REQUEST FOR APPROVAL
Form #EMS-0391
Application for Local Trial Study
Use of Tranexamic Acid by Paramedics for Trauma Patients

1. **Description of the procedure or medication requested and the purpose of our pilot:**

Tranexamic Acid is a Lysine analogue that works to inhibit the formation of plasmin, which is a molecule responsible for clot degradation. It has had multiple medical applications in the past including pre-operative use, menorrhagia, hemophilia and hereditary angioedema. It has recently been shown in multiple studies to reduce mortality in trauma patients meeting specific physiologic criteria or who have obvious signs of massive hemorrhage.

Side effects of TXA include the following:
1. Thromboembolism (DVT and pulmonary embolism)
2. Gastrointestinal effects including nausea, vomiting, diarrhea
3. Headache
4. Fatigue
5. Dizziness
6. Visual Disturbance

Administration:
1. Administer 1 gram of TXA in 100ml of 0.9% Normal Saline. This is to be given over 10 minutes via intravenous or intrasosseous lines. Ideally this is given within the first hour, but should not be given after three hours. This is the dose to be given by pre-hospital personnel.
2. Ideally a second gram of TXA should be infused over the course of 8 hours after the patient arrives at a trauma center.
3. TXA should not be administered through the same line as blood products, recombinant factor VIIa, or Hexend.
4. TXA should not be given IV push
5. TXA should be stored at 59-86 degrees Fahrenheit.

Our pilot is to be implemented in Yolo County. The purpose of our pilot is to determine the following:

1. Are paramedics in Yolo County able to reasonably identify patients who will benefit from the administration of TXA, based on the protocol developed? All patients who meet criteria with signs of shock will be identified. Compliance with recognition and administration of TXA will be monitored.
2. Are paramedics able to successfully and efficiently administer TXA to patients who require it? Mechanical issues around the administration of TXA will be monitored. Short response times, IV or IO access, or other issues with reconstitution of the drug will be assessed.
3. Are trauma receiving hospitals able to receive successful sign out from paramedics regarding the administration of TXA and can they successfully administer the second dose?
4. Are paramedics and trauma receiving hospitals able to report on adverse events quickly and efficiently?

2. **Description of the medical conditions for which the procedure/medication will be utilized:**

   Paramedics would follow established guidelines for administration set forth in the Yolo County EMS protocols. The anatomic and physiologic criteria will be the following:

   1. Blunt or penetrating trauma to the torso with signs and symptoms of hemorrhagic shock including a systolic blood pressure of less than 90 mmHg.
   2. Major amputation of any extremity, proximal to wrist or ankle
   3. Bleeding uncontrolled by direct pressure or tourniquet.
   4. Estimated external blood loss of 500 ml or more in the field.

3. **Alternatives (Please describe any alternate therapy[ies] considered for the same conditions and any advantages and disadvantages)**

   While other antifibrinolytics do exist, they have not been shown to be appropriate or efficacious for pre-hospital use.

4. **An estimate of frequency of utilization**

   Approximately 1-2 patients per month

5. **Other factors or exceptional circumstances:**

   Rural trauma, with extended transport times to out-of-county trauma hospitals.

6. **Any supporting data, including relevant studies and medical literature:**

   Please see attached supporting studies – Attachment A

7. **Recommended policies/procedures to be instituted regarding:**

   We plan to use this medication in the County of Yolo, with the goal of training for implementation by January 2018.

   TXA will be administered to trauma patients who meet the following criteria:

   1. Blunt or penetrating trauma to the torso with signs and symptoms of hemorrhagic shock including a systolic blood pressure of less than 90 mmHg.
   2. Major amputation of any extremity, proximal to wrist or ankle
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3. Bleeding uncontrolled by direct pressure or tourniquet.
4. Estimated external blood loss of 500 ml or more in the field

Medical Control:
UC Davis Medical Center (Trauma Center)
Kaiser Vacaville (Trauma Center)

Treatment Protocols:
See Attachment B

Quality Assurance of the procedure or medication:

1. Agencies participating in the trial will use the fully electronic PCR system (MEDS).
2. We will link ePCR data to the Hospital Registry trauma registry to monitor outcomes and adverse events.
   - We obtain the trauma registry from our two designated trauma receiving centers for Yolo County: Kaiser Vacaville and UC Davis Medical Center.
   - We link the ePCR with the data sent from the trauma registry.
3. Once per month all TXA cases will be reviewed by EMS leadership to screen for Safety or fallout issues.
   - Leadership team is:
     o Dr. Shatz (UDMCU)
     o Dr. Brandy (KV)
     o Dr. Rose (Medial Director)
     o Dr. Wood (Medical Director, AMR)
     o Kristin Weivoda (EMS Administrator)
   - The meetings will be schedule each month after the trial goes live, and will fall in session with our Physician Advisory Meetings hosted the EMS Office.

Description of training and competency testing required to implement the procedure or medication:

During our annual training session a PowerPoint presentation will be used for the initial orientation to the medication. Live demonstrations will be used and demonstration of skills required prior to going live with the protocol along with a written post-test. See attachment D for this PowerPoint.

Post Test is not developed, pending the EMS State Approval for the Trial. The post test will be a 20 question test delivered after the training, 90% needed to pass.

8. Copy of the local EMS System Evaluation and Quality Improvement Program plan for this request:

See Attachment C
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Form #EMSA-0391
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ATTACHMENT A – SUPPORTING ARTICLES
Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial

CRASH-2 trial collaborators*

Summary
Background Tranexamic acid can reduce bleeding in patients undergoing elective surgery. We assessed the ePects of early administration of a short course of tranexamic acid on death, vascular occlusive events, and the receipt of blood transfusion in trauma patients.

Methods This randomised controlled trial was undertaken in 274 hospitals in 40 countries. 20 211 adult trauma patients with, or at risk of, significant bleeding were randomly assigned within 8 h of injury to either tranexamic acid (loading dose 1 g over 10 min then infusion of 1 g over 8 h) or matching placebo. Randomisation was balanced by centre, with an allocation sequence based on a block size of eight, generated with a computer random number generator. Both participants and study staP (site investigators and trial coordinating centre staP) were masked to treatment allocation. The primary outcome was death in hospital within 4 weeks of injury, and was described with the following categories: bleeding, vascular occlusion (myocardial infarction, stroke and pulmonary embolism), multiorgan failure, head injury, and other. All analyses were by intention to treat. This study is registered as ISRCTN86750102, Clinicaltrials.gov NCT00375258, and South African Clinical Trial Register DOH-27-0607-1919.

Findings 10 096 patients were allocated to tranexamic acid and 10 115 to placebo, of whom 10 060 and 10 067, respectively, were analysed. All-cause mortality was significantly reduced with tranexamic acid (1463 [14.5%] tranexamic acid group vs 1613 [16.0%] placebo group; relative risk 0.91, 95% CI 0.85–0.97; p=0.0035). The risk of death due to bleeding was significantly reduced (489 [4.9%] vs 574 [5.7%]; relative risk 0.85, 95% CI 0.76–0.96; p=0.0077).

Interpretation Tranexamic acid safely reduced the risk of death in bleeding trauma patients in this study. On the basis of these results, tranexamic acid should be considered for use in bleeding trauma patients.

Funding UK NIHR Health Technology Assessment programme, Pfizer, BUPA Foundation, and J P Moulton Charitable Foundation.

Introduction
Injuries are major causes of death worldwide.1,2 Every year, more than a million people die as a result of road tracc injuries around the world. Road tracc injuries are the ninth leading cause of death globally, and such injuries are predicted to become the third leading cause of death and disability by 2020. About 1-6 million people die as a result of intentional acts of interpersonal, collective, or self-directed violence every year. More than 90% of trauma deaths occur in low-income and middle-income countries.2 Haemorrhage is responsible for about a third of in-hospital trauma deaths and can also contribute to deaths from multiorgan failure.3

The haemostatic system helps to maintain circulation after severe vascular injury, whether traumatic or surgical in origin.4 Major surgery and trauma trigger similar haemostatic responses, and in both situations severe blood loss presents an extreme challenge to the coagulation system. Part of the response to surgery and trauma is stimulation of clot breakdown (fibrinolysis), which might become pathological (hyper-fibrinolysis) in some cases.4 Antifibrinolytic agents reduce blood loss in patients with both normal and exaggerated fibrinolytic responses to surgery, and do so without apparently increasing the risk of postoperative complications.5 Tranexamic acid is a synthetic derivative of the aminoacid lysine that inhibits fibrinolysis by blocking the lysine binding sites on plasminogen.6 A systematic review of the randomised trials of tranexamic acid in patients undergoing elective surgery identified 53 studies including 3836 participants.7 Tranexamic acid reduced the need for blood transfusion by a third (relative risk [RR] 0.61, 95% CI 0.54–0.70), with no significant reduction in mortality (0.61, 0.32–1.12).8 Because the haemostatic responses to surgery and trauma are similar,4 tranexamic acid might reduce mortality due to bleeding in trauma patients. However, up until now there have been no randomised trials of this drug in such patients.1 We assessed the eEects of the early administration of a short course of tranexamic acid on death, vascular occlusive events, and the receipt of blood transfusion in trauma patients with or at risk of significant haemorrhage.
Methods

Study design and patients

CRASH-2 (Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage 2) is a large placebo-controlled trial of the effects of early administration of a short course of tranexamic acid on death, vascular occlusive events, and the receipt of blood transfusion. The trial was undertaken in 274 hospitals in 40 countries. The first patient was enrolled in May, 2005. The study aims, methods, and protocol have been reported previously. The trial protocol was peer-reviewed and published on The Lancet website in 2005.

