

Tranexamic acid use in the prehospital environment: a literature review

Uso pré-hospitalar do ácido tranexâmico: uma revisão de literatura

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RESUMO: *Introdução:* Estudos demonstram a eficácia do uso do ácido tranexâmico (AT) em ambiente hospitalar no manejo de hemorragias decorrentes do trauma, porém, a eficácia no seu uso em meio pré-hospitalar ainda é discutida. *Objetivos:* Avaliar os estudos referentes ao uso do AT no meio pré-hospitalar. *Métodos:* A estratégia de busca baseou-se na pesquisa de artigos nas bases de dados PubMed/MedLine e SciELO e usou como descritores os termos “tranexamic AND prehospital AND trauma”, em todos os idiomas, o que resultou em 37 artigos após análise final. *Resultados:* Os estudos analisados mostraram redução da taxa de mortalidade quando o AT é administrado em até 3 horas após o trauma. O uso militar do AT já é realizado por alguns países com estudos que confirmam seus benefícios. Não foram encontrados estudos nacionais sobre o assunto e também não foram encontrados artigos em que a classe pediátrica fosse incluída. *Conclusão:* Os resultados das pesquisas analisadas corroboram com a eficácia do uso pré-hospitalar do AT, porém alguns pontos ainda precisam ser analisados em pesquisas futuras como a eficácia e segurança do uso pré-hospitalar de AT em crianças e também seu uso em território nacional, já que não foram encontrados artigos que abordem esses temas. Resultados de estudos em andamento podem esclarecer melhor o seu uso.

Descritores: Ácido tranexâmico; Ferimentos e lesões; Assistência pré-hospitalar; Hemorragia.

ABSTRACT: *Introduction:* Studies demonstrate the efficacy of the use of tranexamic acid (TXA) in hospital environment in the management of bleeding resulting from trauma, however, efficacy in its use in pre-hospital environment is still in discussion. *Objectives:* Evaluate studies related to the use of TXA in the pre-hospital environment. *Methods:* The search strategy was based on the research of articles in the PubMed/MedLine and SciELO databases and used as descriptors the terms “tranexamic AND prehospital AND trauma”, in all languages, which resulted in 37 articles after final analysis. *Results:* The studies analyzed showed a reduction in the mortality rate when TXA is administered within 3 hours of trauma. The military use of TXA is already carried out by some countries with studies that confirm its benefits. No Brazilian studies were found on the subject and no articles were found in which the pediatric class was included. *Conclusion:* The results of the analyzed research corroborate the efficacy of pre-hospital use of TXA, but some points still need to be analyzed in future research such as the efficacy and safety of pre-hospital use of TXA in children and also its use in the national territory as no articles were found to address these topics. Ongoing study results may further clarify its use.

Keywords: Tranexamic acid; Wounds and injuries; Prehospital care; Hemorrhage.

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INTRODUCTION

Trauma injuries are responsible for about of 9% of all deaths in the world¹ and bleeding is the leading cause of preventable deaths due to trauma^{2,3}. Thus, new resources are being studied to be implemented in order to improve the current propaedeutic in trauma scenarios. One of them is the tranexamic acid (TXA), an antifibrinolytic drug that acts preventing the formation of fibrin through competitive inhibition of the plasminogen activators⁴. This prevents the process of fibrinolysis and makes the hemostasis more effective. Its use in the hospital environment in the control of hemorrhages is well described, however, studies that evaluate its use in the pre-hospital environment are still scarce. This study aimed to survey studies that addressed the subject.

AIM OF THE STUDY

This literature review aims to evaluate studies that address the use of tranexamic acid in the pre-hospital environment in trauma victims

METHOD

The research was guided by the combination of the descriptors “tranexamic” and “prehospital” and “trauma”. The search for the articles was conducted by the authors in the databases PubMed, MedLine and SciELO. The research in the databases was made between August 1, 2019 and August 30, 2019, that resulted in 77 articles that were published between 2009 and 2019. The first analysis consisted in the selection of the articles by its title and abstract, that resulted in 54 articles. These articles were fully analyzed and were included in the research just the ones that addressed the proposed subject.

