

PLACE OF TRANEXAMIC ACID IN MODERN MEDICINE

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ABSTRACT

Massive bleedings, both internal and external, are among the leading causes of preventable deaths. The research for the appropriate treatment focuses not only on looking for the new drugs but also relies on finding the new indications for the drugs already known in the pharmacotherapy of different disease. However, such an approach requires new protocols in order to be effective. One of the substances in question is tranexamic acid, which uses due to its antifibrinolytic effect is raising both in prehospital and hospital settings.

KEY WORDS: tranexamic acid, TXA, trauma, bleeding, hemorrhage

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INTRODUCTION

Tranexamic acid (TXA) is a low molecular antifibrinolytic drug [1] that has been used for many years to control hemorrhage in patients with hemophilia and other disorders involving coagulation system. The particular interest in TXA use was initially found by its ability to control massive hemorrhages in the prehospital setting, especially in the tactical environment, due to a statistically significant reduction of risk of death, when used in the early stage of pharmacotherapy [2–4]. The search for the safe and effective drug, which may be used in the prehospital control of hemorrhage is related to the epidemiology of injuries and its impact on the mortality of the overall population. According to the data provided by the WHO on their website, injuries are responsible for up to 10% of global deaths annually. In 2003, they caused the death of 5 million people worldwide, mainly as a result of traffic accidents,

and required hundreds of millions of medical services provided in emergency departments [5, 6]. In 2019, road accidents accounted for the 7th cause of death in countries with low financial status and 10th in countries with a slightly higher status; in highly developed countries, deaths resulting from traffic accidents were outside the top ten causes of mortality [7, 8]. However, regardless of the socio-economical status of the country, the trauma and associated bleeding is the leading cause of mortality and morbidity worldwide [9, 10]. Therefore, we have decided to dig further into the subject of the usage of TXA and perform this literature review regarding the usage, advantages and disadvantages of TXA application in the real-life setting.

Mechanism of action and the usage of TXA

In order to understand and fully appreciate the TXA mechanism of action, one must realize that coagu-

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lation is not just a process of blood clot formation but also it is dissolving by the plasmin [11, 12]. This delicate balance is maintained by various mechanisms. However, in case of major trauma the coagulopathy ensues resulting in uncontrollable bleeding [13]. Patients in this state require more blood transfusions, longer hospitalization time and overall present higher mortality [13]. This state, however, is not just the result of blood loss alone, patients who undergo major trauma with severe blood loss develop coagulopathy also in the mechanism of hemodilution, hyperthermy, acidosis and finally due to the consumption of blood factors they develop disseminated intravascular coagulation [14]. Therefore, a research for the new drugs that would ideally stop or at least slow down this cascade commenced. This result in the production of TXA which is the synthetic amino acid that inhibits the plasma plasminogen activators and to some extent the tissue plasminogen activators, which in turns blocks the conversion of plasminogen into plasmin. Additionally, TXA presents some activity regarding direct plasmin inhibition [1, 15]. The laboratory findings in the studies show reduced D-dimer concentration, a product of cross-linked fibrin breakdown [16].

All of these biochemical properties of TXA allow for an inhibition of fibrinolysis, which is the process of dissolving the blood clot by plasmin, and therefore it maintains the hemostasis. Additionally, TXA has been proven to increase thrombus formation [15]. All of these mechanisms of action resulted in their widespread use in different fields of medicine. The indications for drug administration include primary and generalized fibrinolysis, bleeding associated with the use of fibrinolytic drugs, vaginal

bleeding, e.g. in the course of heavy menstruation, bleeding from the gastrointestinal tract and the urinary tract of various etiologies. These drugs are also used to limit the blood loss resulting from otolaryngological, cardiosurgical, gynecological or abdominal surgery [17–19].

Despite many clinical studies, publications and meta-analyses, no clear consensus regarding the use of TXA in trauma patients has been established [19]. There are studies that prove a significant reduction in mortality in patients with hemorrhages when the TXA was administered within 3 hours following the injury [20]. A statistically significant reduction in the progression of intracranial bleeding and a statistically insignificant improvement in the results in patients with craniocerebral trauma was proven [21]. Studies also indicate a reduction in overall blood loss and a number of a blood transfusion given in patients undergoing elective procedures: knee and hip arthroplasty and the shoulder-scapular joint [22, 23].