Adult trauma patients with significant haemorrhage (systolic blood pressure <90 mm Hg or heart rate >110 beats per min, or both), or who were considered to be at risk of significant haemorrhage, and who were within 8 h of injury, were eligible for the trial. Patients were included if the responsible doctor was substantially uncertain about whether or not to treat with tranexamic acid (ie, entry was governed by the uncertainty principle). Patients for whom the responsible doctor considered that there was a clear indication for tranexamic acid were not randomly assigned. Similarly, patients for whom there was considered to be a clear contraindication to tranexamic acid treatment were not randomly assigned. However, when the responsible doctor was substantially uncertain as to whether or not to treat this agent, these patients were eligible for randomisation.

Consent procedures at participating hospitals were established by local regulation and the appropriate ethics committees. Informed consent was obtained from patients if physical and mental capacity allowed. If patients could not give consent, proxy consent was obtained from a relative or representative. If a proxy was unavailable, then if permitted by local regulation, consent was deferred or waived. When consent was deferred or given by a proxy, the patient was informed about the trial as soon as possible and consent obtained for use of the data collected if needed.

Randomisation and masking

After eligibility had been confirmed and the locally approved consent procedures had been completed, patients were randomly assigned. Randomisation was balanced by centre, with an allocation sequence based on a block size of eight, generated with a computer random number generator. In hospitals in which telephone randomisation was not practicable we used a local pack system that selected the lowest numbered treatment pack from a box containing eight numbered packs. Apart from the pack number, the treatment packs were identical. The pack number was recorded on the entry form which was sent to the international trial coordinating centre in London, UK. Hospitals with reliable telephone access used the University of Oxford Clinical Trial Service Unit (CTSU) telephone randomisation service. The randomisation service used a minimisation algorithm balancing for sex, age, time since injury, type of injury (blunt or penetrating), Glasgow Coma Score, systolic blood pressure, respiratory rate, central capillary refill time, and country, taking into account what packs were available at that hospital. Once the treatment pack number was recorded, the patient was included in the trial whether or not the treatment pack was opened or the allocated treatment started. Both participants and study staP (site investigators and trial coordinating centre staP) were masked to treatment allocation.

Tranexamic acid and placebo ampoules were indistinguishable. Tranexamic acid was manufactured by Pharmacia (Pfizer, Sandwich, UK) and placebo by St Mary’s Pharmaceutical Unit, CardiP, UK. The treatment packs were prepared by an independent clinical trial supply company (Bilcare, Crickhowell, UK). Correct blinding and coding of ampoules was assured by independent random testing of each batch by high performance liquid chromatography to confirm the contents. Emergency unblinding was available by telephoning CTSU.

Procedures

Patients were randomly allocated to receive a loading dose of 1 g of tranexamic acid infused over 10 min, followed by an intravenous infusion of 1 g over 8 h, or matching placebo (0·9% saline). Every patient was assigned a uniquely numbered treatment pack, which contained four ampoules of either tranexamic acid 500 mg or placebo, one 100 mL bag of 0·9% saline (for use with the loading dose), a syringe and needle, stickers with the trial details and randomisation number (for attaching to infusion bags, data forms, and patient medical records), and instructions. Each box contained information leaflets for patients and their representatives, consent forms, and data collection forms. The stickers, instructions, leaflets, and forms were in local languages.

Outcome measures and prespecified subgroup analyses

The primary outcome was death in hospital within 4 weeks of injury. Cause of death was described by the following categories: bleeding, vascular occlusion (myocardial infarction, stroke, and pulmonary embolism), multiorgan failure, head injury, and other. Secondary outcomes were vascular occlusive events (myocardial infarction, stroke, pulmonary embolism, and deep vein thrombosis), surgical intervention (neurosurgery, thoracic, abdominal, and pelvic surgery), receipt of blood transfusion, and units of blood products transfused. Dependency was measured at hospital discharge, or on day 28 if still in hospital, with the 5-point Modified Oxford Handicap Scale. The scale was dichotomised into dead or dependent (dead, fully dependent requiring attention day and night, or dependent but not needing constant attention) or independent (some restriction in lifestyle but independent, minor symptoms, or no symptoms). Data for the use of recombinant Factor VIIa and for gastrointestinal bleeding as a complication...
were also collected. Because the expected complications of the trial treatment were collected on the outcome form, only adverse events that were serious, unexpected, and suspected to be related to the study treatment were reported separately. Outcomes were recorded if they occurred while the patient was still in hospital for up to 28 days after randomisation. Data were sent to the coordinating centre either electronically (by encrypted electronic data forms which could be sent by email or uploaded to a secure server) or by fax, and were entered onto a central database at the trial coordinating centre in London. We monitored the quality of the trial data using a combination of centralised statistical data checking and site visits at which patient outcome forms were compared with clinical case notes.

We planned to report the eNects of treatment on the primary outcome subdivided by four baseline characteristics: (1) estimated hours since injury (<1, 1–3, 3–8 h); (2) systolic blood pressure (≤75, 76–89, ≥90 mm Hg); (3) Glasgow Coma Score (severe 3–8, moderate 9–12, mild 13–15); and (4) type of injury (penetrating only or blunt, which included blunt and penetrating).

Statistical analyses
The statistical analysis plan was sent to all ethics committees and regulatory agencies before unblinding. Because the risk of death might be around 20%, and even a 2% survival difference (corresponding to an RR of death with tranexamic acid of 0.9) would be important, a trial of 20,000 patients was planned, which would then have an 85% chance of achieving a two-sided p value of less than 0.01 and a 95% chance of a two-sided p value of less than 0.05. All analyses were undertaken on an intention-to-treat basis. For each binary outcome, we calculated RRs and 95% CIs, and two-sided p values for statistical significance. The RR gives the number of times more likely (RR >1) or less likely (RR <1) an event is to happen in the tranexamic acid group compared with the placebo group. For analysis of the prespecified subgroups (primary outcome only) we calculated RRs with 95% CIs with two-sided p values. Heterogeneity in treatment eNects across subgroups was assessed with χ² tests. We specified that unless there was strong evidence (p<0.001) against homogeneity of eNects, the overall RR would be considered the most reliable guide to the approximate RRs in all subgroups. Means and SDs were estimated for count outcomes, and we calculated two-sided p values of the diNerence in means of logarithms. A complete case analysis, including only cases for which the relevant outcome data were available, was undertaken. There was no imputation for missing data. During the study, unblinded interim analyses were supplied by an independent statistician to the Data Monitoring and Ethics Committee.

This study is registered as ISRCTN86750102, Clinicaltrials.gov NCT00375258, and South African Clinical Trial Register DOH-27-0607-1919.

Figure 1: Trial profile

Role of the funding source
Funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The Writing Committee had full access to all data in the study and had final responsibility for the decision to submit for publication.

Results
Figure 1 shows the trial profile. 20211 patients were randomly assigned to tranexamic acid or placebo (figure 1), of whom 20 116 were randomly assigned through the local pack system and 95 through telephone randomisation. The data from four patients were removed from the trial because their consent was withdrawn after randomisation. Five patients enrolled in the study were later found to be younger than 16 years. Age was unknown for four patients. 23 patients were enrolled more than 8 h after their injury. Time of injury was not known for 11 patients. Nine patients had haemorrhage from non-traumatic conditions. Three patients were given a pack that diNered from that allocated. The planned consent procedures were not fully followed in 34 patients. The relevant ethics committees were informed and approval for use of data was obtained. All the patients, apart from the four in whom consent was withdrawn, were included in the analysis.

Treatment groups were balanced with respect to all baseline patient characteristics (table 1; the webappendix p 1 shows baseline data of patients with follow-up). Primary outcome data were available for 20 127 (99.6%) randomised patients, 10 060 allocated to tranexamic acid and 10 067 placebo, of whom 19 944 (99.1%) patients were known to have completed the loading dose and 18 965 (94.2%) the 8 h maintenance dose. 3076 (15.3%) patients died, of whom 1086 (35.3%) died on the day of randomisation (figure 2). There were 1063 deaths due to bleeding, of which 637 (59.9%) were on the day of randomisation.
All-cause mortality was significantly reduced with tranexamic acid (table 2). The RR of death with tranexamic acid was 0·91 (95% CI 0·85–0·97, p=0·0035; table 2). The risk of death due to bleeding was significantly reduced (table 2). This eVect was also apparent for deaths due to bleeding on the day of randomisation (282 [2·8%] tranexamic acid group vs 355 [3·5%] placebo group; RR 0·80, 95% CI 0·68–0·93, p=0·0036). There were 33 (0·3%) deaths in the tranexamic acid group versus 48 (0·5%) in the placebo group from vascular occlusion (table 2), including seven versus 22 deaths from myocardial infarction, eight versus five from stroke, and 18 versus 21 from pulmonary embolism, respectively. Deaths from multiorgan failure, from head injury, or due to other causes did not diVer significantly in the tranexamic acid group versus the placebo group (table 2).

Vascular occlusive events (fatal or non-fatal) did not diVer signiWcantly, with 168 (1·7%) patients with one or more vascular occlusive events (myocardial infarction, stroke, pulmonary embolism, deep vein thrombosis) in patients allocated to tranexamic acid versus 201 (2·0%) in those allocated to placebo (table 3).

