Tranexamic acid: A Cost Effective Medication to Decrease Death From Acute Blood Loss in Trauma Patients

Brandon Smith
Pacific University

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Tranexamic acid: A Cost Effective Medication to Decrease Death From Acute Blood Loss in Trauma Patients

Abstract

Background: Trauma is one of the leading causes of death worldwide, with acute blood loss being the cause of death for nearly one third of in-hospital trauma deaths. In response to trauma the clotting cascade begins clotting to stop acute hemorrhaging with subsequent fibrinolysis to maintain proper hemostasis. Tranexamic acid (TXA), an anti-fibrinolytic, has been used in elective surgeries to decrease blood loss. TXA does not currently have widespread use in United States emergency departments or pre-hospital settings. Recombinant Factor VIIa has been used in United States trauma centers but has not demonstrated an improvement in mortality. No randomized control trials have proven to be effective in decreasing mortality from blood loss in trauma patients. Will the administration of tranexamic acid have an effect on mortality due to hemorrhage in trauma patients?

Method: An exhaustive search was conducted using Medline-OVID, CINAHL, EBMR Multifile, and Web of Science using the keywords: trauma, wounds and injuries, and tranexamic acid. Relevant articles were assessed for quality using GRADE. A search on the NIH clinical trials site reveals there are no trials currently registered relating to the use of tranexamic acid (TXA) in trauma patients.

Results: Two studies met inclusion criteria and were included in this systematic review. A randomized, double blind, placebo-controlled trial with 20,211 participants demonstrated a statistically significant reduction in all-cause mortality with no increase in vascular occlusive events when TXA was administered. A retrospective observational study with 896 participants demonstrated a statistically significant reduction in mortality when TXA was administered, with the greatest benefit witnessed in those receiving a massive transfusion. In addition, the cohort receiving TXA also demonstrated a decrease in coagulopathies. The patients receiving TXA were also more severely injured.

Conclusion: TXA has been shown to reduce mortality from acute blood loss if given within three hours and the greatest benefit is conferred if administration is within the first hour. There was no definitive evidence of increased risk of blood clots or death from clotting events. In addition, the low cost of TXA makes the drug affordable for urban and rural emergency departments as well as EMS. A strong recommendation can be made for the use of TXA in trauma. More research is needed to determine the precise mechanism of action in trauma.

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AJ Sommers

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Tranexamic acid: A Cost Effective Medication to Decrease Death From Acute Blood Loss in Trauma Patients

Brandon M. Smith

A Clinical Graduate Project Submitted to the Faculty of the

School of Physician Assistant Studies

Pacific University

Hillsboro, OR

For the Masters of Science Degree, August 11, 2012

Faculty Advisor: James Ferguson, PA-C
Clinical Graduate Project Coordinator: Annjanette Sommers, PA-C, MS
Biography

[Redacted for privacy]
Abstract

**Background:** Trauma is one of the leading causes of death worldwide, with acute blood loss being the cause of death for nearly one third of in-hospital trauma deaths. In response to trauma the clotting cascade begins clotting to stop acute hemorrhaging with subsequent fibrinolysis to maintain proper hemostasis. Tranexamic acid (TXA), an anti-fibrinolytic, has been used in elective surgeries to decrease blood loss. TXA does not currently have widespread use in United States emergency departments or pre-hospital settings. Recombinant Factor VIIa has been used in United States trauma centers but has not demonstrated an improvement in mortality. No randomized control trials have proven to be effective in decreasing mortality from blood loss in trauma patients. Will the administration of tranexamic acid have an effect on mortality due to hemorrhage in trauma patients?

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**Results:** Two studies met inclusion criteria and were included in this systematic review. A randomized, double blind, placebo-controlled trial with 20 211 participants demonstrated a statistically significant reduction in all-cause mortality with no increase in vascular occlusive events when TXA was administered. A retrospective observational study with 896 participants demonstrated a statistically significant reduction in mortality when TXA was administered, with the greatest benefit witnessed in those receiving a massive transfusion. In addition, the cohort receiving TXA also demonstrated a decrease in coagulopathies. The patients receiving TXA were also more severely injured.

