented in table 1.

The studies found were initially evaluated through the analysis of titles and abstracts, and the studies in which the reading of the title and abstract to adopt the inclusion and exclusion criteria were not sufficient were read in full. The inclusion criteria were: publications that addressed the use of TXA in pre-hospital care in trauma patients, published from the year 2017 to July 2021, in the languages: Portuguese, English and Spanish. Studies that addressed only the in-hospital environment, gray literature and duplicates in the databases were excluded. The articles included in the study were read in full and the following data were recorded in a table containing: objective, methodology, intervention and conclusion.

RESULTS

Following the PICO strategy and related descriptors, as shown in Table 1, the review found 449 articles. In the PubMed database, 357 articles were identified, after reading the title and abstract, 67 articles were selected. In the Cochrane Library database, 92 articles appeared, after reading the title and abstract, 11 articles were selected. No articles were found in the VHL and SciELO databases. After reading the title and abstract, 72 articles remained, they were analyzed in their entirety and after applying the inclusion and exclusion criteria, a sample of 06 articles was totaled. Figure 1 illustrates, in detail, the flow of exclusion and inclusion of articles. The articles selected for the review were grouped in table 2 with the objective of indicating more details of each one and enabling the comparison between the information available in the literature.

Figure 1 - Flowchart of the methodological steps used in the integrative review. Brasília, Federal District, Brazil, 2021



Source: the authors, 2021.

DISCUSSION

Recent studies have shown that most deaths from hemorrhage resulting from trauma occur within the first hours of arrival at trauma centers. Due to the impact of time on treatment, several guidelines developed include the use of TXA in PHC within a maximum interval of 03 hours. (15-16)

Although the CRASH-2 (17) and MATTERS(18) studies identified a benefit in reducing mortality in generalized trauma populations, TXA in the trauma patient is believed to be more beneficial in those with CIT, specifically in patients with hyperfibrinolysis. In the context of trauma, the incidence

of hyperfibrinolysis ranges from 2% to 34%. Studies have confirmed that fibrinolysis, defined as 30-minute lysis (LY30) > 3% (current definition of hyperfibrinolysis in trauma patients) on thromboelastogram (TEG), is associated with a 10-fold increase in mortality. (19-20-21)

Although the in-hospital approach to the trauma patient is shifting to TEG-based resuscitation, pre-hospital care does not have access to the same resources, so the assessment is focused only on the patient's clinical signs. The PROMMTT group found patients with lower scores on the Glasgow Coma Scale (GCS), heart rate (HR) > 110 beats per minute (BPM), decreased systolic blood pressure (SBP) (< 90 mmHg)

Chart 2 - Description of the main results obtained by the primary studies included in the sample (n= 6), Brasília, Distrito Federal, Brazil, 2021.

- 9 To assess the efficacy and safety of TXA administered before hospitalization compared with placebo in injured patients at risk of bleeding. - Phase 3, multicenter, double-blind, placebo-controlled, randomized clinical trial that compared outcomes in patients at risk of bleeding receiving TXA (single dose) prior to hospitalization administered during air or ground medical transport.
- Patients in the intervention group received 1 g of TXA on the way to the hospital. Patients randomized to the TXA group were randomly allocated to three in-hospital dosing regimens: patients in the intervention group received no additional TXA, 1 g of TXA over 8 hours, or a bolus of 1 g of TXA followed by 1 g of TXA for 8 hours. Patients who received placebo in the PHC, received placebo in the hospital.
- TXA before hospitalization did not result in significantly lower 30-day mortality and did not result in a higher incidence of thrombotic complications or adverse events. Patients who receive TXA while still in PHC within 1 hour of injury and in those with evidence of severe shock, suggests that it is associated with a lower 30-day mortality. Therefore, the use of TXA in PHC is safe and can be given to patients at risk of bleeding.
- 10 To investigate outcomes and complication rates in trauma patients who received TXA in the ED at an urban level 1 trauma center or in the prehospital setting. - Single-center retrospective cohort study covering an 18-month period from April 2014 to October 2015, after the initiation of a TXA administration protocol in pre-hospital aeromedical care.
- A bolus of 1g of TXA in 100 mL of 0.9% saline or lactated Ringer's solution was administered for 10 min. Subsequent 1 g TXA over the next 8 h was left for clinical judgment and assessment of fibrinolysis according to the parameter of percent clot lysis in 30 min (LY30) on rapid thromboelastography..
- Administration of TXA during air transport did not improve survival compared with administration in the ED. Treatment with TXA was associated with an increased risk of venous thromboembolic events. The PH group had a higher rate of fibrinolysis shutdown compared with the ED group and required fewer blood products and underwent fewer interventions and surgeries.
- 11 To evaluate the efficacy and impact of TXA administration in prehospital settings in reducing mortality, associated thromboembolic events, and blood transfusion in trauma patients. - Retrospective study, which included all adult trauma patients who received TXA in the PHC between January 1st, 2017 and September 30th, 2018 at a level 1 trauma center.
- 1 g IV TXA prior to hospital admission to a level 1 trauma center. The prehospital TXA protocol follows CRASH-2 criteria and is administered by the critical care paramedic team only.
- Pre-hospital administration of TXA is associated with less in-hospital blood transfusion and PTM. There is no significant increase in thromboembolic events and mortality.
- 12 To assess the safety and efficacy of tranexamic acid use in the civilian prehospital setting in cases of traumatic hemorrhagic shock. - The Cal-PAT study is an observational, prospective, multicenter cohort study with a retrospective comparison .
- 1g of TXA in 100 ml of 0.9% saline infused over 10 minutes via IV or IO. Upon arrival at a participating trauma center, patients were re-evaluated for signs of ongoing hemorrhagic shock. Patients who continued to meet criteria received a second dose of 1 gram of TXA in 100 ml of 0.9% saline infused over eight hours via IV infusion.
- The study observed a reduction in mortality at 28 days after the administration of TXA in PHC in patients with signs of traumatic hemorrhagic shock, a decrease in blood products transfusion and a shorter length of stay and ICU, without an increase in thromboembolic events. This study demonstrated that TXA can be administered effectively and feasibly by PHC professionals. Findings support the use of TXA in PHC in adult civilians with traumatic injuries with signs of shock.