Blood product transfusions were given to 5067 (50·4%) patients allocated to tranexamic acid versus 5160 (51·3%) allocated to placebo (table 3). Those allocated to tranexamic acid and transfused received a mean of 6·06 (SD 9·98) blood units, compared with a mean of 6·29 (10·31) for placebo. 4814 (47·9%) patients in the tranexamic acid group received one or more surgical intervention (neurosurgery, or chest, abdominal, or pelvic surgery) versus 4836 (48·0%) in the placebo group (table 3). Only 17 patients received treatment with recombinant Factor VIII (13 in the tranexamic acid group vs four in the placebo group). 132 patients in each group had gastrointestinal bleeding (p=0·99).

Of patients allocated tranexamic acid, 3453 (34·3%) were classiWed as dead or dependent at discharge or 28 days compared with 3562 (35·4%) of those allocated to placebo (RR 0·97, 95% CI 0·93–1·00; p=0·12); 1483 (14·7%) patients in the tranexamic acid group had no symptoms at discharge or day 28 versus 1334 (13·3%) in the placebo group (table 3). 1846 (9·2%) patients were still in hospital at 28 days (958 vs 888).

We had prespeciWed that unless there was strong evidence (p<0·001) against homogeneity of eVcets, the overall RR would be regarded as the most reliable guide as to the approximate RRs in all subgroups. We recorded no such evidence of heterogeneity for any of the prespeciWed subgroup analyses: systolic blood pressure (heterogeneity p=0·51); Glasgow Coma Score at randomisation (p=0·50); type of injury (p=0·37); or time from injury to randomisation (p=0·11). For the last of these analyses, because of digit preference (the tendency when reporting Wgures to round to speciWc digits) the number of patients in the early category (<1 h) was low and the subgroup estimate was imprecise. We therefore (post hoc) deWned the early category as those treated less than or equal to 1 h from injury (Wgure 3).

Table 1: Baseline data of participants

<table>
<thead>
<tr>
<th>Variable</th>
<th>Tranexamic acid (n=10 093)</th>
<th>Placebo (n=10 114)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>8439 (83·6%)</td>
<td>8496 (84·0%)</td>
</tr>
<tr>
<td>Women</td>
<td>1654 (16·4%)</td>
<td>1617 (16·0%)</td>
</tr>
<tr>
<td>Not known</td>
<td>0</td>
<td>1 (0·01%)</td>
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<tr>
<td>Age (years)</td>
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</tr>
<tr>
<td>Mean (SD)</td>
<td>34·6 (14·1)</td>
<td>34·5 (14·4)</td>
</tr>
<tr>
<td>&lt;25*</td>
<td>2783 (27·6%)</td>
<td>2855 (28·2%)</td>
</tr>
<tr>
<td>25–34</td>
<td>3012 (29·8%)</td>
<td>3081 (30·5%)</td>
</tr>
<tr>
<td>35–44</td>
<td>1975 (19·6%)</td>
<td>1841 (18·2%)</td>
</tr>
<tr>
<td>&gt;44</td>
<td>2321 (23·0%)</td>
<td>2335 (23·1%)</td>
</tr>
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<td>Not known</td>
<td>2 (0·02%)</td>
<td>2 (0·02%)</td>
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<td>Time since injury (h)</td>
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<tr>
<td>Mean (SD)</td>
<td>2·8 (2·2)</td>
<td>2·9 (2·6)</td>
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<tr>
<td>≤1</td>
<td>3756 (37·2%)</td>
<td>3722 (36·8%)</td>
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<td>&gt;1–≤3</td>
<td>3045 (30·2%)</td>
<td>3006 (29·7%)</td>
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<td>&gt;3†</td>
<td>3287 (32·6%)</td>
<td>3380 (33·4%)</td>
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<td>6 (0·06%)</td>
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<td>Type of injury</td>
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<tr>
<td>Blunt‡</td>
<td>6812 (67·5%)</td>
<td>6843 (67·7%)</td>
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<tr>
<td>Penetrating</td>
<td>3281 (32·5%)</td>
<td>3271 (32·3%)</td>
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<td>Systolic blood pressure (mm Hg)</td>
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<td>≤75</td>
<td>1566 (15·5%)</td>
<td>1608 (15·9%)</td>
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<td>76–89</td>
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<td>≥90</td>
<td>6901 (68·4%)</td>
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<td>Not known</td>
<td>11 (0·1%)</td>
<td>18 (0·18%)</td>
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<tr>
<td>Respiratory rate (per min)</td>
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<tr>
<td>&lt;10</td>
<td>160 (1·6%)</td>
<td>149 (1·5%)</td>
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<tr>
<td>10–29</td>
<td>8355 (82·8%)</td>
<td>8436 (83·4%)</td>
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<td>≥29</td>
<td>1491 (14·8%)</td>
<td>1429 (14·1%)</td>
</tr>
<tr>
<td>Not known</td>
<td>87 (0·86%)</td>
<td>100 (0·99%)</td>
</tr>
<tr>
<td>Central capillary refi ll time (s)</td>
<td></td>
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<tr>
<td>≤2</td>
<td>3432 (34·0%)</td>
<td>3406 (33·7%)</td>
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<tr>
<td>3–4</td>
<td>4665 (46·2%)</td>
<td>4722 (46·7%)</td>
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<tr>
<td>&gt;4</td>
<td>1699 (16·8%)</td>
<td>1672 (16·5%)</td>
</tr>
<tr>
<td>Not known</td>
<td>297 (2·9%)</td>
<td>314 (3·1%)</td>
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<tr>
<td>Heart rate (beats per min)</td>
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<td></td>
</tr>
<tr>
<td>≤77</td>
<td>875 (8·7%)</td>
<td>871 (8·6%)</td>
</tr>
<tr>
<td>78–91</td>
<td>1727 (17·1%)</td>
<td>1770 (17·5%)</td>
</tr>
<tr>
<td>92–107</td>
<td>2556 (25·3%)</td>
<td>2546 (25·2%)</td>
</tr>
<tr>
<td>&gt;107</td>
<td>4872 (48·3%)</td>
<td>4853 (48·0%)</td>
</tr>
<tr>
<td>Not known</td>
<td>63 (0·62%)</td>
<td>74 (0·73%)</td>
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<tr>
<td>Glasgow Coma Score (total)</td>
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<td></td>
</tr>
<tr>
<td>Severe (3–8)</td>
<td>1799 (17·8%)</td>
<td>1839 (18·2%)</td>
</tr>
<tr>
<td>Moderate (9–12)</td>
<td>1353 (13·4%)</td>
<td>1351 (13·4%)</td>
</tr>
<tr>
<td>Mild (13–15)</td>
<td>6934 (68·7%)</td>
<td>6908 (68·3%)</td>
</tr>
<tr>
<td>Not known</td>
<td>7 (0·07%)</td>
<td>16 (0·16%)</td>
</tr>
<tr>
<td>Any protocol violation</td>
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</tr>
<tr>
<td>39 (4·3%)</td>
<td>39 (4·3%)</td>
<td></td>
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</table>

Data are number (% of group total), unless otherwise indicated. *Includes five patients younger than 16 years. ‡Includes 23 patients randomly assigned more than 8 h after injury. †Includes patients with both blunt and penetrating and those with only blunt injuries.
No emergency unblinding was needed, and there were no adverse events regarded as serious, unexpected, or suspected to be related to the study treatment.

**Discussion**

The results show that the early administration of tranexamic acid to trauma patients with, or at risk of, significant bleeding reduces the risk of death from haemorrhage with no apparent increase in fatal or non-fatal vascular occlusive events. All-cause mortality was significantly reduced with tranexamic acid.

The trial inclusion criteria were clinical and did not depend on the results of laboratory tests. Patients were enrolled if they were judged to have on-going significant haemorrhage, as evidenced by hypotension or tachycardia, or if they were considered to be at risk of significant haemorrhage—e.g., patients with compensated haemorrhage and stable vital signs, or those in whom bleeding might have stopped but who might recommence bleeding following volume resuscitation. The use of clinical inclusion criteria is appropriate in the context of traumatic bleeding in which a range of clinical signs need to be assessed when establishing the presence or absence of haemorrhage, while taking into account remedial measures such as fluid resuscitation. The clinical inclusion criteria, and the large numbers of patients studied in a range of different health-care settings, help these results to be generalised widely.

Our study had strengths and limitations. The randomisation methods ensured that participating clinicians did not have foreknowledge of treatment allocation. Baseline prognostic factors were well balanced. All analyses were on an intention-to-treat basis and, because almost all randomised patients were followed up, there was no need to use imputation methods for missing data. The primary endpoint was all-cause mortality, and the observed reduction in mortality with tranexamic acid was both statistically significant and clinically important. The diagnosis of traumatic haemorrhage can be difficult, and some of the included patients might not have been bleeding at the time of randomisation. This misdiagnosis would have reduced the power of the trial to show an effect of tranexamic acid on mortality from bleeding. Nevertheless, we recorded a significant reduction in death due to bleeding.
Although we recorded no increased risk of non-fatal vascular occlusive events with tranexamic acid, the precision of the estimates was low and we cannot exclude the possibility of some increase in risk. In the context of outcome assessment in clinical trials, estimates of the RR are unbiased even when the sensitivity of diagnosis is imperfect, provided that there are few false positives (high specificity). Therefore, we sought high specificity in the diagnosis of non-fatal vascular occlusive events and stipulated that occlusive events should be recorded only when there was clear clinical evidence. As a result, we might have under-reported the frequency of these events. However, our estimates of the RR of non-fatal occlusive events should be unbiased.

