Tranexamic Acid (TXA) in Tactical Combat Casualty Care

Guideline Revision Recommendation

Committee on Tactical Combat Casualty Care

11 August 2011

**Purpose:** To provide a comprehensive review of the use of tranexamic acid (TXA), examine specified and implied actions, apply classification of recommendations and level of supporting evidence, and submit a recommendation for the revision of the guidelines in Tactical Field Care and Tactical Evacuation Care.

**Background/Discussion:**

*Medicine is a science of uncertainty and an art of probability.* Sir William Osler

The Tactical Combat Casualty Care (TCCC) guidelines, first characterized for special operations forces by Butler in 1996, identify three stages of care: (1) care under fire; (2) tactical field care; and (3) tactical evacuation care. The guidelines have been revised through a series of regularly scheduled meetings of the Committee on Tactical Combat Casualty Care (CoTCCC), a panel comprised of civilian and military medical personnel with experience in trauma and combat operations. A 2/3 majority vote of full membership of the COTCCC is required to approve a change to the TCCC guidelines.

Although the guideline revision process is a rigorous academic endeavor, systematic classification of recommendations and level of supporting evidence has only recently been performed. The current guidelines, however, do not address new developments learned in the study of antifibrinolytics for the adjunct management of hemorrhage in trauma.

The changes approved by the Committee below address these new advances.

Additionally, for more than 20 years, the American College of Cardiology (ACC) and the American Heart Association (AHA) have released clinical practice guidelines to provide recommendations on care of patients with cardiovascular disease. The ACC/AHA guidelines currently use a grading schema based on level of evidence and class of recommendation. The levels of evidence include:

- Level of evidence A: recommendation based on evidence from multiple randomized trials or meta-analyses;
- Level of evidence B: recommendation based on evidence from a single randomized trial or nonrandomized studies;
- Level of evidence C: recommendation based on expert opinion, case studies, or standards of care.

The classes of recommendation include:
- Class I: conditions for which there is evidence and/or general agreement that a given procedure or treatment is useful and effective;
- Class II: conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment;
- Class IIa: weight of evidence/opinion is in favor of usefulness/efficacy;
- Class IIb: usefulness/efficacy is less well established by evidence/opinion;
- Class III: conditions for which there is evidence and/or general agreement that the procedure/treatment is not useful/effective and in some cases may be harmful.

Of 2711 specific recommendations, only 11% of recommendations are supported by level of evidence A, whereas 48% are level of evidence C. Only 19% of class I recommendations have level of evidence A.¹

In addition to prior Level B and C literature supporting TXA use based on Phase I and Phase II clinical trials, there is now Level A evidence supporting the addition of tranexamic acid to the guidelines for the treatment of hemorrhage in civilian and now specifically combat casualties. The CRASH-2² study was performed prospectively with civilian trauma patients and the MATTERS³ study was performed retrospectively but specifically in combat casualties using the latest advanced treatment and resuscitation protocols at the single busiest center in CENTCOM. While a randomized prospective clinical trial in US combat casualties would be ideal, this is not permitted under DoD restrictions.

With these limitations in supporting evidence, the TCCC guidelines have always been dependent on the preponderance of evidence from animal studies, civilian and military trauma experience and expert opinion from military medical personnel ranging from trauma and orthopedic surgeons, emergency and critical care physicians, as well as corpsmen and medics with experience in managing combat casualties.

This paper utilizes the ACC/AHA grading schema for level of evidence and class of recommendation to support the guideline revision recommendation for Tranexamic Acid administration in Tactical Field Care and Tactical Evacuation Care incorporating recent literature and expert opinion.

**Current Recommendations for Tranexamic Acid administration in TCCC:**

**Care under fire:** None

**Tactical Field Care:** None
Tactical Evacuation Care: None

Recommended TCCC Revisions:

Care under fire: None

Tactical Field Care and Tactical Evacuation Care:
(Create #6 Adjunct Medications) BEFORE IV Fluids

- If a casualty is anticipated to need significant blood transfusion (for example: presents with hemorrhagic shock, one or more major amputations, penetrating torso trauma, or evidence of severe bleeding)
  - Administer 1 gram of tranexamic acid in 100 cc in NS or LR as soon as possible but NOT later than 3 hours after injury.
  - Begin second infusion of 1 gm TXA after Hextend or other fluid treatment.
  - Move Fluid Resuscitation to a NEW #7

Add to Text:
- (TXA or intravenous trade name: Cyklokapron) in 100 ml of 0.9% NS or LR over 10 minutes intravenously or via interosseous device.
- Once reconstituted, it should be administered within 24 hours.
- It should NOT be administered through the same line being used for blood products (to include rFIIIa or Hextend. Do not administer as an IV push (may cause hypotension).
- After administration of the first dose, mark on chest wall “1 gm TXA given”
- After administration of the second dose, change chest wall marking to “2 x 1gm TXA given”

CAVEATS
Drug should be first administered as early as possible but NOT initiated beyond 3 hours from wounding.
Treating medic must be trained in drug use and administration.
Drug must be properly maintained between 15-30 °Celsius / 59-86° Fahrenheit.

