Tranexamic Acid Update in Trauma

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KEYWORDS

• Tranexamic acid • Trauma • Coagulopathy • Hemorrhage • Antifibrinolytics
• Surgery

KEY POINTS

- Tranexamic acid (TXA), a synthetic lysine derivative, has previously shown efficacy for reducing blood loss in several surgical procedures.
- TXA has shown a mortality benefit in bleeding trauma patients when administered within 3 hours of injury; however, there is no decrease in blood product transfusions.
- Pharmacokinetics and optimal dosing in trauma patients remain unknown.
- Ongoing and future trials are needed to refine current understanding of TXA's mechanisms of action in trauma patients and to optimize drug administration.

INTRODUCTION

Trauma is the leading cause of death and disability worldwide, with an estimated 5.8 million people dying every year as a result of traumatic injury.[1,2] In both military and civilian settings, hemorrhage remains the most common cause of preventable death after traumatic injury.[3–6] In recent years, there has been considerable interest in antifibrinolytic agents for the prevention of hemorrhagic death in severe trauma patients. The Clinical Randomization of an Antifibrinolytic in Significant Hemorrhage (CRASH)-2 and Military Application of Tranexamic Acid in Trauma Emergency Resuscitation (MATTERs) studies were pivotal, landmark studies that brought the antifibrinolytic agent tranexamic acid (TXA) to the forefront of discussion after evidence suggested improved mortality in civilian and military trauma, respectively.[7,8] Based on results

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from the CRASH-2 trial, in March of 2011, TXA was added to the World Health Organization's list of essential medications. However, widespread adoption by mature trauma systems in the United States has been slow due to concerns about unknown exact mechanism of action, uncertainty surrounding use in patients with concomitant traumatic brain injury (TBI), unknown precise pharmacokinetics in the trauma patient, and safety.[9–11] The results of these landmark studies sparked worldwide debate and prompted funding for several trials to address these and other concerns.[12–18]

This article provides a brief overview of the history of TXA, reviews the known and proposed mechanisms of action, and examines areas of ongoing and future research aimed at addressing unanswered questions.

BACKGROUND

TXA is a synthetic lysine derivative that exerts its action by competitively occupying the lysine binding site of plasminogen, thereby blocking interaction with fibrin and subsequent clot breakdown.[19] TXA has a molecular weight of 157.2 g/mol and its injectable formulation is marketed under the name Cyklokapron. The pharmacokinetics of TXA in healthy individuals after administration of a 10 mg/kg dose demonstrate peak concentrations at 60 minutes postadministration, with a half-life of approximately 2 hours for the terminal elimination phase, and 90% excretion at 24 hours. An antifibrinolytic dose remains in tissues for up to 17 hours and in serum for up to 8 hours. It has also been shown to cross the placental barrier, is excreted in breast milk, and rapidly appears in synovial fluids.[20] The pharmacokinetics in trauma patients may differ, however, and appropriate dosing in this population may not be reflective of clinically effective concentrations previously described in healthy individuals. Pharmacokinetics and effects of TXA on hemostasis and immune systems are currently subjects of large ongoing trials with US government funding.[12,13,15]

In 1986, the Food and Drug Administration (FDA) approved intravenous administration of TXA for the indication of prevention or reduction of bleeding in patients with hemophilia undergoing dental procedures. The oral form of TXA, marketed under the brand name Lysteda, was approved by the FDA in 2009 to control heavy menstrual bleeding.[21] The drug has also been widely studied for the reduction of bleeding in cardiopulmonary bypass (CPB) surgery[22–29] and orthopedic procedures,[30] including its applicability in spine,[31] knee,[32] and shoulder surgery.[33] In the 1990s and early 2000s, the antiinflammatory properties of antifibrinolytics were recognized in patients undergoing CPB surgery. In 2007, Jimenez and colleagues[26] published a paper confirming this observation. The same year, Brohi and colleagues[34] described the protein C pathway and its important role in the development of coagulopathy and hyperfibrinolysis following trauma. This important work gave rise to new interest in antifibrinolytics and their effects on the intimate relationship that exists between inflammatory and coagulation pathways.

A 2012 meta-analysis of surgical studies evaluating TXA included 129 trials (1972 through 2011) with 10,488 subjects mostly in elective surgical procedures, the majority for cardiac surgery. Pooled results from 95 trials evaluating risk of blood product transfusion demonstrated that TXA had a 38% risk reduction of perioperative blood product administration (pooled relative risk [RR] 0.62, 95% confidence interval [CI] 0.58–0.65, $P = .001$). With adequate allocation concealment, 32 trials showed similar results (pooled RR 0.68, 95% CI 0.62–0.74, $P = .001$) and the same was true of 69 trials with adequate blinding (pooled RR 0.63, 95% CI 0.59–0.68, $P = .001$). When analyzing the effect of TXA on death, they found that fewer deaths occurred in the TXA group (RR 0.61, 95% CI 0.38–0.98, $P = .04$). However, when evaluating only those studies with