One weakness of this trial is that it provides limited insight into how tranexamic acid reduces the risk of death in bleeding trauma patients. Early coagulation abnormalities are frequent in severely injured trauma patients and are associated with substantially increased mortality. Recent research showing that hyperfibrinolysis is a common feature of these abnormalities raises the possibility that antifibrinolytic agents such as tranexamic acid might operate via this mechanism. Furthermore, intravenous tranexamic acid administration has an early (within 4 h) antifibrinolytic effect. However, although this mechanism is plausible, because we did not measure fibrinolytic activity in this trial we cannot conclude that this agent acts by reducing fibrinolysis, rather than another mechanism. Further studies are needed into the mechanism of action of tranexamic acid in bleeding trauma patients. Measurement of blood loss is difficult in trauma patients. Much of the bleeding occurs at the scene of the injury and the bleeding that occurs in hospital is often concealed and difficult to quantify, such as, for example, bleeding into the chest, abdomen, pelvis, and soft tissues. However, we did not find any substantial reduction in the receipt of a blood transfusion or the amount of blood transfused in trauma patients. This finding could be an indication of the dilution in estimation of blood loss in trauma patients when assessing the need for transfusion. Another possible explanation is that after the loading dose, tranexamic acid was infused over 8 h, whereas decisions about transfusion are made soon after admission. Finally, fewer deaths occurred in patients allocated to tranexamic acid than to placebo, and the patients who survived as a result of tranexamic acid administration would have had a greater opportunity to receive a blood transfusion (competing risks).

The tranexamic acid loading dose was given within 8 h of injury, followed by a maintenance infusion over 8 h. We chose the early administration of a short course of tranexamic acid because most deaths from bleeding occur on the day of the injury and we postulated that the drug would act by reducing bleeding. Generally, after the first day, the risk of death from haemorrhage is

<table>
<thead>
<tr>
<th></th>
<th>Tranexamic acid (n=10 060)</th>
<th>Placebo (n=10 067)</th>
<th>RR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Vascular occlusive events</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any vascular occlusive event</td>
<td>168 (1.7%)</td>
<td>201 (2.0%)</td>
<td>0.84 (0.68–1.02)</td>
<td>0.084</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>35 (0.3%)</td>
<td>55 (0.5%)</td>
<td>0.64 (0.42–0.97)</td>
<td>0.035</td>
</tr>
<tr>
<td>Stroke</td>
<td>57 (0.6%)</td>
<td>66 (0.7%)</td>
<td>0.86 (0.61–1.23)</td>
<td>0.42</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>72 (0.7%)</td>
<td>71 (0.7%)</td>
<td>1.01 (0.73–1.41)</td>
<td>0.93</td>
</tr>
<tr>
<td>Deep vein thrombosis</td>
<td>40 (0.4%)</td>
<td>41 (0.4%)</td>
<td>0.98 (0.63–1.51)</td>
<td>0.91</td>
</tr>
<tr>
<td><em>Need for transfusion and surgery</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood product transfused</td>
<td>5067 (50.4%)</td>
<td>5160 (51.3%)</td>
<td>0.98 (0.96–1.01)</td>
<td>0.21</td>
</tr>
<tr>
<td>Any surgery</td>
<td>4814 (47.9%)</td>
<td>4836 (48.0%)</td>
<td>1.00 (0.97–1.03)</td>
<td>0.79</td>
</tr>
<tr>
<td>Neurosurgery</td>
<td>1040 (10.3%)</td>
<td>1059 (10.5%)</td>
<td>0.98 (0.91–1.07)</td>
<td>0.67</td>
</tr>
<tr>
<td>Chest surgery</td>
<td>1518 (15.1%)</td>
<td>1525 (15.1%)</td>
<td>1.00 (0.93–1.06)</td>
<td>0.91</td>
</tr>
<tr>
<td>Abdominal surgery</td>
<td>2487 (24.7%)</td>
<td>2555 (25.4%)</td>
<td>0.97 (0.93–1.02)</td>
<td>0.28</td>
</tr>
<tr>
<td>Pelvic surgery</td>
<td>683 (6.8%)</td>
<td>648 (6.4%)</td>
<td>1.05 (0.95–1.17)</td>
<td>0.31</td>
</tr>
<tr>
<td>Median (IQR) units of blood product transfused†</td>
<td>3 (2–6)</td>
<td>3 (2–6)</td>
<td>...</td>
<td>0.59‡</td>
</tr>
<tr>
<td><em>Dependency</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No symptoms</td>
<td>1483 (14.7%)</td>
<td>1334 (13.3%)</td>
<td>1.11 (1.04–1.19)</td>
<td>0.0023</td>
</tr>
<tr>
<td>Minor symptoms</td>
<td>3054 (30.4%)</td>
<td>3061 (30.4%)</td>
<td>1.00 (0.96–1.04)</td>
<td>0.94</td>
</tr>
<tr>
<td>Some restriction</td>
<td>2016 (20.0%)</td>
<td>2069 (20.6%)</td>
<td>0.97 (0.92–1.03)</td>
<td>0.36</td>
</tr>
<tr>
<td>Dependent (not requiring constant attention)</td>
<td>1294 (12.9%)</td>
<td>1273 (12.6%)</td>
<td>1.02 (0.95–1.09)</td>
<td>0.63</td>
</tr>
<tr>
<td>Fully dependent</td>
<td>696 (6.9%)</td>
<td>676 (6.7%)</td>
<td>1.03 (0.93–1.14)</td>
<td>0.57</td>
</tr>
<tr>
<td>Alive (disability status not known)</td>
<td>54 (0.5%)</td>
<td>41 (0.4%)</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Dead</td>
<td>1463 (14.5%)</td>
<td>1613 (16.0%)</td>
<td>0.91 (0.85–0.97)</td>
<td>0.0035</td>
</tr>
</tbody>
</table>

Data are number (%), unless otherwise indicated. Counts are for numbers of patients with at least one such event. RR=relative risk. *Includes both fatal and non-fatal events. †Transfused patients only. ‡Analysis used logarithmic transformation of mean units of blood products transfused.

Table 3: Vascular occlusive events, need for transfusion and surgery, and level of dependency.
reduced but the risk of vascular occlusive events might remain. We therefore selected a regimen that would allow for the effect of tranexamic acid on the early risk of haemorrhage without extending into the period when the risk of vascular occlusive events might be increased by this treatment. The absence of any increase in vascular occlusion with tranexamic acid, whether fatal or non-fatal, provides reassurance that this regimen is safe. Although the effect of this drug on all-cause mortality did not vary substantially according to the time from injury, there was some suggestion that early treatment might be more effective. However, even if this were not the case, the fact that most deaths from haemorrhage occur in the first few hours after injury implies that every effort should be made to treat patients as soon as possible.\textsuperscript{15–17}

The dose of tranexamic acid used in this trial was based on studies of this drug in surgical patients in which loading doses range from 2.5 mg/kg to 100 mg/kg, and maintenance doses from 0.25 mg/kg/h to 4 mg/kg/h, delivered over 1–12 h.\textsuperscript{16} Findings from studies of the effect of different doses of tranexamic acid on blood loss and blood transfusion showed no significant difference between high and low doses. Studies in cardiac surgery have noted that a 10 mg/kg loading dose of tranexamic acid followed by an infusion of 1 mg/kg/h produces plasma concentrations sufficient to inhibit fibrinolysis, and that a larger dose does not provide any additional haemostatic benefit.\textsuperscript{18,19} In emergency situations, the administration of a fixed dose is practicable since determining the weight of a seriously injured patient can be difficult. We therefore selected a fixed dose within the range shown to inhibit fibrinolysis and provide haemostatic benefit that would be efficacious for larger patients (>100 kg) but also safe in smaller patients (<50 kg), to the extent that the dose per kg that smaller patients would receive has been used in surgical trials without adverse effects. The possibility that a higher dose of tranexamic acid would have a greater treatment effect remains open to debate and warrants further study.

The knowledge that tranexamic acid reduces the risk of death from traumatic bleeding raises the possibility that it might also be effective in other situations in which bleeding can be life threatening or disabling. Traumatic brain injury is commonly accompanied by intracranial bleeding, which can develop or worsen after hospital admission. Traumatic intracranial haemorrhage is associated with an increased risk of death and disability, and irrespective of location, haemorrhage size is strongly correlated with outcome.\textsuperscript{20–22} If tranexamic acid reduced intracranial bleeding after isolated traumatic brain injury, then patient outcomes might be improved. Studies that assess the effect of tranexamic acid on the extent of intracranial bleeding are needed.