Classes of Recommendation and Level of Evidence

I. Early administration of 1 gram of TXA to casualties who are anticipated to receive blood transfusions

a. Recommendation: Class I

b. Specified/Implied Actions:
   - Hemorrhage is a common contributor to death in combat casualties (Level B)
   - Hemostatic resuscitation improves survival (Level B)
• Antifibrinolytics (specifically TXA) have been shown to decrease bleeding in hemophilia and menorrhagia (Level B)
• Tranexamic acid has FDA approval to decrease bleeding in hemophilia and menorrhagia (Level B)
• Tranexamic acid has been shown to benefit civilian trauma patients (Level B)
• Tranexamic acid has been shown to benefit combat casualties when a rigorous hemostatic resuscitation is followed (Level B)
• Early administration (<3 hours) of TXA after injury appears to improve survival (Level B)
• Arrival to Level II and III care facilities in a combat setting within three hours of injury are not guaranteed (Level C)
• Storage of TXA in field conditions will be problematic with its temperature limitations (Level C)
• Identification of who needs TXA, administration of TXA and monitoring for complications requires skills of an advanced practice medic (Level C)
• Level of Evidence: B

SUPPORTING INFORMATION FOR THE USE OF TRANEXAMIC ACID (TXA) in TCCC

1. Background.
   a. Hemorrhage is the leading cause of preventable death among combat casualties. Patients who require a massive blood transfusion (greater than 10 PRBCs within 24 hours) have an improved survival when an early aggressive hemostatic resuscitation is followed. Patients at the greatest risk of exsanguination often present with a clinically significant coagulopathy that has recently been linked to systemic anticoagulation through a Protein C-dependent pathway, and activation of fibrinolysis. The activation of fibrinolysis accompanying the massive generation of thrombin in the period immediately following trauma has been well described and is readily observed by the elevated levels of D-dimers, fibrin split products (FSP) and plasmin-antiplasmin complexes found in blood samples drawn from trauma patients on presentation. Fibrinolysis can occasionally overwhelm clot formation following trauma, a phenomenon that can be directly observed in real time by thromboelastography (TEG) or rotational thromboelastometry (ROTEM). Such hyperfibrinolysis occurs only in the most severely injured patients (approximately 4% of trauma patients in major civilian US trauma centers) and portends extremely poor outcomes.
b. Coagulation system responses to trauma and surgery are broadly similar and activation of fibrinolysis has been observed in a surgical patients. The safety and efficacy of using TXA to treat trauma patients was recently evaluated in a large randomized, placebo-controlled clinical trial called “The Clinical Randomization of an Antifibrinolytic in Significant Hemorrhage” (CRASH-2)\(^1\). In this trial, 20,211 adult trauma patients in 274 hospitals in 40 countries with, or at risk of, significant bleeding (HR>110, SBP<90, clinical judgment) were randomized to either TXA or placebo administered as a loading dose of 1 gram over 10 minutes followed by an infusion of 1 gram over 8 hours. The primary outcome was death in hospital within 4 weeks of injury. Secondary outcomes included vascular occlusive events, transfusions, and surgical interventions. Patients were randomized and treated within 8 hours of injury. Patients were excluded from randomization only if the treating physician considered the patient to have either a clear indication for use of TXA or a clear contraindication. This randomization scheme reflects application of the uncertainty principle, or clinical equipoise in decision-making. Only 14 patients out of 20,225 screened were excluded from randomization, because they died before they could be randomized.\(^8\) The treatment and placebo groups were well-balanced across a wide range of prognostic variables. The overall mortality rate in the cohort studied was 15.3%, of whom 35.3% died on the day of randomization. A total of 1063 died due to hemorrhage; 59.9% of these died on the day of randomization. A subgroup at particularly high risk of death included those patients presenting with a SBP<75 (3,161 of 20,125; 15.7%). Overall, this study included a large and very diverse trauma population, with most patients facing a relatively low mortality risk. Nevertheless, over 3,000 patients in the study would likely have been candidates for treatment under a damage control resuscitation (and possibly massive transfusion) procedure. The authors reported that TXA use resulted in a statistically significant reduction in the relative risk of all-cause mortality of 9% (14.5% vs. 16.0%, RR 0.91, CI 0.85-0.97; p = 0.0035). This 1.5% absolute risk reduction means that one would have to treat 67 trauma patients with TXA to prevent one from dying of any cause (number needed to treat = 1/absolute risk reduction). Note that this NNT reflects the underlying mortality risk in the CRASH-2 study (15%). The authors also reported a reduction in relative risk of death due to bleeding of 15% (4.9% vs. 5.7%, RR 0.85, CI 0.76-0.96; p = 0.0077). Similarly, the authors reported a relative risk reduction in death due to bleeding on the day of randomization of 20% (2.8% vs. 3.5%, RR 0.80, CI 0.68-0.93; p = 0.0036). It was in this group of most severely injured patients that use of TXA was associated with the greatest reduction in risk of death. Further subgroup analysis suggested that the benefit of TXA was greater in patients treated within 3 hours of injury compared to those treated later and in patients with a presenting systolic blood pressure of \(\leq 75\) mmHg compared to those with normal systolic blood pressures. There was no difference in rate of vascular occlusive events between the two arms of the study (1.7% for TXA vs. 2.0% for placebo, p = 0.084). No unexpected adverse events were reported. There were no differences in
need for transfusion or surgery between the two arms (blood product transfused in 50.4% of patients for TXA vs. 51.3% for placebo, p = 0.21; any surgery in 47.9% of patients for TXA and 48.0% for placebo, p = 0.79). A recent post-hoc analysis of the CRASH-2 data suggests that the greatest benefit of TXA administration is likely to occur when patients receive the medication soon after injury. In this analysis, TXA given between 1 and 3 hours post-trauma reduced the risk of death due to bleeding by 21% (147/3037 [4.8%] vs. 184/2996 [6.1%], RR 0.79, CI 0.64-0.97; p = 0.03). Treatment given after 3 hours seemed to increase the risk of death due to bleeding (144/3272 [4.4%] vs. 103/3362 [3.1%], RR 1.44, CI 1.12-1.84; p = 0.004).9