**Conclusion:** TXA has been shown to reduce mortality from acute blood loss if given within three hours and the greatest benefit is conferred if administration is within the first hour. There was no definitive evidence of increased risk of blood clots or death from clotting events. In addition, the low cost of TXA makes the drug affordable for urban and rural emergency departments as well as EMS. A strong recommendation can be made for the use of TXA in trauma. More research is needed to determine the precise mechanism of action in trauma.

**Keywords:** Trauma, tranexamic acid, mortality, human
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Table I: GRADE Quality of Assessment and Summary of Findings

List of Abbreviations

DVT   Deep Venous Thrombosis
FFP   Fresh Frozen Plasma
ISS   Injury Severity Score
TXA   Tranexamic Acid
PRBC  Packed Red Blood Cells
MT    Massive Transfusion
TXAMT Treatment group receiving TXA and Massive Transfusion
No-TXAMT Group receiving Massive Transfusion, and no TXA
PT    Prothrombin time
PTE   Pulmonary Thromboembolism
aPTT  activated partial Thromboplastin Time
SBP   Systolic Blood Pressure
RTS   Revised Trauma Score
NIH   National Institute of Health
rFVIIa recombinant Factor VIIa
CRASH-2 Clinical Randomization of an Antifibrinolytic in Significant Hemorrhage
MATTERs Military Application of Tranexamic Acid in Trauma Emergency Resuscitation
GRADE Grading of Recommendations, Assessment, Development and Evaluations
GCS   Glasgow Coma Scale
MI    Myocardial Infarction
NNT   Number Needed to Treat
Tranexamic acid: A Cost Effective Medication to Decrease Death From Acute Blood Loss in Trauma Patients

BACKGROUND

Worldwide 5.8 million people die annually from trauma, with 44% of those deaths attributed to homicide and road traffic crashes.1 Of the deaths attributed to hemorrhage, 33% - 56% occur pre-hospital.2 Up to one third of trauma deaths occur in-hospital due to acute hemorrhage.3 Following trauma, the clotting cascade activates to reduce bleeding and subsequently begins lysing the clots to maintain proper hemostasis.

Studies have demonstrated that trauma is the primary cause of coagulopathy following trauma.4 Hyperfibrinolysis is a possible complication following severe trauma, leading to increased bleeding and higher mortality rates.4, 5 Tranexamic acid (TXA) is a synthetic derivative of the amino acid lysine that inhibits fibrinolysis.6 The exact mechanism of action in trauma patients is not well understood.7 There is evidence that TXA also reduces inflammatory response, further demonstrating the lack of understanding the mechanism of action in trauma.8, 9 Studies have also shown that systemic inflammation occurs following trauma, suggesting that the anti-inflammatory action may be as beneficial as the antifibrinolysis.10, 11 TXA is currently used in the United States for elective surgeries, post partum hemorrhage and heavy menstrual bleeding but is not widely used in emergency departments. Recombinant Factor VIIa is used in some U.S. emergency departments despite conflicting evidence supporting its efficacy in reducing mortality from trauma.12, 13 The cost of 1gm TXA in 10mL solution is $91.99 (CVS Pharmacy staff, April 2012, personal communication). Morse et al12 examined rFVIIa in patients requiring massive transfusion with standard dosing of 4mg. The cost of rFVIIa
2mg and 5mg is $3340 and $8350 respectively (wholesale cost, Novo Nordisk US staff, April 2012, personal communication). A cost analysis of the CRASH-2 Trial has demonstrated TXA is cost effective in low, middle, and high income settings.\textsuperscript{14} TXA has been shown to reduce the number of units of packed red blood cells (PRBC) needed for transfusion following surgery.\textsuperscript{15} Studies of TXA have demonstrated a small number of adverse reactions but overall it has proven to be safe in multiple trials.\textsuperscript{16-19} Death from trauma is avoidable and one of the top causes of death worldwide. An effective medication has the potential to save thousands of lives annually. Will the administration of tranexamic acid have an effect on mortality due to hemorrhage in trauma patients?

