Tranexamic acid in remote damage control resuscitation

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With the advent of remote damage control resuscitation and far-forward surgery, a renewed emphasis has been placed on examining a variety of pharmacologic adjuncts to controlling blood loss before definitive operative intervention. In this paper, the authors review the current state of the art for tranexamic acid (TXA) and its potential benefits to those patients who are in need of a massive transfusion. Specifically addressed are its biologic and pharmacologic properties, as well the results of a number of recent studies. The 2010 CRASH-2 trial randomized in excess of 20,000 patients and demonstrated a reduction in all-cause mortality from 16.0 to 14.5% and death due to bleeding from 5.7 to 4.9%. The 2012 Military Application of Tranexamic Acid in Trauma Emergency Resuscitation study provided a retrospective analysis of 896 wounded cared for at a military hospital in Afghanistan. This study demonstrated a 23.9%-17.4% reduction in all-cause mortality. Finally, they discuss the potential complications associated with TXA use as well as areas of future research, which are needed to solidify our knowledge of TXA and its potential beneficial effects on controlling bleeding.

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INTRODUCTION

The advent of remote damage control resuscitation (RDCR) for patients injured far from definitive surgical care has sparked an interest in alternative temporizing measures to minimize hemorrhage associated with traumatic injury. In this article, we review one such adjunct—tranexamic acid (TXA)—addressing its potential for application to RDCR and identifying areas where more information may be needed.

BACKGROUND AND PROMISING RESULTS IN TRAUMA

TXA is an antifibrinolytic that exerts its action primarily by binding to plasminogen and interfering with conversion to plasmin, thereby inhibiting fibrinolysis and diminishing blood loss.[1] TXA has also been shown to modulate the inflammatory response to injury, but the exact mechanism in surgery and trauma is poorly understood.[2-4] Although TXA has been available since the early 1960s and successfully used in hemophilia patients and in cardiac and orthopedic surgery patients,[5-9] it has not been extensively utilized in the trauma population until the Clinical Randomization of an Antifibrinolytic in Significant Hemorrhage (CRASH)-2 study reported its results in 2010. In that prospective trial, 20,211 patients were randomly assigned to receive either TXA or placebo after traumatic injury. In-hospital mortality was reduced from 16 to 14.5% in the TXA group. Furthermore, when TXA was given within 3 hours after injury, mortality attributable to bleeding was reduced from 5.7 to 4.9%.[10,11] Limitations of the CRASH-2 study are recognized. There was no systematic reporting of adverse events, there was a relative paucity of patients who actually received transfusion (approx. 50%), and there were very few patients cared for in developed countries where standardized care for the critically injured would have been expected to occur.

The Military Application of Tranexamic Acid in Trauma Emergency Resuscitation (MATTER) study specifically applied TXA to the critically injured combat victim.[12] In this retrospective review of 896 patients, 293 patients received TXA to temporize hemorrhage. Unadjusted mortality was reduced in the TXA group (17.4% vs. 23.9%; $p = 0.03$). The survival advantage was greatest in the 231 patients that received massive transfusion (MT)

(>10 units of red blood cells per 24 hr) (28.1% vs. 14.4%; p = 0.004). The use of TXA was also, in an adjusted analysis, independently associated with survival (odds ratio 7.228; 95% confidence interval, 3.016-17.332).[12]

SELECTED OBSERVED COMPLICATIONS

Potential adverse effects of TXA were noted in both trauma studies. In the CRASH-2 study, if TXA treatment was initiated more than 3 hours after injury, there was a significant increase in mortality (from 3.1 to 4.4%; p = 0.004).[11]

The authors proposed that the increased hemorrhagic deaths when TXA was initiated more than 3 hours after injury may have been due to the development or exacerbation of disseminated intravascular coagulation (DIC). They noted that patients in later phases of trauma can develop a thrombotic DIC and that antifibrinolytics could be contraindicated during this period.[11] The authors also pointed out that patients arriving late to the hospital may be more likely to suffer hypothermia and acidosis and that these factors may explain the reduced efficacy of TXA when administered late. The likelihood of delayed arrival at hospital is greater in RDCR applications, almost by definition. Therefore, timing issues and the potential progression of patients to a state where TXA is ineffective or contraindicated are of particular importance in RDCR.