c. **TXA experience in combat-related hemorrhage:** A recent registry-based study of combat injured troops receiving blood in Afghanistan (January 2009 - December 2010) at the Bastion Role 3 facility has demonstrated findings supportive of TXA use in this population. In a review of 896 combat casualties treated at Bastion over this time frame, 32.7% (N=293) received TXA (mean ± SD dose: 2.3 ± 1.3g) while 67.2% (N=603) did not receive TXA. In the overall cohort, the TXA group was more severely injured (ISS: 25.2±16.6 vs. 22.5±18.5; p<0.001), required more blood (11.8±12.1 vs. 9.8±13.1 pRBC units; p<0.001), and had a lower Glasgow Coma Score (7.3±5.5 vs. 10.5±5.5; p<0.001) and initial systolic blood pressure (112±29.1 vs. 122.5±30.3 mmHg), but also had a lower unadjusted mortality than the no-TXA group (17.4% vs. 23.9%; p=0.028). In the massive transfusion cohort (N=321; 24 hour transfusion: 21.9±14.7 pRBC; 19.1±13.3 FFP and 3.5±3.2 apheresis platelet units), mortality was also lower in the TXA (mean ± SD dose: 2.4 ± 1.4g) compared to the no-TXA group (14.4% vs. 28.1%; p=0.004). In a multivariate regression model, TXA use in the massive transfusion cohort was independently associated with survival (odds ratio: 7.28; 95% confidence interval: 3.02-17.32. For all patients requiring at least one unit of blood after combat injury, patients receiving TXA had higher rates of DVT (2.4% vs. 0.2%, p = 0.001) and PE (2.7% vs. 0.3%, p =0.001), but were also more likely to have injury patterns associated with higher risk of thromboembolic events; including higher mean ISS (25 vs 23, p < 0.001), more severe extremity injuries (extremity AIS >=3 66.6% in TXA group, 47.3% non-TXA, p < 0.001), and more commonly GCS < or = 8 (63.3% vs. 35.6%, p < 0.001). These survival benefit findings associated with TXA use support the hypothesis that the use of this adjunct, in conjunction with component-based resuscitation following combat injury, is associated with improved survival. This association is most prominent in those requiring massive transfusion. ²
Kaplan-Meier survival curve of the overall cohort, patients receiving TXA or no-TXA, \( p = 0.006 \) (Wilcoxon Statistic).