Tranexamic acid might also have a role in bleeding conditions apart from traumatic injury. Post-partum

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### Table: Mortality by subgroups

<table>
<thead>
<tr>
<th>Time from injury (h)</th>
<th>Tranexamic acid allocated</th>
<th>Placebo allocated</th>
<th>Risk ratio (99% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤1</td>
<td>5003/747 (13.6%)</td>
<td>5013/734 (15.7%)</td>
<td>0.97 (0.75–1.00)</td>
</tr>
<tr>
<td>&gt;1–≤3</td>
<td>463/3037 (15.2%)</td>
<td>528/2996 (17.6%)</td>
<td>0.87 (0.75–1.00)</td>
</tr>
<tr>
<td>&gt;3</td>
<td>491/3272 (15.0%)</td>
<td>502/3362 (14.9%)</td>
<td>1.00 (0.86–1.17)</td>
</tr>
<tr>
<td>≥4</td>
<td>411; p=0.11</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Systolic blood pressure (mm Hg)</th>
<th>Tranexamic acid allocated</th>
<th>Placebo allocated</th>
<th>Risk ratio (99% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥90</td>
<td>702/6878 (10.2%)</td>
<td>736/6761 (10.9%)</td>
<td>0.94 (0.82–1.07)</td>
</tr>
<tr>
<td>76–89</td>
<td>280/1609 (17.5%)</td>
<td>313/1689 (18.5%)</td>
<td>0.94 (0.78–1.14)</td>
</tr>
<tr>
<td>≤75</td>
<td>478/1562 (30.6%)</td>
<td>562/1599 (35.1%)</td>
<td>0.87 (0.76–0.99)</td>
</tr>
<tr>
<td>≥90</td>
<td>798/1789 (44.5%)</td>
<td>862/1830 (47.9%)</td>
<td>0.95 (0.86–1.04)</td>
</tr>
<tr>
<td>GCS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe (3–8)</td>
<td>1134/6788 (16.7%)</td>
<td>1233/6617 (18.1%)</td>
<td>0.92 (0.83–1.02)</td>
</tr>
<tr>
<td>Moderate (9–12)</td>
<td>329/3272 (10.1%)</td>
<td>360/3250 (11.7%)</td>
<td>0.86 (0.72–1.03)</td>
</tr>
<tr>
<td>Mild (13–15)</td>
<td>447/6915 (6.5%)</td>
<td>592/6877 (7.3%)</td>
<td>0.88 (0.75–1.04)</td>
</tr>
<tr>
<td>GCS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injury type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blunt</td>
<td>1463/10060 (14.5%)</td>
<td>1613/10067 (16.0%)</td>
<td>0.91 (0.85–0.97)*</td>
</tr>
<tr>
<td>Penetrating</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Two-sided; p=0.0035</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\*Two-sided p=0.0035

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**Figure 3:** All-cause mortality by subgroups

GCS=Glasgow Coma Score. *95% CI.
haemorrhage is a leading cause of maternal mortality, accounting for about 100,000 maternal deaths every year.23 Although evidence suggests that this drug reduces post-partum bleeding, the quality of the existing trials is poor and none has been large enough to assess the eMect of tranexamic acid on endpoints that are important to women.24 A large trial is being undertaken to assess the eMect of tranexamic acid on the risk of death and hysterectomy in women with post-partum haemorrhage.25

In conclusion, tranexamic acid could be given in a wide range of health-care settings, and safely reduced the risk of death in bleeding trauma patients in our study. The option to use tranexamic acid should be available to doctors treating trauma patients in all countries, and this drug should be considered for inclusion on the WHO List of Essential Medicines. On the basis of these results, tranexamic acid should be considered for use in bleeding trauma patients.

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Military Application of Tranexamnic Acid in Trauma Emergency Resuscitation (MATTERs) Study

Jonathan J. Morrison, MB ChB, MRCS; Joseph J. Dubose, MD; Todd E. Rasmussen, MD; Mark J. Midwinter, BMedSci, MD, FRCS

Objectives: To characterize contemporary use of tranexamnic acid (TXA) in combat injury and to assess the effect of its administration on total blood product use, thromboembolic complications, and mortality.

Design: Retrospective observational study comparing TXA administration with no TXA in patients receiving at least 1 unit of packed red blood cells. A subgroup of patients receiving massive transfusion (>10 units of packed red blood cells) was also examined. Univariate and multivariate regression analyses were used to identify parameters associated with survival. Kaplan-Meier life tables were used to report survival.

Setting: A Role 3 Echelon surgical hospital in southern Afghanistan.

Patients: A total of 896 consecutive admissions with combat injury, of which 293 received TXA, were identified from prospectively collected UK and US trauma registries.

Main Outcome Measures: Mortality at 24 hours, 48 hours, and 30 days as well as the influence of TXA administration on postoperative coagulopathy and the rate of thromboembolic complications.

Results: The TXA group had lower unadjusted mortality than the no-TXA group (17.4% vs 23.9%, respectively; P=.03) despite being more severely injured (mean [SD] Injury Severity Score, 25.2 [16.6] vs 22.5 [18.5], respectively; P=.001). This benefit was greatest in the group of patients who received massive transfusion (14.4% vs 28.1%, respectively; P=.004), where TXA was also independently associated with survival (odds ratio = 7.228; 95% CI, 3.016-17.322) and less coagulopathy (P=.003).

Conclusions: The use of TXA with blood component-based resuscitation following combat injury results in improved measures of coagulopathy and survival, a benefit that is most prominent in patients requiring massive transfusion. Treatment with TXA should be implemented into clinical practice as part of a resuscitation strategy following severe wartime injury and hemorrhage.


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See Invited Critique at end of article

VASCULAR DISRUPTION WITH concomitant hemorrhage is a leading cause of death in civilian and military trauma. Experience from the wars in Iraq and Afghanistan has led to advances in resuscitation for hemorrhagic shock, with identification of optimum ratios of blood components to be used in this setting. These new strategies are based on early and balanced administration of packed red blood cells (PRBCs), fresh frozen plasma (FFP), platelets, and cryoprecipitate to restore circulating volume and clotting factors. Despite these advances, the effectiveness of a medication to improve mortality in the setting of hemorrhagic shock has not been established.

The CRASH-2 trial demonstrated that the antifibrinolytic agent tranexamic acid (TXA) resulted in reduced mortality following civilian trauma. Tranexamic acid is a lysine analog that occupies binding sites on the plasminogen molecule, inhibiting fibrinolysis. It has an established safety and efficacy profile and its primary effect of inhibition of clot breakdown portends a favorable effect on patients with hemorrhage from vascular disruption. Because plasmin is known to have proinflammatory effects, other beneficial effects have been suggested. Despite their value, the CRASH-2 results are not fully applicable to wartime injury as the study was performed in civilian hospitals, many of which lacked modern trauma and resuscitation practices. In addition, they provide no information on measures of coagulopathy or injury severity, and the mechanism of injury was mostly blunt rather than penetrat-
ing. Finally, only half of the patients in the CRASH-2 trial actually received a transfusion, and a similarly low percentage required an operation. To our knowledge, there has been no report to date on the use of TXA in the management of severe combat injury. The UK Defence Medical Service has used TXA since 2009 as part of a massive transfusion protocol, and the US Combat Casualty Care program has deferred use altogether. The objectives of this study are to report the experience of the use of TXA in the combat setting and to characterize its effect on measures of coagulopathy and survival following wartime injury.

### METHODS

#### DESIGN AND STUDY GROUPS

A retrospective cohort study was performed with patients having been treated at a single surgical hospital at Camp Bastion, southern Afghanistan. Approval for the MATTERs Study was established through the UK Joint Medical Command Research Pillar and the US Army’s Medical Research and Materiel Command. From January 1, 2009, through December 31, 2010, consecutive patients who received at least 1 unit of PRBCs within 24 hours of admission following combat-related injury were identified using the UK Joint Theatre Trauma Registry. This included all coalition military personnel (designated North Atlantic Treaty Organization [NATO] military) and Afghan police, military, and civilians (designated host nationals) (Table 1). Information on US troops treated at this facility during this time was cross-referenced using the US Joint Theater Trauma Registry. Patients, regardless of designation, were required to have stable physiology prior to discharge. In the case of NATO military, this required stabilization for aeromedical evacuation; host nationals remained until they were clinically ready to be transferred to an Afghan national medical facility or to home.

Prior to 2010, TXA was administered at the discretion of the surgeon or anesthetist on the basis of clinical judgment and, in some instances, following demonstration of hyperfibrinolysis on rotational thromboelastography. Thereafter, as part of a major hemorrhage protocol or clinical practice guideline, TXA was administered to patients requiring emergency blood products or patients with evidence of hyperfibrinolysis. A standard dosing regimen consisted of an intravenous bolus of 1 g, repeated as felt indicated by the managing clinician. Patients who received TXA were assigned to the treatment group (TXA group) and compared with those who did not receive TXA (no-TXA group). Patients who received 10 or more units of PRBCs within

### Table 1. Demographic Data, Mechanism of Injury, Injury Severity, Physiology, and Transfusion Requirement for Overall and Massive Transfusion Groups