DEVELOPMENT

Use of TXA in the hospital environment

Its hospital use in trauma victims is based on the CRASH-2 study in the literature. It was the first randomized clinical trial that evaluated the use of the drug in trauma-suffering patients. It was conducted in the United States in 2010 and involved more than 20,000 patients. It showed a reduction in the mortality rate for all causes in 28 days in patients in which TXA was administered [1,463 patients (14.5%) in the group in which TXA vs. 1613 patients (16%) were administered in the placebo group; relative risk (RR) 0.91; 95% confidence interval (CI) 0.85 to 0.97; $p = 0.0035$]. Risk of bleeding-related death also showed a reduction [489 patients (4.9%) in the TXA vs 574 patients

(5.7%) in the placebo group; RR 0.85; 95% CI 0.76 to 0.96; $p = 0.0077$]. The study also showed that TXA administered ≤ 1 hour after trauma was more effective compared to that administered within 1-3 hours after trauma. Its use after the 3-hour period showed an increase in bleeding-related mortality [144 out of 3,272 patients (4.4%) died in the TXA vs 103 group of 3362 patients (3.1%) in the control group; RR 1.44; 95% CI 1.12 to 1.84; $p = 0.004$]⁵.

Recently, the results of a new stage of studies related to the use of TXA in the hospital environment, CRASH-3, were published. It evaluated the effects of TXA in patients suffering from traumatic brain injury (TBI). The study included 12,737 adult patients who were selected in the period 2012-2019 who presented a Glasgow Coma Scale (GCS) lower than 12 or with the presence of intracranial bleeding evidenced in imaging tests and without evidence of important extracranial bleeding. There was a decrease in the risk of death related to the TBI [18.5% vs. 19.8%; RR 0.94 (95% CI 0.86 to 1.02)]. It also showed similarity in the risk of thrombotic events between the two groups [RR 0.98 (95% CI 0.74 to 1.28)]⁶.

Use of TXA in the pre-hospital environment

A German study published in 2016 was the first study that evaluated the pre-hospital use of TXA in civilian patients. The study included 516 patients in total, 258 in each group, who were transported to the hospital by the Air Rescue Services in Germany from 2014 to 2016. It showed a reduction in mortality in the first hours after trauma (mortality at 6 hours 1.9% vs 9.3%, $p < 0.001$; mortality in 12 hours 3.5% vs 10.9%, $p = 0.002$; mortality in 24 hours 3.5% vs 10.9%, $p = 0.01$). Intra-hospital mortality throughout the hospitalization period was also lower in the TXA group, but showed no statistical significance (14.7% vs 16.3%; $p = 0.72$)⁷.

This study, however, had some limitations such as: the exact time of TXA administration has not been specified; the administration of TXA was done at the physician's discretion, without presenting a standardized algorithm; the cause of death was not documented, making it impossible to perform an analysis whether TXA had a reduction in bleeding mortality.

Another study that evaluated the pre-hospital use of TXA was conducted in Qatar and published in 2019. It had a total of 204 patients, 102 in each group, selected between January 2017 and September 2018. This study used the same selection protocol of the CRASH-2 (patients over 16 years of age who presented confirmed or suspected bleeding, with systolic blood pressure (SBP) < 90 mmHg and/or heart rate (HR) > 110 bpm and less than 3 hours after the trauma occurred). The patients were randomized and the case group received 1g of TXA on the way to the hospital, while the control group received 1g of placebo.

The results showed lower serum lactate indices ($p = 0.001$) and a lower shock index rates ($p = 0.03$) in patients of the case group. It also demonstrated a lower mean in the need for transfusion of bags in the TXA group (3 units vs 8 units, $p = 0.01$). The overall mortality rate was also lower, but without statistical significance [odds ratio (OR) 0.78; 95% CI 0.42-1.45; $p = 0.75$]. The study, however, showed a worse result in relation to the probability of occurrence of thromboembolic events in the case group (OR 2.0; 95% CI 0.37-11.40)⁸.

