Application of Tranexamic Acid in Trauma and Orthopedic Surgery

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KEYWORDS

• Tranexamic acid • Orthopedics • Trauma • Transfusion • Hemorrhage • Antifibrinolytics

KEY POINTS

- Tranexamic acid has been approved by the Food and Drug Administration for the past 30 years as an antifibrinolytic and has recently been added to the World Health Organization's list of essential medications.
- Tranexamic acid is not only effective, but safe in trauma and orthopedics with no increased morbidity including deep venous thrombosis or pulmonary embolism. Furthermore, it is inexpensive and the cost-savings with its use have been confirmed.
- Tranexamic acid has become readily integrated into joint replacement and spine surgeries, although the optimal timing and dosing have not been established. Significant reduction in blood loss and transfusion requirements in this setting was again demonstrated.
- The role of tranexamic acid in orthopedic trauma is emerging, and to date there have only been a small number of heterogeneous studies, which mostly pertained to hip fractures. Results in this cohort are promising, however.
- Significant future investigation, particularly with regards to orthopedic trauma, is needed to maximize the benefit from this drug. Furthermore, optimal timing and dosing should be confirmed.

INTRODUCTION

The use of tranexamic acid (TXA) as an antifibrinolytic agent was initially approved by the Food and Drug Administration to reduce bleeding in hemophiliacs undergoing tooth extraction.[1] Over the ensuing 30 years its use has extended to virtually every aspect of medicine from acute trauma to elective surgeries and extensive investigation for its myriad applications continues. The use of TXA in traumatically injured patients has gained international recognition, because hemorrhage is the number one preventable cause of death in this population.[2] The World Health Organization added the drug to its list of essential medications in 2011 after several investigations suggested it may significantly reduce death caused by hemorrhage.[1]

As a synthetic derivative of lysine, TXA competitively inhibits the conversion of plasminogen to plasmin, effectively prohibiting fibrin degradation

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and dissolution of formed clot.[3] In addition, its theorized anti-inflammatory properties have been proposed as a secondary mechanism for reducing mortality in hemorrhaging patients.[4] It may be administered intravenously, intra-articularly, topically into the surgical field, or even orally.[5] Dose of the drug and timing of administration have also been examined and recommendations vary based on the circumstances of its use.

Orthopedic surgeons have incorporated TXA into multiple elective surgeries as a means of reducing blood loss and transfusion requirements.[6] The safety and efficacy of TXA for total hip and total knee arthroplasty have been demonstrated, although debate continues regarding the most appropriate route for administration.[7,8] Multiple studies have also demonstrated the safety and use of TXA in reducing blood loss during elective spine surgery.[9,10] Unfortunately, the role for TXA in orthopedic trauma has yet to be elucidated, although the limited results from its use in hip and femur fractures to date are encouraging.[11,12]

TRANEXAMIC ACID

TXA (trans-4-[aminomethyl] cyclohexane carboxylic acid) (Fig. 1) was first developed in Japan in 1962 in an attempt to synthetically capture the plasminogen-inhibiting capabilities of lysine more effectively.[13,14] The initial goal of this research was to reduce postpartum deaths caused by hemorrhage, yet its use in medicine and surgery has continued to expand.

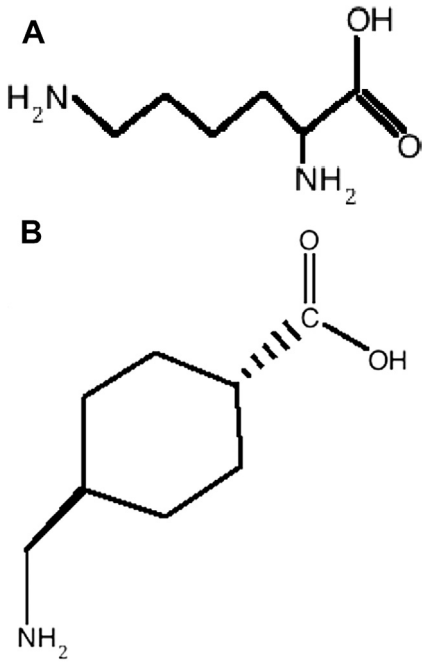

Fig. 1. Structure of lysine (*A*) and its synthetic derivative tranexamic acid (*B*).

Mechanism and Pharmacokinetics

The interaction of plasminogen and the plasmin heavy chain is reversibly inhibited by TXA blockade of lysine-binding sites on plasminogen (Fig. 2).[15] Failure of fibrinolysis results as plasminogen is unable to bind to the fibrin molecules. At higher doses, TXA is secondarily able to directly inhibit plasmin activity and formation.[13] The plasma concentration needed to achieve approximately 80% inhibition of fibrinolysis is 10 μg/mL and maximum concentration is achieved approximately 1 hour after intravenous (IV) dosing.[14,16,17] The antifibrinolytic effects of TXA last from 8 to 17 hours after administration.[17–19]

Dosing and Timing of Administration

Orthopedic applications of TXA have effectively used IV, intra-articular, topical, and oral dosing

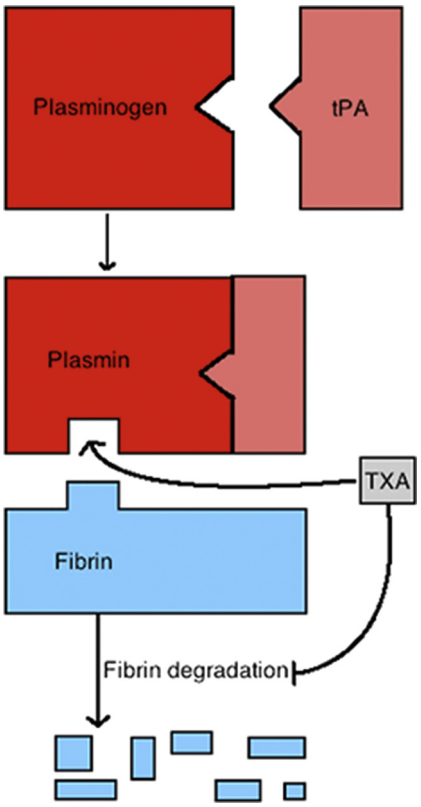

Fig. 2. Tissue plasminogen activator (tPA) binding to and activating plasminogen to plasmin. The lysine binding site for fibrin is blocked by tranexamic acid (TXA) thus inhibiting fibrin degradation and promoting clot stabilization.