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TRANEXAMIC ACID USE IN EMERGENCY MEDICINE

Mahdi Al-Jeabory[1, 2], Wladyslaw Gawel[2], Aleksandra Gasecka[3], Lukasz Szarpak[1, 4, 5], Wojciech Wieczorek[1, 6]

[1]Reseach Unit, Polish Society of Disaster Medicine, Warsaw, Poland
[2]Research Unit, Polonia University, Czestochowa, Poland
[3]1st Chair and Department of Cardiology, Medical University of Warsaw, Warsaw, Poland
[4]Henry JN Taub Department of Emergency Medicine, Baylor College of Medicine, Houston, TX, USA
[5]Institute of Outcomes Research, Maria Sklodowska-Curie Medical Academy, Warsaw, Poland
[6]Department of Emergency Medicine, Medical University of Warsaw, Warsaw, Poland

ABSTRACT

The most common cause of potentially preventable trauma deaths is hemorrhage. Therefore, it is crucial to understand the mechanisms regulating bleeding and clotting. The physiological mechanisms that control the coagulation process are called the coagulation cascade. In this study, we analyzed the medical literature for published articles on the use of TXA for bleeding. The MEDLINE electronic database was searched for. The keywords we have used were: "tranexamic acid", "bleeding", "hemorrhage", "treatment", "prevention", "patient blood management", "anti-fibrinolytic", "surgery", "surgery", "trauma", "injury" and "traumatic brain injury". When managing the traumatic patient, time is of the essence and the same holds true for the TXA application. The largest study regarding the use of TXA in the emergency medicine CRASH-2 found that the administration of TXA within 3 hours following injury significantly reduces the mortality and that every 15-min delay in administering TXA results in increased bleeding and decreased survival by 10%, offering no benefit if administered after 3 hours. In summary, TXA is a safe and reliable agent which greatly increases the survival rate in traumatic patients suffering blood loss, reducing mortality while being safe.

KEY WORDS: tranexamic acid; TXA; bleeding; emergency medicine; trauma

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INTRODUCTION AND MECHANISM OF ACTION

The most common cause of potentially preventable trauma deaths is hemorrhage [1]. Therefore, it is crucial to understand the mechanisms regulating bleeding and clotting [2, 3]. The physiological mechanisms that control the coagulation process are called the coagulation cascade. This process relies on the sequences of proteolytic events that take place on the surface of platelets [4]. For academic purpose, the cascade is divided into the intrinsic and extrinsic pathways [5] which both result in the formation of the blood clot. However simultaneously with the blood clot formation in order to avoid excessive thrombosis, the process called fibrinolysis takes place [6]. The key enzyme that is involved in the process of dissolving the blood clot [7] called fibrinolysis is the plasmin [8], which is an activated form produced from the plasminogen by the tissue plasminogen activator and urokinase [9]. The inhibition of plasmin results in stabilization of the clot [10] and thus reduces blood loss. One of the agents used to stop excessive bleeding and prevent exsanguination is tranexamic acid (TXA) which is the anti-fibrinolytic amino acid derived from lysine [11]. It acts via the competitive inhibition of lysine binding sites

ADDRESS FOR CORRESPONDENCE:
Mahdi Al-Jeabory, Polonia University, 4/6 Pulaskiego St, 42–200 Czestochowa, Poland
e-mail: mmahdi@interia.pl
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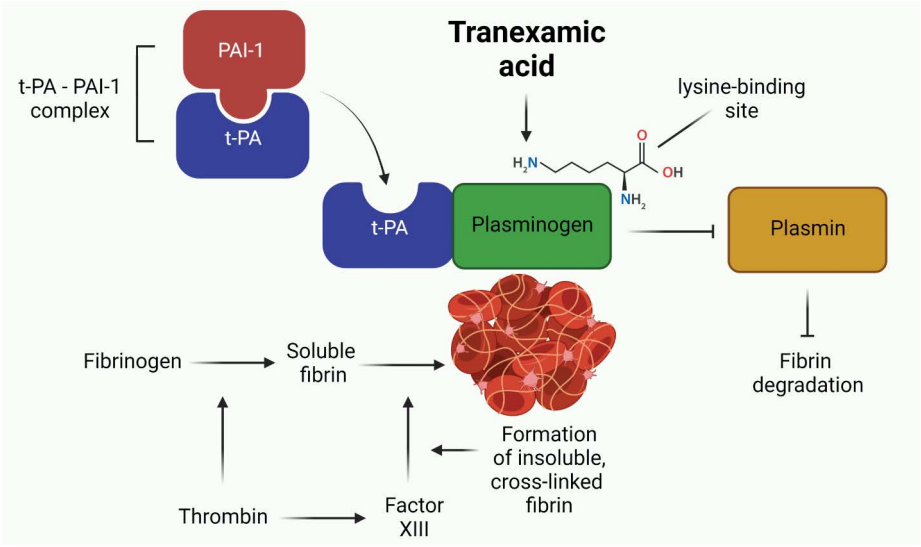

FIGURE 1. Functional diagram of Tranexamic Acid. Created with BioRender.com, licensed version

of plasminogen [12] resulting in the prevention of attachment of said enzyme to the fibrin, stabilizing the clot, and reducing bleeding [13] while increasing survival of patients [14, 15] (Fig. 1). The inhibition of fibrinolysis is particularly important in patients suffering from massive blood loss as this leads to the loss of coagulation factors, acquired coagulopathy, and exsanguination [16, 17]. The bleeding and concurrent loss of coagulation factors lead to disseminated intravascular coagulation (DIC) which might be alleviated by TXA administration both in chronic DIC [18] and acute traumatic DIC [19, 20]. The TXA comes in many forms and found used in many clinical situations ranging from tooth extraction [21] to cardiac surgeries [22] and major trauma [23]. However, in this review, we have focused on the TXA role in the management of bleeding in the emergency medicine setting.

