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The Place of Intravenous Tranexamic Acid as an Antifibrinolytic For Severe Trauma Related Critical Haemorrhage in a Mature Trauma System

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ABSTRACT

Trauma is a common health issues all over the world and a major cause of mortality and morbidity. Critical haemorrhage is the key pathology leading to multiple adverse consequences in trauma. Standard measures to control haemorrhage are less effective in such situations. Intravenous Tranexamic acid is an antifibrinolytic agent which stabilize fibrin clot and prevent further bleeding. The role of Tranexamic acid in acute trauma related bleeding was evaluated in many studies. Most of the severe trauma patients are nowadays managed in mature trauma systems and place of Tranexemic acid in such systems are controversial. The aim of this review is to discuss evidences and guidelines in this area in view of the use of Tranexemic acid in a mature trauma system.

Introduction

Trauma is very common and affects more than 5 million people worldwide every year. It accounts for about 9% of global mortality and consumes significant amount of health budget across all countries [1]. Nearly half a million people are hospitalized following trauma in Australia per year with 12 thousand deaths annually [2]. The incidence of severe trauma increases annually despite preventative measures and is a major health issue in both high- and low-income countries [1]. Critical Haemorrhage is a main concern in trauma care, which leads to multiple adverse consequences. Haemorrhage could be secondary to direct penetrating injury or blunt trauma to visceral organs or vascular structures. Initial response to haemorrhage is increasing heart rate and peripheral vascular resistance to maintain systemic blood pressure. If bleeding continues (exceeds 20% of total blood volume) then compensation fails and activates depressor reflex. Hypotension and bradycardia with syncope are cardinal features in this phase [3]. Unless bleeding is controlled or blood volume is replaced, poor perfusion proceeds to organ dysfunction called "shock" [3,4]. Shock is a treatable cause of trauma related deaths [5]. Primary objective of a mature trauma care system is to control this critical haemorrhag [6]. Direct pressure, combat application tourniquet, splinting of long bone fractures are some of bleeding control measures. However, when the bleeding is massive and concealed, local measures are ineffective. Several studies were looking at the role of antifibrinolytic agents in controlling bleeding following trauma [7]. Tranexemic Acid (TXA) is one of those agents studied widely and aim of this article is to evaluate the place of TXA in mature trauma system.

Coagulation Process and Antifibrinolytics

Trauma results in bleeding by injury to blood vessels. Severity of bleeding depends on size and site of the blood vessel. When a blood vessel is injured from a blunt or penetrating trauma the initial response is vasoconstriction to minimize further blood leakage through the vessel. Next step is aggregation of platelets to form a platelet plug and block the site of vessel damage. Fibrin is a linear protein which polymerizes and produce homeostatic clot with platelet. Finally clotting factors trigger production of fibrin, which form a mesh like net to keep the platelet plug stable. This plug is the primary protective mechanism of preventing bleeding from damaged blood vessels in trauma [8]. Antifibrinolytics

are drugs that prevent breakdown of fibrin products formed in response to bleeding. Fibrinolysis is a protective process in the body to prevent formation of unnecessary fibrin clots. Tissue plasminogen precursors, which are converted to plasmin, breakdown fibrin into degradation products and dissolve the clot. Antifibrinolytics are drugs that inhibit this process. There are few types of antifibrinolytics (Table 1) with different plasmin blocking mechanisms [9,10].

Table 1: Types of antifibrinolytics.

Antifibrinolytics	Chemical group	Mechanism
Tranexamic acid (TXA) ε-Aminocaproic acid	Lysine analogues	Reversely blocking the lysine binding sites of plasmin
Aprotinin	Lerine protease inhibitor	Active inhibition of plasmin