Use of TXA in the military environment

The use of this drug in the pre-hospital environment in military personnel is already known. Military forces such as the United States of America (USA), the United Kingdom (UK) and Israel have been using it for almost 10 years. The MATTERS study evaluated 896 USA and UK military patients who had combat injuries. Of these, 293 received the TXA on the way to the hospital service. The results showed a lower mortality rate in the TXA group compared to the control group (17.4% vs 23.9%, respectively; $p = 0.03$) despite having worse injuries (average value of the Injury Severity Score (ISS) 25.2 vs 22.5, respectively; $p < 0.001$). In patients who received massive blood transfusion the benefit in reducing mortality was even higher (14.4% vs 28.1%; $p = 0.004$)^{9,10}.

Use of TXA in remote places

In places where there is difficulty accessing or that are very far from the reference hospital, the administration of TXA in trauma victims can take time if administered only in the hospital, which promotes its use even during pre-hospital care.

In countries such as Canada, some air services, such as the service of the province of Alberta, make use of TXA during transportation to the hospital, often enabling better bleeding control before arriving at the referral service¹¹.

In isolated locations, with few physicians, where often the first care does not have a doctor, TXA can be administered by other health professionals as demonstrated in this study from South Africa, which evaluated its administration by nurses without decreased efficacy¹².

Ongoing studies

Currently there are two studies evaluating the use of TXA in the pre-hospital environment, STAAMP and PATCH. STAAMP is a multicenter study involving adult patients who are transported from the scene to the hospital by air medical services. The studied population will consist of those patients who have SBP < 90 mmHg or HR > 110 bpm and with less than 2 hours of trauma. They will be

randomized into a case group, which will receive 1g of TXA on the way to the hospital and a control group, which will receive placebo. The study is estimated to have at least 994 patients during the 3-year period of the research and the results are expected to be published in 2020¹³.

Another study that is running is PATCH, a multicenter study being conducted in Australia and New Zealand. The study aims to determine the impact of pre-hospital administration of TXA on the survival and recovery of trauma victims. Patients who during hospital transport have a COAST score greater than or equal to 3 and less than 3 hours after the trauma occur will be randomized between the group receiving TXA and the placebo group on the way to the hospital. The study will evaluate mortality and functionality recovery rates within 6 months of trauma. It will also evaluate the coagulogram, incidence of vascular events, need for blood transfusion and time of hospitalization of patients. The study is expected to be finalized in early 2021^{14,15}.

Topics not covered in the articles

In our analysis, no studies were found in which the pediatric class was included in the sample of the patients studied. Even if its use in the in-hospital environment, during pediatric surgeries, is already part of medical practice, with results that show a decrease in bleeding resulting from surgery¹⁶, studies in which the focus is its use is intended to prevent bleeding resulting from trauma should still be performed.

Although there are Brazilian pre-hospital care services that already use TXA in their protocols for the care of polytraumatized patients, no national studies were found that verify its effectiveness in reducing mortality and its safety. Only studies that confirm their in-hospital cost-effectiveness in its use in trauma-suffering patients were found¹⁷.

CONCLUSION

The results of the analyzed studies seem to show that pre-hospital use of TXA is effective and that it presents a reduction in mortality if applied within 3 hours after the occurrence of trauma.

The presence of military studies that show benefit from its use in patients victims of penetrating trauma shows that its use could be of great value in the national territory, since this type of trauma has a high incidence in Brazil, as well as studies that have had as a scenario rural and remote areas, since our territory is of great extension and often TXA could not be administered in the hospital for often presenting more than 3 hours since the occurrence of trauma. The lack of Brazilian articles that address the

theme, however, makes the evaluation of its applicability and security in the national environment limited.

All studies analyzed excluded children from their samples, which makes it impossible to assess the benefit and safety of TXA in these patients in the presence of trauma.

The result of future studies and those in progress should better clarify about the safety and effectiveness of

TXA in the pre-hospital.

Even though it appears to be a very promising drug in the control of bleeding resulting from trauma, initial measures of bleeding control, rapid transportation to the reference hospital and use of appropriate techniques of resuscitation and blood component use is still very effective and able to save lives.

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