Kaplan-Meier survival curve of the massive transfusion group receiving TXA\(^{MT}\) or no-TXA\(^{MT}\), \( p = 0.004 \) (Wilcoxon Statistic).

2. **TXA Mechanism**
   a. TXA is an anti-fibrinolytic that inhibits both plasminogen activation and plasmin activity, thus preventing clot break-down rather than promoting new clot formation. TXA (trans-4-(aminomethyl) cyclohexanecarboxylic acid) is a small molecule (MW 157.2) inhibitor
of plasminogen activation, and inhibitor of plasmin activity. It occupies the lysine-binding sites on plasminogen thus preventing its binding to lysine residues on fibrin. This reduces plasminogen activation to plasmin. Similarly, blockade of lysine-binding sites on circulating plasmin prevents binding to fibrin, and thus prevents clot break-down.

b. TXA is 10 times more potent \textit{in vitro} than an older drug of the same class, aminocaproic acid. At therapeutically relevant concentrations, TXA does not affect platelet count or aggregation or coagulation parameters. It is excreted largely unchanged in urine and has a half-life of about 2 hours in circulation. Dosing should be adjusted for renal impairment, but no adjustment is needed for hepatic impairment. TXA (intravenous trade name: Cyklokapron) is supplied in ampoules of 1000 mg in 10 ml water for injection.

3. FDA position
a. \textbf{FDA-approved use}: Intravenous administration of TXA (under the brand name Cyklokapron\textsuperscript{®}, Pfizer) was approved by the FDA in 1986 for short-term use (2-8 days) for prevention or reduction of bleeding in patients with hemophilia undergoing dental procedures. The FDA approved use of the oral form of TXA (Lysteda\textsuperscript{TM}, Ferring Pharmaceuticals) for menorrhagia (to control heavy menstrual cyclic bleeding) in 2009.

b. \textbf{Unlabeled use}: \textit{Although tranexamic acid is an FDA-approved drug and has undergone a gamut of regulatory and clinical testing, it is not specifically an FDA-approved indication to stop uncontrolled hemorrhage in severe trauma patients.} The antifibrinolytic effect of tranexamic acid was first reported in 1966.\textsuperscript{10} Tranexamic acid has been studied in many clinical settings, including hemophilia\textsuperscript{11}, intraoperative and postoperative bleeding\textsuperscript{12}, gastrointestinal hemorrhage\textsuperscript{13}, traumatic hyphema\textsuperscript{14} and hereditary angioedema\textsuperscript{15}.

c. It has been studied in randomized trials to control bleeding during surgery, and most recently in trauma as discussed above. It is widely used in non-trauma surgeries and has been used on a limited basis by at least one major US civilian trauma center (Massachusetts General Hospital).\textsuperscript{16} It may be given at the discretion of individual providers, based on their assessment of the clinical condition of the patient.

4. \textbf{Potential adverse events with TXA}:
   a. Adverse events associated with TXA use have been reported. These include acute gastrointestinal disturbances (nausea, vomiting and diarrhea, generally dose-related), visual disturbances (blurry vision and changes in color perception, especially with prolonged use), and occasional thromboembolic events (e.g., deep venous thrombosis, pulmonary embolism, generally observed in the setting of active intravascular clotting such as thrombotic DIC). Its use is thus contraindicated in the settings of acquired defective color vision and active intravascular clotting. TXA should be used carefully in the setting of urinary tract bleeding as ureteral obstruction due to clotting has been
reported. TXA should not be given with activated prothrombin complex concentrate or factor IX complex concentrates as this may increase the risk of thrombosis. Another adverse risk noted in a retrospective review in patients who had undergone pulmonary endarterectomy with hypothermia was an increase in seizure activity (when compared to aprotinin) in patients without structural brain lesions (7 versus 0, p=0.02) 17 The doses given were high dose (on the order of 3-6 times the dose used in the two trauma studies)*