INDICATIONS FOR TXA USE

We analyzed the medical literature for published articles on the use of TXA for bleeding. The MEDLINE electronic database was searched for. The keywords we have used were: "tranexamic acid", "bleeding", "hemorrhage", "treatment", "prevention", "patient blood management", "anti-fibrinolytic", "surgery", "surgery", "trauma", "injury" and "traumatic brain injury".

The TXA is approved by the Federal Drug Administration only for heavy menstrual bleeding [24] and short-term prevention in patients with hemophilia [25]. The European Medicines Agency allows for wider usage including prevention and treatment of hemorrhages due to general or local fibrinolysis in adults and children as young as one-year-old [26]. However, due to the high efficacy in stopping the bleeding, the TXA found widespread off-label use [27] including gynecological complications [28], trauma [25], and surgeries [29]. The most common gynecological emergency where the TXA found its use it postpartum hemorrhage which ranks among the five most common causes of maternal mortality worldwide [30]. The largest study on this particular subject showed that not only TXA is effective in terms of stopping the bleeding and reducing mortality but also is safe and does not increase the thrombosis rate [31]. These findings were challenged by the TRAAP study group which presented data showing no statistically significant benefit of TXA administration in the management of postpartum hemorrhage complications [32]. Additionally, TXA is a safe drug that can be administered to breastfeeding woman [33], which greatly increases their survival chances in bleeding injuries.

When managing the traumatic patient, time is of the essence and the same holds true for the TXA application. The largest study regarding the use of TXA in the emergency medicine CRASH-2 found that the administration of TXA within 3 hours following injury significantly reduces the mortality and that every 15-min delay in administering TXA results in increased bleeding and decreased survival by 10%, offering no benefit if administered after 3 hours

[34]. The study group led by Roberts reached similar conclusions regarding the application of TXA [35].

Special attention was given to TXA administration in head trauma, as it is the leading cause of mortality worldwide regarding trauma patients [36]. The CRASH-3 study focused entirely on head trauma patients presented evidence that while effective in reducing bleeding, the group of patients who benefit from administration of TXA is limited to those who are not initially in the critical condition, underlining the need for triage and proper indication to TXA therapy [37]. Additionally, time-dependent manner of survival and advantage of TXA therapy was present similarly to CRASH-2 study results, while it did not apply to patients suffering severe head trauma. When managing and accessing the brain injury one must particularly take note of intracranial hematoma as its pressure causes further damage to the brain tissue [38]. The TXA was shown to be a viable agent in reducing the size of intracranial hemorrhage by some studies [39], however, this is challenged by others that did not support this finding [40, 41].

In patients undergoing operations for severe bone trauma e.g. hip fractures, TXA was found to be a reliable and safe drug for reducing blood loss [42], resulting in lower transfusion rates [43].

Emergency medicine and its application find its role in combat medicine as both disciplines cooperate and learn from each other [44]. Similarly, to the civilian setting, hemorrhage is the leading cause of preventable death [45]. The advancement in care provision along with the improved protocols leads to a reduction of trauma-related deaths, despite the increase of trauma severity [46]. The largest study in the military setting MATTER (Military Application of Tranexamic acid in Trauma Emergency Resuscitation) found that the application of TXA resulted in increased survival, especially in patients requiring massive transfusion [47]. Additionally, a study by Walker found that the TXA application in head trauma improves neurological outcomes in short term, but not in the long term, indicating that TXA might be useful as a bridging therapy between battlefield first aid and neurosurgical intervention via reduction of intracranial hemorrhage [48]. Some findings however suggest that the TXA is a double-edged sword. An analysis of military trauma patients from Afghanistan and Iraq found that the administration of TXA was an independent risk factor for venous thromboembolism [49]. Regardless of these findings TXA remains a viable and safe tool, which is included in the Tactical Combat Casualty Care guidelines [50].

CONTRAINDICATIONS FOR TXA ADMINISTRATIONS

While the use of TXA was found beneficial in patients undergoing hemodialysis who suffered from cerebral hemorrhages [51] or acute gastrointestinal bleeding [52], the overall consensus is that chronic kidney disease or acute renal failure shall be considered a relative contraindication due to the reports of acute cortical necrosis [53] and ureteric clots [54]. Although the use of TXA in elective surgery patients with preexisting venous thromboembolic events (VTE) was found safe [55], the wide accepted consensus is that the history of VTE is the contraindication for TXA administration [56].

CONCLUSIONS

TXA is a safe and reliable agent which greatly increases the survival rate in traumatic patients suffering blood loss, reducing mortality while being safe.

Conflict of interest

All authors declare no conflict of interest.

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