Current Evidence and Guidelines for Tranexamic Acid use in Trauma

Amongst all antfibrinolytics, TXA was trialled in severe trauma to control bleeding. A large randomized study, "Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage-2 (CRASH-2)" evaluated 20,000 trauma patients in 40 countries by using TXA within 8 hours of injury in the treatment arm [11]. All-cause mortality was low in treatment group (14.5% versus 16% with RR 0.91). Death from haemorrhage was significantly low (4.9% versus 5.7% with RR 0.85). There were no significant vascular occlusive events such as myocardial infarction, pulmonary embolism. Overall conclusion was that TXA should be considered as a treatment for trauma related bleeding. However, follow up study of CRASH-2 demonstrated that TXA given after 3 hours of the event failed to prevent life threatening bleeding [12]. This concluded that the better approach is to administer TXA acid at site of trauma in early hours. Further analysis of CRASH-2 patients in Trauma Audit and Research Network (TARN) study recommends administration of TXA within 3 hours of injury in wide spectrum of traumatic bleeders from mild to very severe injuries [13]. A German study assessed 258 civilians with major trauma (mean Injury Severity Score - ISS of 24) retrospectively and concluded significant reduction of early mortality with prehospital TXA administration within 3 hours of the incident [14]. International Trauma Life support (ITLS) guidelines recommends considering TXA in trauma patients who show evidence of bleeding and in less than 3 hours of injury [15]. Recommendation from European guideline was to administer first dose of TXA on the way to hospital (pre-hospital). Few trauma guidelines recommend TXA in major trauma related bleeding [15-17] (Table 2).

Table 2: Major guidelines on TXA in trauma care.

Guideline	Recommendation on TXA	Class of recommendation	Level of evidence
International Trauma Life Support (ITLS) [15]	TXA should be considered in those patients who show signs of hemorrhagic shock, including tachycardia (>110 bpm) and hypotension (SBP<100) and are less than 3 hours from injury		
European guidelines for management of bleeding and coagulopathy following major trauma [16]	Administer TXA as early as possible to the trauma patient who is bleeding or at risk of significant hemorrhage	1	A
	TXA be administered to the bleeding trauma patient within 3 hours after injury	1	B
	Administration of the first dose of tranexamic acid en route to the hospital	2	C
American College of Surgeons Committee on Trauma [17]	Prehospital TXA use should never supersede field bleeding control techniques, rapid transport to a trauma center, or the administration of blood or plasma.		

Tranaxemic Acid use in Mature Trauma System

Nowadays most of trauma patients are managed in mature trauma systems in high income countries. Trauma related death rate has fallen by 50% with the introduction of mature trauma system in Victoria, Australia [18]. Beneficial effects of TXA in such system is debatable. The main conflict in CRASH- 2 study is that majority of patients were managed in underdeveloped trauma centres [19]. Controversial evidences regarding use of TXA in mature trauma systems were reported by newer studies. A prospective study in a mature trauma system of United States demonstrated that the trauma patients who were given TXA with physiological levels of fibrinolysis had higher incidence of mortality compared to those who were not given TXA. Furthermore, TXA found to be a predictor of mortality in patients with physiological fibrinolysis in this study (p=0.018) [20]. At the same time, administration of TXA in trauma patients with hyperfibrinolysis failed to demonstrate reduction of mortality in another study [21]. In this study hyperfibrinolysis is defined by LY-30 equals or more than 3%. Hyperfibrinolysis is assessed by Thromboelastography test, which measures visco-elastic properties of the clotting blood in trauma patients [22].

Thromboelastography provides additional information related to traumatic bleeding and has future prospects in mature trauma systems. A prospective study of 385 severe trauma patients (ISS >15) revealed that TXA does not independently improve outcome

for total or non-shock cohorts. There was mortality benefit only in shock cohort of the study group. This study fails to recommend TXA in non-shock severe trauma patients in a mature trauma care in a high-income country [23]. Another study tested TXA in 1,217 consecutive trauma patients (mean ISS 28), who had blood transfusions with or without emergency procedures over 5 years in a single mature trauma system of Florida. TXA was associated with higher mortality in high acuity patients, irrespective of the time of administration [24]. A cohort of 1,476 patients were evaluated in multiple level 1 mature trauma centres in France. Use of TXA was not associated with lowering hospital mortality in this study [25]. Military health services accept highest number of trauma patients. The Military Application of Tranexamic Acid in Trauma Emergency Resuscitation (MATTER) study in Afghanistan trauma centre demonstrated higher incidence of deep vein thrombosis and pulmonary embolism in patients received TXA than who did not get TXA (2.7% versus 2.4%). Those patients suffered from major trauma with mean ISS of 25.2 [26].

Conclusion

It is still not clear that which group of trauma patients benefit from administration of TXA. Specially trauma patients managed in a mature trauma system in high income countries, fail to demonstrate improved outcomes with TXA. Further large-scale randomized studies will be useful to understand the place of TXA in mature trauma care.

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