13 To assess the safety and mortality impact of pre-hospital administration of TXA by paramedics in cases of traumatic injury with signs of hemorrhagic shock. - The Cal-PAT study is an ongoing, prospective observational, multicenter cohort study with a retrospective chart review comparison designed to determine the effect of early administration of TXA in patients with trauma and signs of hemorrhagic shock.

1g of TXA in 100 ml of 0.9% saline infused over 10 minutes IV or IO. Upon arrival at a participating trauma center, patients who received TXA at the PHC were re-evaluated by trauma team members for signs of ongoing hemorrhagic shock. Patients who continued to meet study criteria received a second dose of 1 gram of TXA in 100 ml of 0.9% saline infused over 8 hours via IV.

The administration of TXA can be safe in the pre-hospital environment, with no significant change in the observed adverse events and with a decrease in the use of blood products in cases of trauma-induced hemorrhagic shock. Given the current sample size, no statistically significant decrease in mortality was observed. Furthermore, this study demonstrates that it may be feasible for paramedics to safely identify and administer TXA in the prehospital setting.

14 To investigate pre- and intra-hospital administration of TXA and its relationship with morbidity and mortality in consecutive trauma patients admitted to a Level 1 Trauma Center ICU.- A population-based 7-year prospective cohort study. Conducted to investigate seriously injured patients admitted to the ICU of a Level 1 trauma center.

The pre-hospital TXA dosage was 1 g bolus, the in-hospital dosage of TXA was also 1 g bolus, and the 1 g infusion was repeated over 8 hours, at the discretion of the surgeon and/or intensivist responsible for the treatment.

Patients with TXA had similar results compared to patients without TXA, despite being more severely injured. The rate of thromboembolic complications was low despite liberal use of pre-hospital and in-hospital TXA. There was no difference in morbidity and mortality between patients with and without TXA.

Caption (Source: the authors, 2021): TXA: tranexamic acid. PHC: pre-hospital care. ED: emergency department. PH: pre-hospital. TEG: thromboelastogram. MTP: massive transfusion protocol. ISS: Injury Severity Score. SBP: systolic blood pressure. IV: intravenous. IO: intraosseous.

Note: numbers 9, 10, 11, 12, 13, 14 in the 1st column of the table refer to the articles that make up this review

and increased score injury severity (ISS) as significant predictors of coagulopathy. (22)

Thus, there was consensus in the results obtained in this study and in the existing literature regarding the inclusion criteria for the administration of TXA, taking into account age \geq 16 years with continuous significant bleeding, SBP $<$ 90 mmHg and/or HR $>$ 110 BPM, or considered to be at risk of significant bleeding, and being within 3 h of the trauma. However, the present study (14) showed that for the administration of the second dose of TXA there was greater criterion, leaving the clinical judgment of the surgeon, anesthesiologist or intensivist and assessment of fibrinolysis according to the parameter of LY30 in the TEG.