5. **Considerations for Use.**
   a. TXA has been studied in patients with subarachnoid hemorrhage (SAH). TXA was shown to reduce bleeding in SAH, but increase cerebral ischemia, possibly due to vasospasm or increased microvascular thrombosis. Since TXA use had no effect on mortality or quality of life in these studies, its use is not recommended in this population. At this time, there is no role for TXA or other antifibrinolytics in managing SAH. It should be noted that treatment with TXA in these studies was modeled on the prolonged (3-4 times per day for 2-8 days) dosing used in hemophilia. A dosing regimen shorter in duration might avoid this outcome, and remains a topic for further investigation.
   b. It is worth noting, as discussed above, that the relative contraindication to using antifibrinolytics in SAH was known prior to the initiation of CRASH-2. Thus, it is possible that treating physicians tended to exclude patients with TBI from trial enrollment. Nevertheless, about 18% of patients had a GCS score of 3-8 (17.8% for TXA, 18.2% for placebo), probably indicating severe TBI, and 13.4% had GCS scores of 9-12 (p>0.05, NS, for both groups), indicating moderate TBI. Mild or no TBI (GCS 13-15) was present in 68.7% (TXA) and 68.3% (placebo). While GCS scores can be depressed for a variety of reasons such as global hypoperfusion, it would be reasonable to expect that a substantial fraction of trauma patients with depressed GCS had in fact sustained a TBI. The authors did report that death from head injury was the same in both groups (6.0% for TXA and 6.2% for placebo, RR 0.97, CI 0.87-1.08, p=0.6). They also reported that stroke rates (0.6% for TXA and 0.7% for placebo) and neurosurgery rates (10.3% for TXA and 10.5% for placebo) were similar between the groups. These data are reassuring; if a major safety concern were present for perhaps one third of the patients in the trial (those with depressed GCS among whom TBI patients are common) a negative effect on outcomes would be expected.
   c. Critics of the CRASH-2 study have noted that it would have been helpful to know outcomes for patients’ with TBI, since TXA has not proven to be beneficial in subarachnoid hemorrhage (SAH). As a result, the CRASH-2 Intracranial Bleeding Study was a prospective randomized controlled trial nested within the CRASH-2 trial, conducted to quantify the effects of an early short course (1 g over 10 minutes, within 8 hours of injury) of TXA on intracranial hemorrhage in patients with TBI. 18 This portion of the trial involved 270 patients who had a documented head injury (GCS ≤14 and an
abnormal CT scan of the head) and were at risk of significant extracranial bleeding (133 patients allocated to TXA and 137 allocated to placebo), and found new focal cerebral ischemic lesions occurred in 6 (5%) patients in the TXA group, compared to 12 (9%) in the placebo group (RR 0.51, CI 0.18-1.44). Mortality was higher in the placebo group (18% for placebo, 11% for TXA, RR 0.47, CI 0.21-1.04). In addition, mean total hemorrhage growth was higher in the placebo group. This trial shows that neither moderate benefits nor moderate harmful effects can be excluded, however, the analyses suggest that TXA might improve outcomes for patients with TBI and should be further evaluated in future research. The CRASH-3 trial will further examine the effectiveness of the early administration of a short course of TXA in patients with TBI.

d. Hextend® is commonly used as a resuscitation fluid in trauma patients. Several studies have demonstrated that this product may interfere with hemostasis through a number of mechanisms including fibrinolysis. Due to poorly defined potential interactions between Hextend® and TXA, which may blunt the antifibrinolytic activity of TXA, TXA should not be given through the same IV as Hextend®, and Hextend® should not be used as a carrier fluid for this medication.

e. Use of TXA in conjunction with pro-coagulant drugs sometimes administered to trauma patients, such as recombinant factor VIIa (Novoseven) or activated prothrombin complex concentrate (APCC), could result in thrombotic complications. Of note, only 17 patients enrolled in the CRASH-2 trial received Novoseven (13 in the TXA group and 4 in the placebo group). It is also possible that a subgroup of patients not identified in the CRASH-2 trial, such as those with traumatic brain injury, may be at particularly high risk of thrombotic or other complications if treated with TXA. It is very reassuring, however, that no increase in vascular occlusive events was observed in this study, despite the significantly increased baseline risk of such complications in this population. The rate of deep vein thrombosis reported is difficult to interpret due to the lack of a consistent screening procedure, and the variable clinical importance of this complication. However, the rates of myocardial infarction, stroke and pulmonary embolism may be more informative. These complications are relatively simple to diagnose, and are of clinical importance. None of these complications were more common in the treatment arm, while myocardial infarction was significantly less common in the TXA group (p=0.035). These data strongly argue against a safety problem with respect to vascular occlusive events.