METHOD

An exhaustive search of available medical literature was conducted using Medline-OVID, CINAHL, EBMR Multifile, and Web of Science using the keywords: trauma, wounds and injuries, and tranexamic acid. The search was then narrowed to include only English language articles. The bibliographies of the articles were further searched for relevant sources. Articles with primary data evaluating efficacy of TXA in trauma patients were included. Relevant articles were assessed for quality using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE).\textsuperscript{20} A search on the National Institute of Health (NIH) clinical trials site revealed no currently registered trials, at any phase, relating to the use of tranexamic acid in trauma patients.

RESULTS

The initial result of the search yielded 131 articles for review. After screening relevant articles for primary data and human studies, a total of 2 articles met inclusion
criteria. These articles include one randomized controlled trial\textsuperscript{21} and one retrospective observational study\textsuperscript{22}.

**CRASH-2 Trial**

This randomized, double blind, placebo-controlled trial\textsuperscript{21} investigated the effect of TXA administration on mortality, vascular occlusive events, and volume of blood transfusion. The placebo packaging was indistinguishable from the TXA. The trial enrolled 20,211 adult trauma patients in 274 hospitals in 40 countries, with, or at risk of, significant bleeding and assigned participants to the TXA group or the placebo group. The primary outcome was mortality within 4 weeks of injury, and cause of death described as: bleeding, vascular occlusive, multiorgan failure, head injury or other. Secondary outcomes included myocardial infarction, stroke, pulmonary embolism and deep vein thrombosis, surgical intervention, required blood transfusion and number of units of PRBC. In addition data for the use of recombinant Factor VIIa and for GI bleed were also collected\textsuperscript{21}.

Eligibility criteria consisted of patients with significant hemorrhage and SBP $< 90$mmHg or heart rate $> 110$ beats per minute, or both, or deemed to be at risk for significant hemorrhage; and within 8 hours of injury. Patients were randomly assigned when the attending provider was uncertain if TXA was required. If the provider was certain TXA was indicated or was contraindicated, the patients were assigned to the respective cohort without randomization. The randomization service employed an algorithm to maintain prognostic balance, it considered sex, age, time since injury, type of injury, Glasgow Coma Scale (GCS), Systolic Blood Pressure (SBP), respiratory rate, central capillary refill time, country, and whether or not TXA was available at that
hospital. Patients receiving TXA were given a loading dose of 1gm IV over 10 minutes, followed by an infusion of 1gm over 8 hours\textsuperscript{21}.

Treatment groups were balanced to all baseline patient characteristics. There were 10,060 patients allocated to the TXA cohort and 10,067 to placebo cohort with 99.1\% of patients completing the loading dose and 94.2\% completing the maintenance dose. Of the 3076 patients who died, 35.3\% died on the day of randomization. And, of the 1063 deaths attributed to bleeding, 59.9\% occurred on the day of randomization.\textsuperscript{21}

Tranexamic Acid administration significantly reduced all-cause mortality (RR 0.91, 95\% CI 0.85-0.97, p=0.0035, NNT = 67) and death due to bleeding was also significantly reduced overall (RR 0.85, 95\% CI 0.76-0.96, p=0.0077) and on the day of randomization (RR 0.80, 95\% CI 0.68-0.93, p=0.0036). Deaths from vascular occlusion, although not significant, were fewer in the TXA cohort. There was a statistically significant reduction in event rates of myocardial infarction (MI) with TXA administration, while there was not a statistically significant difference in rates of stroke, deep venous thrombosis (DVT), and pulmonary thromboembolism (PTE). Only 50\% of patients received a blood transfusion in this study, with no difference between the TXA and the no-TXA groups. The TXA group received a mean of 6.06 units of PRBC while the no-TXA group received a mean of 6.29 units. Surgical intervention was performed in 48\% of patients in each group. 13 patients in the TXA group received recombinant Factor VIIa and only 4 patients in the no-TXA group received it.\textsuperscript{21}