Contraindications for TXA application

The contraindications for the TXA application include mainly the diseases that lead to hypercoagulation, mainly history of venous thrombosis and pulmonary embolism, arterial thrombosis (angina pectoris), history of myocardial infarction and disseminated intravascular coagulation. Additionally, severe renal insufficiency and seizures are also among contraindications for TXA application. As with any drug, the history of intolerance or allergy to the TXA automatically declines the use of this drug. TXA should be avoided in pregnant and lactating women, as well as children below 1 year of age

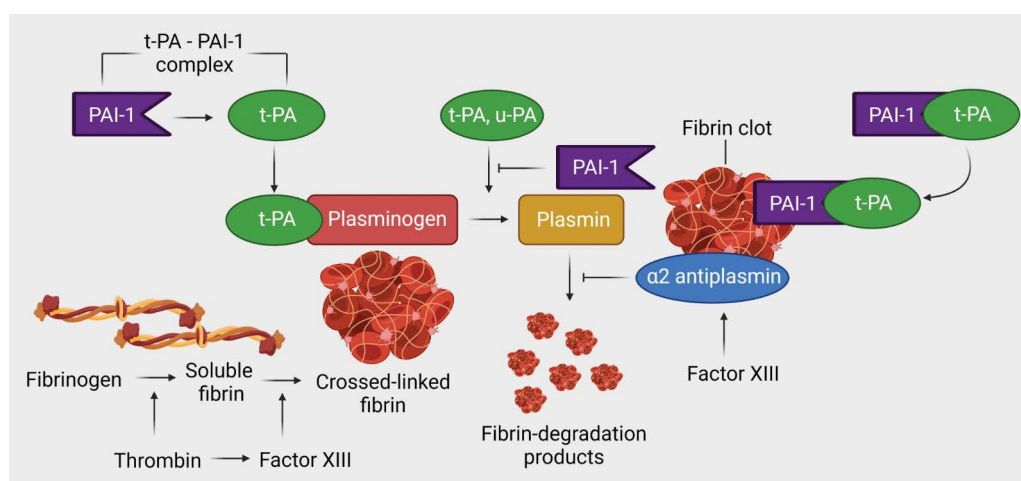


FIGURE 1. Management of tranexamic acid (created with BioRender.com, licensed version)

[24, 25]. One has to be careful when administering TXA in patients who are at risk of slower drug elimination e.g. with renal inefficiency, cardiac or neurological diseases [26, 27]. As TXA has proven to bind to GABA_A receptors, thus blocking GABA-mediated inhibition in the central nervous system, these patients are at risk of developing seizures following TXA administration [28]. This complication may be managed by administering the anesthetic agents that would modulate the receptors blocked by TXA, e.g. propofol [29].

TXA as drugs in Poland

In Poland, the drug is available as EXACYL (Sanofi) in three forms oral tablets at a dose of 500 mg, solution for injection at a dose of 100 mg/ml and the solution for digestion with the concentration of 100 mg/ml. When administered orally, it is absorbed quickly and the maximum concentration in the blood serum is reached after 2–3 hours, while after 6 hours following the administration, the drug is not detected. The half-life of the drug administered in the oral form is 1 hour, while in the intravenous form it is 3 hours. The drug is eliminated mainly by kidneys in urine (90%) unchanged within 12 hours after administration [35–37].

Tranexamic acid dosing

The off-label dosing of tranexamic acid has not been established. It is recommended to administer the TXA in a dose of 1 g diluted in 100 ml of 0.9% NaCl within 10 minutes for up to 3 hours from the hemorrhagic injury and to re-administer the drug in a dose of 1 g for the next 8 hours as an intravenous infusion [30–34]. One should pay attention to the factors that may impair the blood clot formation e.g., drop in body temperature or disturbance in the overall fluid status [30]. No consensus regarding the dosing of TXA in patients with craniocerebral injuries or undergoing elective orthopedic surgery has been established [23, 35, 36]. The advantages of using TXA in pre-hospital management have been proven during randomized clinical trials CRASH-2 and CRASH-3, which were carried out by the London School of Hygiene and Tropical Medicine. Dosage and application regimens may be found in the recommendations of various groups, such as Task Force for Advanced Bleeding Care in Trauma, International Trauma Life Support, Tactical Combat Casualty Care or The Committee for Tactical Emergency Casualty Care (C-TECC) [37, 38].

CONCLUSION

New studies constantly show up in the medical literature regarding the possible label use of TXA. These studies report that TXA administration in the emergency settings, both in pre and hospital environment, significantly increases the survival rate of the patients suffering from severe hemorrhagic injuries. Additionally, this relatively cheap and easily available drug may increase the safety of the patients who undergo major elective surgery, due to the reduction of required blood transfusions. Due to the lack of unified dosing protocols and ongoing discussions regarding safety and indications for the TXA administration further analysis of literature is required to establish the consensus on TXA therapy.

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