6. **Considerations for Use.** TXA (intravenous trade name: Cyklokapron) is supplied in ampoules of 1000 mg in 10 ml water for injection.

   a. Infuse 1 gram of tranexamic acid in 100 ml of 0.9% NS over 10 minutes intravenously (more rapid injection has been reported to cause hypotension). Hextend® should be avoided as a carrier fluid.

   b. Infuse a second 1-gram dose intravenously over 8 hours infused with 0.9% NS carrier.
c. There are presently no data from randomized controlled trials to support administration of further doses to trauma patients.

7. Storage
   a. Room temperature (15-30 °Celsius / 59-86° Fahrenheit)

8. Guidelines for administration in the deployed setting.
   a. The early use of TXA should be strongly considered for any patient requiring blood products in the treatment of combat-related hemorrhage and is most strongly advocated in patients judged likely to require massive transfusion (e.g., significant injury and 3 or 4 risk factors/indicators of massive transfusion).
   b. Use of tranexamic within 3 hours of injury is associated with the greatest likelihood of clinical benefit. The greatest benefit was seen when TXA was administered within 1 hour of wounding. Due to this time constraint, the uncertainty of battlefield evacuation and a good safety profile in the doses previously used in trauma patients, use in the prehospital setting is recommended if patient monitoring and storage requirements can be met. For these reasons, use by advanced practice medics only is recommended. (Advanced practice medics are defined as: SOF 18D or Paramedic to include PJ, SOAR, FP-C)

9. Benefits: In an evaluation on TXA use by the military, Maj Andrew Cap made the following analysis:
   
   a. Approximately 25% of the roughly 6,000 soldiers who died between the OIF and OEF conflicts to date had potentially survivable injuries (1,500 soldiers). Theoretically, if all 1,500 had been treated with TXA, and the group had experienced a reduction in mortality of 1.5% as in the CRASH-2 trial, 23 lives would have been saved at a cost of about $5,200 per life ($120,000 overall). For perspective, the cost to the US military of procuring one unit of packed red blood cells is approximately $100 (personal communication, COL F. Rentas, Director, Armed Services Blood Program Office, July 2010). This does not include the costs of blood storage and shipment to theater, disposables and nursing time associated with blood administration, or blood unit cross-matching. The costs of administering TXA are thus substantially lower than the costs of administering one unit of red blood cells.
   
   b. In a paper supplied in response to an RFI to USAISR about preventable deaths due to non-compressible hemorrhage, the following estimate was provided by the CoTCCC:

   Non-Compressible Hemorrhage

   How Many Lives Could Have Been Saved in Iraq or Afghanistan If We Had Had an Effective Intervention?
22 August 2010

Note: The exact answer to this question unknowable. The methodology below is one way to postulate a reasonable approximation to this question.

If you take the Kelly paper (J Trauma 2008) and use that as a starting point:
- Total fatalities in both groups: 982
- Total potentially preventable deaths: 232
- % of fatalities that were potentially preventable (both groups): 24%
- Potentially preventable deaths from non-compressible hemorrhage: 115 (page S-23)
- % of total fatalities that were both potentially preventable and resulted from non-compressible hemorrhage: 12%

Then taking the number of fatalities in OEF and OIF: (Washington Post fatality numbers as of 22 Aug 10)
- OEF 1220
- OIF 4403
- Total 5623

Using the 12% of total fatalities that were both potentially preventable and that resulted from non-compressible hemorrhage as calculated above and applying that to the total fatalities in OEF/OIF:
- 675 estimated potentially preventable fatalities due to non-compressible hemorrhage

The hardest part of the equation is determining what fraction of these estimated 675 potentially preventable fatalities (due to non-compressible hemorrhage) might have been saved by tranexamic acid. Based on the most relevant data in wartime injuries (from the MATTERS paper) the potential benefit, or the number of patients required to treat with TXA to achieve a mortality benefit of one patient, was 7. This translates to a potential 96 US lives saved had TXA been used.

10. References.
3. Tranexamic acid decreases mortality following wartime injury: the Military Application of Tranexamic acid in Trauma Emergency Resuscitation Study (MATTERS) MAJ
Jonathan J. Morrison, MB ChB, MRCS, RAMC(V), LT COL (sel) Joseph J. Dubose, MD, USAF MC, COL Todd E. Rasmussen, MD, USAF MC, SURG CAPT Mark Midwinter, BMedSci, MD FRCS RN (submitted for publication)


8. Personal communication with study director, Ian Roberts


16. Massachusetts General Hospital; panel discussion, Dr. Hasan Alam, AAST 2010, Boston, MA


Additional References
Lysteda. 2010.

36. CRASH-2 c. FAQ. http://www.crash2.lshtm.ac.uk/.