The authors found that limitations to this study included the difficulty of diagnosing traumatic hemorrhage and that some patients were not bleeding at the time of randomization may have been included in the study, possibly reducing the power of the
trial. They also discussed the difficulty of diagnosing vascular occlusive events, which required clear clinical evidence, thus, there was a risk of underreporting. The authors recommended that tranexamic acid be considered for inclusion on the WHO List of Essential Medicines, and considered for use in bleeding trauma patients.\textsuperscript{21}

**MATTERs Study**

In this retrospective observational study\textsuperscript{22} the authors compared the administration of TXA to no-TXA in patients suffering trauma and requiring at least one unit of PRBC. They also examined patients requiring a massive transfusion (designated as TXA\textsuperscript{MT} and no-TXA\textsuperscript{MT}), greater than 10 units of PRBC. This study included only patients treated at a Role 3 Echelon surgical hospital in Afghanistan. The authors reviewed 896 consecutive admissions from trauma due to combat injury for which the patients had received at least one unit of PRBC transfusion. Of those admitted, 293 received TXA. The patients included in the study consisted of US and UK military members as well as Afghan nationals. The data were compiled from both the UK and US trauma registries. Standard dosing for the military is a single 1gm TXA IV bolus initially and repeated as deemed necessary by the attending clinician. The authors further investigated patients receiving a massive transfusion and split them into two groups: those receiving TXA, 125 patients, and those not receiving TXA, 196 patients.\textsuperscript{22}

The primary endpoint was mortality, which was investigated at 24 hours, 48 hours, and 30 days. Secondary endpoints included transfusion requirements, coagulation parameters (Prothrombin Time (PT), activated Partial Thromboplastin Time (aPTT)), and thrombotic events (DVT, PTE). Hypocoagulopathy was defined as PT > 18 seconds and aPTT > 55 seconds based on data from a previous study.\textsuperscript{23} Data collected included
admission physiology, treatment timelines, and a 24-hour transfusion requirement (PRBCs, Fresh Frozen Plasma (FFP), platelets, and cryoprecipitate). The Glasgow Coma Scale score, systolic blood pressure and respiratory rate at admission were used to generate a Revised Trauma Score (RTS), which is inversely related to trauma mortality.24 The authors calculated the Injury Severity Score (ISS)25 from time of admission and utilized the Abbreviated Injury Scale to report the anatomical injury pattern for 4 body regions (head, chest, abdomen, and extremity).24 The guidelines established for inclusion in the study included hypotension: Systolic Blood Pressure < 90mm Hg or lower, a GCS ≤ 8, and severe injury as an Abbreviated Injury Scale score ≥ 3.22

The data analysis demonstrated that the mean dose of TXA administered within one hour of injury was 2.3gm. Overall, those receiving TXA had a higher Injury Severity Scale (ISS) score, a higher percentage of patients with severe extremity injury, a lower Revised Trauma Score, and a greater percentage of patients presenting with a depressed GCS score and hypotension. In patients receiving massive transfusion, the TXA^MT group had a greater percentage of patients with severe extremity injury and a great percentage of patients with a depressed GCS score compared to the no-TXA^MT group. The TXA cohort required a greater number of PRBC units, while the massive transfusion subgroup, transfusion requirements were similar in the TXA^MT and no-TXA^MT groups. In addition, the ratio of PRBC:FFP was equivalent in both the overall cohorts and massive transfusion subgroups. However, in the massive transfusion subgroups, the TXA^MT group received more cryoprecipitate than the no-TXA^MT group. In both the overall cohorts and MT subgroups, rates of DVT and PTE were higher in the TXA group. PTE was not indicated as the cause of death in any patient in the study. When evaluating hypocoagulopathy at
time of admission and in the ICU, TXA significantly improved coagulation markers. Reduction in the mortality rate of patients receiving TXA was significant at 48 hours and 30 days in both the entire study and the MT subgroup.22

The MATTERs Study authors concluded that TXA is effective in decreasing all-cause mortality (RR 0.73, p=0.03, NNT = 15) and hypocoagulopathy in trauma patients receiving at least one unit of PRBC, and identified the greatest efficacy in reducing mortality in patients receiving a massive transfusion (RR 0.51, p=0.004, NNT = 7). The authors speculated that the higher rates of DVT and PTE in those receiving TXA may be due to the higher injury burden or due to the survivorship phenomenon as the TXA cohort had a relative risk reduction of mortality of 27% overall and 49% in the MT cohort. The authors recommended that early administration of TXA following severe wartime vascular disruption with hemorrhage should be implemented into clinical practice.22