<table>
<thead>
<tr>
<th>Variable</th>
<th>Overall (N=896)</th>
<th>Massive Transfusion (N=231)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TXA (n=293)</td>
<td>No TXA (n=603)</td>
</tr>
<tr>
<td></td>
<td>P Value*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>TXA (n=125)</td>
<td>No TXA (n=196)</td>
</tr>
<tr>
<td></td>
<td>P Value*</td>
<td></td>
</tr>
<tr>
<td>Demographic data</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>24.9 (9.6)</td>
<td>23.1 (10.1)</td>
</tr>
<tr>
<td>Male, %</td>
<td>97.3</td>
<td>94.2</td>
</tr>
<tr>
<td>Host national, No. (%)</td>
<td>116 (39.6)</td>
<td>261 (43.3)</td>
</tr>
<tr>
<td>NATO military</td>
<td>177 (60.4)</td>
<td>342 (56.7)</td>
</tr>
<tr>
<td>Mechanism of injury, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GSW</td>
<td>25.3</td>
<td>36.7</td>
</tr>
<tr>
<td>Explosion</td>
<td>74.7</td>
<td>62.4</td>
</tr>
<tr>
<td>Injury severity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ISS, mean (SD)</td>
<td>25.2 (16.6)</td>
<td>22.5 (18.5)</td>
</tr>
<tr>
<td>AIS score &gt;3, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Head</td>
<td>9.9</td>
<td>13.4</td>
</tr>
<tr>
<td>Chest</td>
<td>22.2</td>
<td>22.2</td>
</tr>
<tr>
<td>Abdomen</td>
<td>14.7</td>
<td>16.4</td>
</tr>
<tr>
<td>Extremity</td>
<td>66.6</td>
<td>47.3</td>
</tr>
<tr>
<td>RTS, mean (SD)</td>
<td>5.53 (2.14)</td>
<td>6.04 (2.69)</td>
</tr>
<tr>
<td>Admission physiology, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GCS score ≤8</td>
<td>63.3</td>
<td>35.6</td>
</tr>
<tr>
<td>SBP ≤90 mm Hg</td>
<td>22.8</td>
<td>13.8</td>
</tr>
<tr>
<td>24-h Transfusion, mean (SD), units</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PRBCs</td>
<td>11.8 (12.1)</td>
<td>9.8 (13.1)</td>
</tr>
<tr>
<td>FFP</td>
<td>10.3 (10.8)</td>
<td>8.6 (11.7)</td>
</tr>
<tr>
<td>Platelets</td>
<td>1.6 (2.2)</td>
<td>1.4 (2.7)</td>
</tr>
<tr>
<td>Cryoprecipitate</td>
<td>1.6 (2.7)</td>
<td>0.5 (1.3)</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time in ED, mean (SD), min</td>
<td>36 (25)</td>
<td>56 (55)</td>
</tr>
<tr>
<td>Time in OR, mean (SD), min</td>
<td>170 (121)</td>
<td>115 (74)</td>
</tr>
<tr>
<td>Lowest body temperature, mean (SD), °C</td>
<td>36.1 (1.1)</td>
<td>36.4 (0.9)</td>
</tr>
<tr>
<td>Pulmonary embolism, No. (%)</td>
<td>8 (2.7)</td>
<td>2 (0.3)</td>
</tr>
<tr>
<td>Deep venous thrombosis, No. (%)</td>
<td>7 (2.4)</td>
<td>1 (0.2)</td>
</tr>
</tbody>
</table>

Abbreviations: AIS, Abbreviated Injury Scale; ED, emergency department; FFP, fresh frozen plasma; GCS, Glasgow Coma Scale; GSW, gunshot wound; ISS, Injury Severity Score; NATO, North Atlantic Treaty Organization; OR, operating room; PRBCs, packed red blood cells; RTS, Revised Trauma Score; SBP, systolic blood pressure; TXA, tranexamic acid.

*Statistically significant values (P < .05) are bold.
END POINTS

Primary end points were 24 and 48 hours and in-hospital mortality. In-hospital mortality for US and UK patients included that which occurred within 30 days either at the hospital in Afghanistan or at any point throughout the aeromedical evacuation chain. For non-US and non-UK patients, in-hospital mortality included that which occurred within 30 days of being admitted to the surgical facility in Afghanistan. Secondary end points included transfusion requirements and coagulation parameters (prothrombin time and activated partial thromboplastin time). Determination of coagulopathy using these measures was made at 2 points: (1) admission to the emergency department of the surgical hospital; and (2) admission to the intensive care unit following the initial operation. Hypocoagulopathy was defined as a prothrombin time longer than 1.5 times the midpoint of normal (>18 seconds) or an activated partial thromboplastin time greater than 1.5 times the normal range (>55 seconds). Additional end points included TXA dose and timing as well as the incidence of thrombotic events such as deep venous thrombosis (DVT) or pulmonary thromboembolism (PTE).

Data collected included demographic characteristics, admission physiology, treatment timelines, and 24-hour transfusion requirement (PRBCs, FFP, platelets, and cryoprecipitate). The Glasgow Coma Scale (GCS) score, systolic blood pressure (SBP), and respiratory rate at admission were used to generate a Revised Trauma Score, which is inversely related to trauma mortality. The Abbreviated Injury Scale (AIS) was used to report the anatomical injury pattern for 4 body regions (head, chest, abdomen, and extremity) and to calculate the Injury Severity Score (ISS) at admissions (on a scale of 1-75). The following definitions were established: hypotension as an SBP of 90 mm Hg or lower; a significantly reduced conscious level as a GCS score of 8 or lower; and severe injury as an AIS score of 3 or higher.

STATISTICAL ANALYSIS

Comparison between the TXA and no-TXA groups was performed using a χ² test, and differences in means were assessed using t test or Mann-Whitney rank sum test. Continuous variables were dichotomized using defined cutoff values recorded at the time of admission: GCS score (≤8 vs >8), SBP (≤90 vs >90 mm Hg), ISS (≤15 vs >15), and body region AIS scores (2:3 vs -3). The following parameters were analyzed with univariate analysis for inhospital mortality: sex, national status, mechanism of injury, ISS higher than 15, GCS score of 8 or lower at admission, SBP of 90 or lower at admission, body region AIS scores of 3 or higher, time in the emergency department (in minutes), time in the operating room (in minutes), hypocoagulopathy on admission, lowest body temperature (in degrees Celsius), and TXA administration. Factors achieving significance (P < 0.15) were entered into a multivariate, stepwise logistic regression analysis to identify those independently associated with mortality. To assess risk of DVT and PTE, a similar analysis was performed to determine the relation of the previously listed factors with this diagnosis. Adjusted odds ratios with 95% confidence intervals were derived from logistic regression and significance was set at P < 0.05 after adjustment for risk factors.

Follow-up (in days) was calculated and based on the time from the date of injury to the date of the last hospital record or 30 days, whichever was longest. Mantel-Cox log-rank test and Kaplan-Meier life table analysis was used to report survival in the treatment and nontreatment groups in the overall (TXA vs no-TXA) and MT (TXA vs no-TXA) cohorts.

RESULTS

DEMOGRAPHIC CHARACTERISTICS

Eight hundred ninety-six patients constituted the overall MATTErs Study cohort. Of these, 293 (32.7%) received intravenous administration of TXA (mean [SD] dose, 2.3 [1.3] g) within 1 hour of injury. Table 1 demonstrates the demographic characteristics, mechanism and severity of injury, and physiological and pathological end points of the overall and MT cohorts. There was a similar distribution of NATO military and host national patients among the TXA and no-TXA groups of the overall and MT cohorts. In the overall cohort, the TXA group had a higher ISS and a higher percentage of patients with severe extremity injury (Table 1). Additionally, the TXA group had a lower Revised Trauma Score and a greater percentage of patients presenting with a depressed GCS score and hypotension. The difference in injury severity was not as marked in the MT cohort, although the TXA group had a greater percentage of patients with severe extremity injury as well as a greater proportion of patients with a depressed GCS score than the no-TXA group.

Transfusion requirements in the overall cohort were higher for the TXA group compared with the no-TXA group (Table 1). The PRBC:FFP ratio in the TXA and no-TXA groups was the same (1:0.87 and 1:0.88, respectively). In the MT cohort, requirements were the same between the TXA and no-TXA groups with the exception of cryoprecipitate. The PRBC:FFP ratio in the TXA group and no-TXA group was the same (1:0.88 and 1:0.87, respectively). In the overall cohort, the rate of PTE and DVT were greater in the TXA group compared with the no-TXA group. This trend was similar in the MT cohort, where the TXA group had a higher rate of PTE compared with the no-TXA group. There were no fatalities attributed to PTE in either cohort.

HYPOCOAGULOPATHY AND MORTALITY

Figure 2 illustrates the percentage of patients considered hypocoagulopathic on admission to the emergency department and intensive care unit following operation. In both the overall and MT cohorts, there was a de-
crease in the percentage of patients in the TXA groups with hypocoagulopathy between these 2 points. Table 2 illustrates mortality in the 2 cohorts. In the overall cohort, the absolute reduction in in-hospital mortality for the TXA group was 6.5%, while the absolute reduction in the TXA-H group was 13.7% (relative reduction of 49%). The following parameters had P < .15 in univariate analysis of mortality in the overall cohort: host national status (P = .08), ISS of 15 or higher (P < .001), head AIS score of 3 or higher (P < .001), chest AIS score of 3 or higher (P = .005), abdominal AIS score of 3 or higher (P < .001), extremity AIS score of 3 or higher (P = .08), GCS score of 8 or lower (P < .001), SBP of 90 mm Hg or lower (P < .001), evidence of hypocoagulopathy on admission (P = .001), and received TXA (P = .02). The following parameters had P < .15 in univariate analysis in the MT cohort: ISS of 15 or higher (P < .001), head AIS score of 3 or higher (P < .001), chest AIS score of 3 or higher (P < .001), GCS score of 8 or lower (P < .001), SBP of 90 mm Hg or lower (P < .001), hypocoagulopathy (P < .001), and TXA (P = .02).
patients receiving tranexamic acid (TXA) vs no TXA. \( P = .006 \), Mantel-Cox log-rank test.

\( (P < .001) \), GCS score of 8 or lower \( (P < .001) \), SBP of 90 mm Hg or lower \( (P = .001) \), and received TXA \( (P = .003) \). Table 3 illustrates findings from the multivariate logistic regression analysis of factors having met model inclusion criteria \( (P < .15) \). As illustrated, in the overall cohort, a GCS score of 8 or lower, hypotension, and the presence of coagulopathy were independently associated with mortality. In the MT group, a GCS score of 8 or lower and an ISS of 15 or higher were associated with mortality, while TXA use was independently associated with survival. In a separate analysis, none of the clinical parameters had an association with DVT or PTE in either the overall or MT cohort. As such, no parameters, including administration of TXA, were associated with DVT or PTE.