The MATTER study reported a statistically increased incidence of thromboembolic events (pulmonary embolism and deep venous thrombosis) in those receiving TXA. The authors stated that the increased incidence of thrombotic complications was likely a result of the increased injury severity among the patients that received TXA (Injury Severity Score: 25.2 vs. 22.5). Whether these adverse events were related to more severely injured patients surviving secondary to the use of TXA or to TXA's potential prothrombotic mechanism is unknown.[12]

TXA complications have also been observed in civilian use. TXA acts as a gamma-aminobutyrate (GABA) antagonist, inducing GABA-driven inhibition of the central nervous system and reducing the seizure threshold.[13] In cardiac surgery, especially open-heart procedures, increased postoperative seizures have been observed at doses of TXA similar to those used in trauma.[5,14,15] The incidence of seizures following use in trauma has not been reported.

CURRENT USE OR TRENDS IN TRAUMA

With this information, how can clinicians integrate TXA in the resuscitation pathway of critically injured patients with massive blood loss? In the civilian sector, there is growing interest in the use of TXA in early treatment of patients with traumatic hemorrhage. Inclusion of TXA as part of standardized transfusion protocols[16] and even use in the prehospital setting has been discussed.[17] The British military incorporated TXA into standardized treatment protocols in 2010,[11] while the US military adopted it slightly later.[18,19] Specifically with respect to potential applications in RDCR, the Tactical Combat Casualty Committee guidelines[18] call for the judicious use of fluids and tourniquets to minimize hemorrhage. For patients expected to require an MT, the use of TXA as an adjunct is warranted; currently, the use of TXA is limited to care providers with advanced skills.

POTENTIAL FOR USE IN RDCR

TXA is relatively inexpensive, has minimal storage requirements, and has a good safety profile for its approved indications. Considering this and its reported efficacy in trauma, TXA has potential for applications in RDCR. TXA may reduce blood loss and decrease deaths from hemorrhage by its known antifibrinolytic mechanisms.

Potential other benefits may include mitigation of inflammatory changes[3,4] and potentially other pathophysiologic responses associated with hemorrhagic shock.[2] However, a number of factors must be carefully considered before generalized application to RDCR is accepted. Additionally, more information is needed in a number of areas of special relevance to RDCR.

POTENTIAL HAZARDS IN RDCR

Although the observed survival benefits associated with TXA outweigh the risks based on currently available information, much remains to be learned regarding the optimal use and timing of TXA in trauma (A.E. Pusateri et al., unpublished data). Specifically with respect to RDCR, more information is needed in the following areas:

1. With increasing interest in hypotensive resuscitation in the prehospital setting, the issue of (relative) hypotension becomes increasingly important. Prolonged (relative) hypotension, for example, during situations where casualty evacuation is delayed, may impact glomerular filtration rate[20] and the ability of the kidney to clear TXA from the blood. Altered pharmacokinetics may influence both efficacy and risk for complications related to the use of TXA in trauma patients.
2. Storage under field conditions.
3. Potential interactions with other drugs, such as fibrinogen concentrate or prothrombin complex concentrates, which may also have future applications in RDCR. Additionally, more information is also needed regarding its use with prehospital fluids and blood products in conjunction with TXA.
4. Further information regarding optimal patient selection and optimal treatment regimens will be important. Further information is needed on patients most

likely to benefit and those in which TXA may be contraindicated. Current data from the MATTER study would support its use in that subset of patients expected to require a MT.
5. Information is needed on the potential impact of prolonged evacuation during which the patient may progress to a "contraindicated" DIC-like state following TXA treatment during the first 3-8 hours.
6. RDCR is likely to take place in austere conditions where the array of in-hospital therapies is not available. More information is needed on how best to prevent or manage complications such as seizures or thrombosis under the field conditions expected for RDCR.

CONCLUSION

Though a number of questions remain regarding TXA and its underlying mechanism of action and potential complications, the CRASH-2 and MATTER studies have demonstrated the feasibility of TXA as a temporizing measure in critically bleeding patients. As use in trauma expands, it will be important to systematically address questions related to patient selection, dosing, adverse side effects, and others. These questions, as well as RDCR-specific questions, must be addressed when considering the use of TXA in RDCR. In planning, training, and research, close attention should be given on how to treat or prevent complications of TXA in RDCR and, ideally, on how to identify patients that are not likely to benefit and who should not receive TXA. That having been said, the recent studies documenting improved survival with early TXA use in trauma patients make the prospects for eventual application of TXA in RDCR promising.

CONFLICT OF INTEREST

None.

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