DISCUSSION

Tranexamic acid is a cost effective, life saving drug that is not currently widely used in United States emergency departments. Following the publication of the CHASE-2 Trial, Massachusetts General was the only emergency department utilizing the drug for trauma patients26, and more may be utilizing the medication at this time. In 2011, TXA was added to the WHO List of Essential Medicines based on its efficacy, safety, cost and the high number of deaths related to trauma worldwide. While some emergency departments have medications that are much more expensive at their disposal for trauma patients, TXA is a medication that can significantly improve mortality at a fraction of the cost of drugs like recombinant Factor VIIa. Due to the demonstrated importance of early
administration, TXA should be considered in pre-hospital settings as well.\textsuperscript{2, 27-29}  
Research has shown that transportation directly to major trauma centers has reduced overall mortality but has increased the time from injury to presentation at a hospital, further supporting the use of TXA in pre-hospital settings.\textsuperscript{30}  
The US military has issued proposed guidelines for its use including an intramuscular autoinjector for use in the battlefield.\textsuperscript{31, 32}  
Australia has proposed guidelines for pre-hospital use as well.\textsuperscript{33}  
Tranexamic acid has been proven to be safe with no increase in blood clots or death related to the administration of the drug. It also has demonstrated improvement in coagulopathies from the time of initial marker compared to the next laboratory draw in the ICU. In addition, further subgroup analysis of patients with traumatic brain injury by CRASH-2 collaborators, found they could not exclude moderate benefits nor moderate harmful effects, however data suggested outcomes might improve following TBI when TXA was administered.\textsuperscript{34}  
Recombinant Factor VIIa has proven to improve mortality at 24 hours, but has failed to demonstrate a mortality improvement at 30 days.\textsuperscript{12, 13, 35}  
This data suggests that Recombinant Factor VIIa, a drug that is more expensive than TXA, also increases cost of hospital admission due to an emergent procedure and ICU stay with no benefit to mortality rates. An August 2011 recommendation to the Committee on Tactical Combat Casualty Care (TCCC) has recommended a TXA 1gm IV bolus over 10 minutes followed by another TXA 1 gm infusion over 8 hours. The TCCC also noted the cost of administering TXA is lower than that of administering one unit of PRBC in a combat setting. The CRASH-2 collaborators found TXA is most effective when administered within the first hour post injury, and the greatest likelihood of benefit requires administration within the first 3 hours.\textsuperscript{29}  
TXA is the only drug, at this time that
has demonstrated an all-cause and bleeding death mortality benefit in a prospective, randomized, controlled-trial.

While the studies\textsuperscript{21, 22} demonstrated that TXA is effective, they both have limitations. In the CRASH-2 trial, receiving providers made the decision between a strong indication for TXA, a contraindication for TXA or a lack of certainty. When the provider was unsure, that patient was then randomized, and in response to ethical constructs when the provider deemed there to be a strong indication or contraindication for TXA, patients were placed in the TXA or no-TXA cohorts, respectively. The TXA group required more units of blood than the no-TXA cohort suggesting, as the MATTERs trial did, that efficacy increases with severity of hemorrhage or the data could be due to the survivorship bias in which patients who survive longer require more units of blood products. Further analysis from the full data set\textsuperscript{36} of the CRASH-2 Trial data demonstrated inconsistencies with the MATTERs Study in the massive transfusion subgroup analysis, with 40\% mortality and 14.4\% mortality respectively, however, when compared to no-TXA, the RR was 0.53 in the CRASH-2 Trial and 0.51 in the MATTERs Study. The inconsistency in the TXA groups may be due to a limitation in the CRASH-2 Trial which allowed the receiving physician to determine a definite indication for TXA and place the patient in the TXA group. Another possible cause of the inconsistency may be due to the location of the study in which no United States facilities were involved and 75\% of the participants were from India, Colombia, Egypt, Nigeria, Georgia and Ecuador,\textsuperscript{32} which may not have had the capabilities to manage patients with severe hemorrhage.
The MATTERs Study is limited due to being an observational study. Conversely, this retrospective study was able to provide more details about the patient’s severity that was not available in the CRASH-2 trial. Injury severity score, revised trauma score and abbreviated injury scale were documented providing a better description of the acuity of the patients. Due to the retrospective nature of the study, there were no clinical practice guideline parameters for the administration of TXA. The authors suspect there is little variation as all patients were treated at the same facility.22 The secondary outcomes examined also had potential for errors as there were no predefined criteria prior to the study. Follow up with the UK and US service members was complete. However, follow up with Afghan nationals was not completed following their discharge from the medical facility. Afghan national patients were discharged only when they were stable making it unlikely there was a significant number of unreported deaths. No deaths from PTE were demonstrated in either cohort in the MATTERs Study.