**LIFE TABLE ANALYSIS**

Figure 3 illustrates survival curves for the 2 groups in the overall cohort. The TXA group had better 30-day survival compared with the no-TXA group \( (P = .006) \).
To our knowledge, the MATTERs Study suggests that a beneficial mechanism other than hemostasis may be present. Specifically, there is no difference in mortality between the TXA and no-TXA groups until the 48-hour point, a time at which bleeding is less likely to be the prime cause of death. Although hemostasis is important at and beyond 24 hours, it is also possible that attenuation of the inflammatory response plays a role in the survival benefit associated with TXA. In a study of TXA in cardiac surgery, Jimenez et al.\textsuperscript{15} reported that the drug was independently associated with a reduced inflammatory response. The prospective randomized arm of the study was terminated early because of the marked benefit observed with TXA in reducing not only the inflammatory response but also rates of shock and ventilatory support.\textsuperscript{5} As one of several studies that have shown reduced bleeding and transfusion requirements with TXA in cardiac surgery,\textsuperscript{21-23} Casati et al.\textsuperscript{17} reported lower postoperative levels of D-dimer and interleukin 6 with use of the drug. Several of these studies emphasize the interconnected nature of the fibrinolytic and inflammatory pathways, noting the potential benefit of inhibiting not just acute fibrinolysis but also secondary fibrinolysis as a means to reduce systemic inflammation.

The higher rate of DVT and PTE in the TXA group should be taken in the context of a higher injury burden, which is associated with thrombotic events.\textsuperscript{24,25} The number of venous thrombotic events in this study is too small to assess any independent risk of TXA; however, in light of the evidence of correction of hypocoagulability, it is plausible that the higher rates of thrombotic events relate to the TXA. Conversely, the increased rate of these events may reflect a survivorship phenomenon in the TXA group that has a relative risk reduction of mortality of 27% in the overall cohort and 49% in the MT cohort.

As a retrospective analysis of the trauma registries of the US and UK militaries, this study has a number of limitations worth noting. Because the clinical practice guideline, which included TXA use, was not introduced until the later part of the study period, there is the possibility that slight variations in the indications for use and dosing of the medication occurred. However, because this study reflects TXA use at 1 surgical facility during 24 consecutive months, it is unlikely that its use varied significantly throughout the period.

Measures of coagulation in our study provide new insight into the effect of TXA after trauma. The observation that TXA resulted in an improved coagulation profile supports the clot-stabilizing effect of this medication (Figure 2). It is worth noting that the TXA and no-TXA groups in both the overall and MT cohorts received similar, blood component–based resuscitation (Table 1). The PRBC:FFP ratio in each of the groups is the same, indicating that the improvement in coagulopathy was the result of something other than different use of blood products. These findings also suggest that the increased transfusion requirements in the TXA groups were more related to severity of injury and not to worsening coagulopathy. The observation of the improved coagulation profile corroborates the CRASH-2 findings, which demonstrated reduced mortality from hemorrhage.\textsuperscript{7}

Figure 4 illustrates survival curves for both groups from the MT cohort. The TXA\textsuperscript{MT} group had superior 30-day survival compared with the no-TXA\textsuperscript{MT} group ($P=.004$).

\textbf{COMMENT}\textsuperscript{E6}

To our knowledge, the MATTERs Study is the first to examine the effectiveness of TXA in the management of wartime injury. Findings show that TXA improves markers of coagulation and results in lower mortality. The observation of improved survival confirms findings from the CRASH-2 trial and extends them to a population of patients with wartime injuries.\textsuperscript{7} The measures of injury severity and physiology in our study were not available in the CRASH-2 trial but now provide insight into which patients may benefit most from TXA. Findings suggest that the beneficial effect of TXA is more prominent in those with higher injury severity. Additionally, laboratory values not reported in the CRASH-2 trial afford new evidence of a clot-stabilizing effect of TXA during a critical time of injury management.

The mortality advantage shown with TXA in the CRASH-2 trial was subtle (absolute reduction of 1.5%); however, not all patients in that study were severely injured.\textsuperscript{7} For example, only half received a transfusion or required an operation. The 6.5% absolute reduction in mortality in our study in which all patients required a blood transfusion and an operation suggests a more significant benefit in those more severely injured. In light of these findings, it is tempting to speculate that the modest injury profile of the CRASH-2 cohort introduced a conservative bias against the TXA effect. This proposition is supported by observations from our study that show the effect to be greatest (absolute reduction of 13.7%) in the MT group. To place this in context, the number of patients required to be treated with TXA to achieve a mortality benefit of 1 was 67 in the CRASH-2 trial. Findings from our study in a more severely injured cohort suggest that as few as 7 patients need to be treated to provide that same benefit.
The retrospective nature of this study prevents in-depth understanding of the incidence of venous thrombotic events. Specifically, the incidence of these events was quantified using diagnostic codes to query each of the trauma registries. This method did not provide insight on the method used to screen for or diagnose these events or quantify in detail their clinical significance. Better knowledge of any association of TXA with venous thrombotic events will require a prospective study with these clinical end points in mind.

As this was a retrospective analysis, the exact cause or time of death was not able to be discerned in those who died. It is therefore likely that some patients who died very early in the course of their admission are included in the study cohort. Such patients are less likely to be affected by any therapeutic intervention such as TXA and thus risk introducing an immediate mortality bias. However, as there was no difference in mortality rates between cohorts at the 24-hour period, it is likely that such patients who died very early in their course were evenly distributed across the groups.

Finally, inclusion of host national patients limits the ability of this study to ascertain 30-day outcome information as most of these patients are discharged before this period. As all patients were discharged only when physiologically stable as a matter of safe and ethical care, we are confident that there is no hidden cohort of mortality after censoring. Additionally, the proportion of host national patients to NATO military patients was equally distributed across all of the study arms, making any bias related to patient demographic characteristics unlikely.

In conclusion, findings from the MATTERs Study demonstrate that the use of TXA in conjunction with a blood component–based resuscitation following combat injury results in improved measures of coagulopathy and survival. This benefit is present in all who receive blood transfusions in this setting but is most prominent in those requiring MT. On the basis of these findings, early administration of TXA following severe wartime vascular disruption with hemorrhage should be implemented into clinical practice.

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Author Contributions: Study concept and design: Morisson, Dubose, Rasmussen, and Midwinter. Acquisition of data: Morisson, Dubose, Rasmussen, and Midwinter. Analysis and interpretation of data: Morisson, Dubose, Rasmussen, and Midwinter. Drafting of the manuscript: Morisson, Dubose, Rasmussen, and Midwinter. Critical revision of the manuscript for important intellectual content: Morisson, Dubose, Rasmussen, and Midwinter. Statistical analysis: Morisson, Dubose, Rasmussen, and Midwinter. Administrative, technical, and material support: Morisson, Rasmussen, and Midwinter. Study supervision: Dubose, Rasmussen, and Midwinter.
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Disclaimer: The viewpoints expressed in this article are those of the authors and do not reflect the official position of the US Department of Defense or the UK Defence Medical Service.

Previous Presentations: This paper was presented at the SWAN XIX Trauma Conference of the South West Australian Trauma Network; July 29, 2011; Sydney, Australia; and at the Advanced Technology Applications for Combat Casualty Care 2011 Conference of the Combat Casualty Care Research Program; August 16, 2011; Fort Lauderdale, Florida.

Additional Contributions: We are grateful to the staff at the UK Joint Theatre Trauma Registry (Academic Department of Military Emergency Medicine, Royal Centre for Defence Medicine, Birmingham) and US Joint Theatre Trauma Registry (US Army Institute of Surgical Research, Fort Sam Houston, San Antonio) for providing the data required for this study.

REFERENCES


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**INVITED CRITIQUE**

**Antifibrinolytics in Trauma Patients**

**Does It MATTER?**

Our understanding of the coagulation system defects associated with injury continues to evolve. Hyperfibrinolysis has been identified as one of these coagulation abnormalities. Recently, the therapeutic impact of the antifibrinolytic tranexamic acid was examined in the CRASH-2 study. Despite a subtle but significant outcome benefit, direct application of these results to clinical practice was made challenging by several factors, including the inclusion criteria that effectively diluted out those patients who were actually bleeding. These results became even more difficult to interpret when an analysis of the time from injury to treatment demonstrated an increase in the risk of death due to bleeding if the antifibrinolytic was administered beyond 3 hours.

The MATTERs Study, however, specifically targeted the cohort of patients who were actively bleeding and demonstrated a strong association with improved survival. It is a retrospective study and as such does have its limitations. Its data predate and cross over the CRASH-2 release date, highlighting the lack of standardized indications and dosing used throughout the study period. Like the studies before it, the MATTERs Study also failed to quantify the degree of hyperfibrinolysis or its response to treatment. In addition, a detailed analysis of the timing of treatment, a critical factor emphasized by the CRASH-2 trial, could not be performed.

And yet, when put into the context of the early mortality benefit and neutral risk profile demonstrated in the CRASH-2 trial, the MATTERs Study provides even further evidence that in trauma patients who are bleeding, tranexamic acid may be beneficial. Thus, the mechanism of action, role of point-of-care tests in directing treatment, dosing, and optimal timing all warrant further investigation.

This work is an important contribution to our understanding of coagulopathy in trauma. The authors should be congratulated for setting up a registry that allowed for data capture under such austere operating conditions and for analyzing their experience. Their commitment to the care of the injured soldier and the advancement of science stands as an example to us all.