The CRASH-2 study (17), a multicenter, randomized, double-blind, placebo-controlled clinical trial in 274 hospitals in 40 countries, including 20,211 adult patients with significant

or at risk traumatic bleeding (SBP $<$ 90 mmHg and/or HR $>$ 110 bpm) who were admitted within 8 hours after the injury. The primary outcome was mortality at 4 weeks post-injury. This study recommended the use of TXA at the loading dose of 1 gram (g) for 10 minutes (min) followed by an infusion of 1 g for 8 hours (h), corroborating the results obtained in the present study and recommendations found in the literature that recommend 1 g intravenous (IV) or intraosseous (IO) over 10 min, followed by 1 g over 8 h or 20–25 mg/kg followed by continuous administration of 1–2 mg/kg/h. (23)

It was reported on CRASH-2 (17) that all-cause mortality was significantly reduced with TXA (14.5% versus 16%). The risk of death due to bleeding was also significantly reduced in the TXA group (4.9% versus 5.7%). There were no significant differences in blood product transfusions in the TXA group (50.4% versus 51.3%), and in the num-

ber of units transfused (mean 6.1 versus 6.3). However, only 50% of patients required transfusions.

In contrast, the results obtained in the present review showed similar mortality in the TXA and placebo groups at 30 days, ISS without significant difference and the control group had a greater need for transfusion and patients who received TXA with prehospital severe shock (SBP \leq 70 mmHg) had a lower 30-day mortality compared to the placebo group. Except in 16.6% (12) which observed a reduction in mortality after 28 days in the TXA group compared to the control group (3.6% versus 8.3%). This mortality difference was greater in critically injured patients with ISS $>$ 15 (TXA: 6% versus control: 14.5%).

On the other hand, MATTERS (18), a retrospective observational study that examined the impact of TXA included trauma patients who required at least 1 unit of transfusion within 24 hours of

admission after combat-related injury. The primary endpoint was mortality (24 and 48 hours, in-hospital). Of the 896 patients, 293 (32.7%) received TXA. The TXA group had a higher ISS (25.2 versus 22.5), a higher incidence of hypotension (22.8% versus 13.8%) and an ECG ≤ 8 at admission (63.3% versus 35.6%), and greater need for blood products (25.7 units versus 20.3 units). The MATTERS study showed that even significantly more injured, the TXA group found an absolute reduction of 6.5% in hospital mortality and 6.6% in 48-hour mortality. (18)

The data found in the study (14), disagrees with the results obtained in the present review, which showed that the ISS was similar between the groups in the study and that there was also no difference between patients with SBP ≤ 90 mmHg who received TXA and those who did not. These results also contradict the CRASH-2 study (17), in which he considered SBP ≤ 90 mmHg and presented a significant reduction in mortality.

The incidence of thrombotic complications associated with TXA in trauma is controversial. A retrospective study (24) follow-up to MATTERS (18) to reassess the use of TXA in military

hospitals reported a higher incidence of venous thromboembolism (VTE) in patients receiving TXA and showed that the use of TXA was an independent risk factor for VTE with an overall rate of 15.6%. Similarly, another retrospective study conducted in California showed that the TXA group had more deep vein thrombosis (DVT) and pulmonary embolism (PE) (12% versus 0%), and a tendency for more acute renal failure (28% versus 15%). (25)

In contrast, the CRASH-2 study (17), demonstrated that there was no significant increase in thrombotic events (TXA: 1.7% versus control: 2%). However, when treatment was given 3 hours after the injury, it resulted in an increased risk of death due to bleeding (4.4% versus 3.1%). These data should be viewed with caution, as they were performed mainly in developing countries and only half of the patients required transfusions. In agreement with CRASH-2 (17), the present integrative review showed in 4 studies that no differences were found in complications between the study groups, there was no increase in the incidence of pulmonary embolism, deep vein thrombosis, seizures or arterial thrombotic complications between groups. (9,12-13-14)

CONCLUSION

The findings of this review underscore the clinical relevance of using TXA as an adjunct in the pre-hospital management of traumatic hemorrhage administered up to 3 hours, however, the benefit is more pronounced when administered soon after injury (<1 hour) at a dose of 1g IV. or IO in 100 ml of saline solution infused for 10 min, up to 1 hour after injury, followed by 1 g in 8 hours. TXA is a safe measure that is able to reduce coagulopathy and mortality.

The study in question also draws attention to the most frequent possible complications resulting from the indiscriminate use of TXA, such as: hypotension resulting from rapid bolus administration, deep vein thrombosis, pulmonary embolism, seizure and acute kidney injury. Emphasizing the importance of adequate inclusion criteria and, when available, assess LY30 in TEG. Given the above, more research is needed to confirm the real safety of TXA in PHC, since there is little literature involving this context and the patients who will benefit.

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