CONCLUSION

Tranexamic Acid has been demonstrated to be a cost effective method of reducing all cause mortality and mortality due to hemorrhage in trauma patients when administered within 3 hours of injury. More specifically, the evidence supports its use with patients requiring a transfusion. The benefits of this treatment outweigh the risks in the setting of traumatic hemorrhage. The overall combined quality of the studies reviewed is moderate based on the GRADE criteria. A strong recommendation for the use of tranexamic acid in trauma patients with acute blood loss requiring at least one unit of packed red blood cells can be given. Tranexamic Acid should also be considered for use in pre-hospital settings due to the demonstrated increase in efficacy with early administration. Research
to better understand the mechanism of action of tranexamic acid in acute blood loss is needed. Further randomized controlled studies designed to evaluate the effect on mortality may be unlikely.
References


control study followed by a randomized double-blind controlled trial. *Crit Care.*
2007;11:R117.

2007;38:1336-1345.


### Table 1: GRADE evidence profile: Tranexamic acid for trauma patients with acute blood loss

#### Abbreviations:
- TXA: Tranexamic Acid.

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<td>1 RCT</td>
<td>CRASH-2</td>
<td>1463/10,060 (1613/10,067) 0.91 NNT 67</td>
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<tr>
<td>MATTERs</td>
<td>1 Observational</td>
<td>MATTERs</td>
<td>51/293 (144/603) 0.73 NNT 16</td>
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#### Mortality (All-Cause)

| CRASH-2            | 198/3747 (286/3704) 0.69 NNT 42 | Moderate Critical |
| MATTERs            | 51/293 (144/603) 0.73 NNT 16 | Moderate Critical |

#### Mortality from blood loss

1. **Mortality from blood loss** in patients receiving at least one unit of PRBC and receiving intervention within one hour of injury

| CRASH-2            | 90/225 (3/4) 0.53 NNT 3 | Moderate Critical |
| MATTERs            | 18/125 (55/196) 0.51 NNT 7 | Moderate Critical |

2. **Mortality after receiving Massive Transfusion (> 10 units PRBC) and receiving intervention within one hour of injury**

#### Pulmonary Embolism events

1. **Pulmonary Embolism events**

| CRASH-2            | 40/10,060 (41/10,067) 0.98 NNH 10,418 | Moderate Important |
| MATTERs            | 8/293 (2603) 9 NNH 42 | Moderate Critical |

#### Deep Vein Thrombosis events

1. **Deep Vein Thrombosis events**

| CRASH-2            | 40/10,060 (41/10,067) 0.98 NNH 10,418 | Moderate Important |
| MATTERs            | 7/293 (1/603) 12 NNH 46 | Moderate Important |

**Abbreviations:**

- bCause of death is unknown in the MATTERs trial due to being a retrospective study.

- Data obtained from the CRASH-2 Trial data set.

- No deaths were observed from PE in the MATTERs Study, due to the retrospective nature, guidelines for diagnosing vascular occlusive events was unknown by the authors. Mortality from all vascular occlusion in the CHASE-2 Trial was 33 (0.3%) and 48 (0.5%) in the TXA and no-TXA cohorts respectively.