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**Kenji Inaba, MD**

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**Financial Disclosure:** None reported.

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ATTACHMENT B - DRAFT PROTOCOLS
(Attached at the end of application)
ATTACHMENT C - EMS QI PLAN AND LETTERS OF SUPPORT
EMS CQI Plan for TXA Trial

Study Participants and QI Leaders

1. Yolo County EMS
   • John S Rose, MD, Medical Director
   • Kristin Weivoda, EMS Administrator

2. American Medical Response
   • Jack Wood, MD, Medical Director
   • Dennis Carter, AMR

3. UC Davis Medical Center
   • David Shatz, MD, FACS, Division of Trauma Surgical Critical Care

4. Kaiser Vacaville
   • Christopher Bandy, MD FACS, Chief of Trauma & Emergency Surgery

Description of Study Participant Roles:

1. Yolo County EMS will form a TXA committee that will meet monthly to review all cases in Yolo County. This committee will compile a formal report to give to the EMS Authority, and EMS Commission if requested - after 18 months.
2. Hospital Trauma Directors: Responsible for reporting adverse events immediately, updating trauma registry and reporting on TXA use at the quarterly Trauma Audit Committee meetings.
3. AMR and local agency medical directors: Responsible for agency QI (in addition to the LEMSA) as well as error reporting and adverse event reporting.

Data Elements

1. Yolo County’s EMS system has a fully integrated and electronic patient record system (ePCR). This electronic system allows us to collect the following, searchable information:
   • Date and Time of Incident
   • Incident Number
   • Primary Impression
   • Mechanism of Injury
   • Patient Age
   • Weight
   • Gender
   • Time of Injury
   • Dose and Time of TXA administration
   • Pre and Post TXA vital signs
• Narrative Details

2. The ePCR data will be linked to the county-wide trauma registry. This registry is kept current by the trauma centers in Yolo County and continually monitored by Yolo County EMS. Data elements will include:
   • Date and Time of Incident
   • Receiving Hospital
   • ICD-9 code
   • Mechanism of Injury
   • Procedures performed
   • Date and Time to OR
   • Transfused blood products
   • Disposition (outcome)
   • Complications

3. The linked data will be used to track:
   • Serious Adverse Events
   • Mortality
   • Cause of Death
   • Discharge Diagnosis
   • Blood product administration and type along with number of units given
   • Hospital days
   • ICU days
   • Ventilator Use
   • OR use

4. 100% of patients who receive TXA will be reviewed by the above criteria within 60 days of administration.

5. Any serious adverse events attributed to the use of TXA will be reported by the EMS crew or the receiving hospital within 48 hours. We have obtained letters of commitment from the receiving hospitals for this reporting.

EMS QI Plan

QI for the system will be completed by ePCR data points

GOALS

1. 100% of patients meeting criteria will receive TXA by the transporting provider
   a. Monitor all patients who meet inclusion criteria
   b. Monitor all patients who meet inclusion criteria AND received TXA

2. 100% of patients will have pre and post-TXA vital signs documented by the transporting provider.
a. Monitor all patient who received TXA AND had documented pre and post vital signs
   b. Monitor total number of patients that received TXA
3. 100% of TXA patients with serious adverse events to the medication will be reported to Yolo County EMS Trauma Coordinator within 48 hours of occurrence.
   a. Monitor linked data between ePCR and trauma registry for complications
   b. Monitor adverse events reported directly to Yolo EMS by either trauma center or paramedics.

CQI Flags:
Any study patient who:
   1. Met inclusion criteria and did NOT receive TXA
   2. Received TXA and did not have Pre and Post Vital Signs Documented
   3. Received TXA and experienced a serious adverse event that was not reported within 48 hours to Yolo County EMS
Ms. Weivoda,

I have reviewed your proposed trial pertaining to the use of TXA for hemorrhagic shock in the pre-hospital setting. I agree with your current concept and would be honored to assist in the capacity of clinical oversight and/or review of data and results.

Please keep me informed regarding the progress of study implementation and education of providers.

Thank you for the opportunity to assist you in this project.

Sincerely,

W. Christopher Bandy, MD, FACS
Chief of Trauma & Emergency Surgery
Trauma Medical Director
Chris.Bandy@kp.org
707-624-1574
To Whom It May Concern:

This letter is in support of the petition by Yolo County EMS Agency to participate in EMSA trial in the use of TXA in trauma patients. I will be representing UC Davis Health System Trauma Division in the independent review of each case of TXA sent to UCDHS by Yolo EMS Agency. Please do not hesitate to contact me with any questions.

Sincerely,

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University of California, Davis Medical Center
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Shock: Traumatic Hemorrhagic

STATEMENT

For trauma patients who survive to reach the hospital, bleeding is the most common cause of death. Rapid identification of the shock state, application of appropriate interventions, early administration of Tranexamic acid (TXA), and rapid transportation to a trauma center greatly decreases mortality and morbidity in bleeding trauma patients.

The treatment goals for shock related to trauma include:

- Maintaining adequate oxygen delivery
- Limiting ongoing blood loss
- Maintaining intravascular volume
- Limiting on-scene/in-hospital time
- Early administration of Tranexamic acid (TXA)
- Rapid transportation to Level I/II

PURPOSE

To identify the principles and practice for the initial diagnosis and treatment of hemorrhagic shock in trauma patients. Applies to all patients presenting with hemorrhagic shock.

INDICATIONS

- Adults (Age 18 or greater) with hemorrhagic shock from trauma.
- Estimated blood loss of 500 mL.
- Patients who considered to be high risk for significant hemorrhage.
- Must have obvious bleeding external wounds neck to mid-thigh or suspected severe internal injuries from blunt or penetrating trauma.
- Trauma occurred within last 3 hours.
- Must have sustained tachycardia 110 beats per minute and/or sustained hypotension with systolic blood pressure 90 mmHg or less

CONTRAINdications

- Non-hemorrhagic shock.
- Any patients under the age of 18 years of age.
- Traumatic arrest with greater than five minutes of CPR, without return of
vital signs.

- Penetrating cranial injury.
- Traumatic brain injury with brain matter exposed.
- Isolated drowning or hanging victims.
- Documented cervical cord injury with motor deficit.
- Non-traumatic hemorrhagic shock.
- Hemorrhagic shock stabilized with other hemostatic agents/measures.
- Isolated traumatic brain injury.

**PROCEDURE**

I. Control bleeding per Bleeding Control Protocol
II. Assure adequate ABC’s
III. Provide supplemental oxygen
IV. SBP goal 70-90mmHg
V. Limit Crystalloid infusion unless:
   a) If polytrauma with head injury and/or spinal cord injury; maintain target SBP > 90mmHg or age related SBP
   b) If SBP below 70mmHg; infuse up to 10 ml/kg of crystalloid bolus to achieve SBP goal
VI. Administer Tranexamic acid (TXA) 1 gram mixed in 100 ml Normal Saline infused over 10 minutes. No Repeat.
   a) Hypovolemic shock secondary to trauma in patients who meet all of the following conditions:
      i. Greater than 18 years old or 100 lbs.
      ii. Less than 3 hours post injury
      iii. SBP < 90mmHg – Observed or reported
      iv. Risk of significant bleeding, blood transfusion, or surgery
      v. Note: include trauma patients with associated spinal injury or head injury
VII. Maintain normothermia
VIII. Give a full detailed report to the receiving trauma team

**SPECIAL CONSIDERATIONS**

- A number of other potential causes of hypotension exist in the presence of trauma and must be considered:
  a) Cardiac tamponade
  b) Tension pneumothorax
  c) Pulmonary contusion with resulting pulmonary dysfunction
  d) Hemothorax with resulting pulmonary dysfunction
  e) Myocardial infarction or contusion (i.e. cardiogenic shock)
  f) Spinal cord injury (i.e. neurogenic shock)
  g) Traumatic Brain Injury
  h) Effects of pharmacologic or toxicologic agents
- Hypotension is a late sign of shock. Under most circumstances heart rates of > 20 bpm above normal are NOT due to pain or anxiety. This is an indication of shock until proven otherwise.
- Assess for history of anticoagulation therapy and reverse if possible.
- Cold IV fluids should be avoided for risk of hypothermia and coagulopathy.
- Hemorrhagic shock in the elderly may be present with systolic blood pressures > 90mmHg and apparently normal vital signs. A high index of suspicion in the elderly is required.
Hemorrhagic Shock
Tranexamic Acid (TXA)

Yolo County EMS Agency
Objectives

- Recognize hemorrhagic shock signs and symptoms
- Explain the importance of early control of hemorrhage in trauma patients
- Describe the management and ongoing evaluation of hemorrhagic shock
- List the components of damage control resuscitation
Hemorrhagic Shock

- Feared by all
- Respected by many
- Foreign to none
Time to Trauma Death

- 50% deaths occur at scene within minutes:
  - CNS injury 40-50%
  - Hemorrhage 30-40%

- 50% after hospital arrival:
  - 60% die within first 4 hrs
  - 84% die within first 12 hrs
  - 90% die within first 24 hrs

- Hemorrhage accounts for 50%
  - Deaths in the first 24 hours
Historic Trauma
Trimodal Death Distribution

Immediate

Early

Late
Hemorrhage Trauma Deaths

Civilian: 40%
Military: 50%
Hemorrhagic Shock Definition

Hemorrhagic Shock

- Reduction in tissue perfusion below that necessary to meet metabolic needs

Inadequate Perfusion
## Injuries Prone to Hemorrhage

<table>
<thead>
<tr>
<th>Vascular</th>
<th>Solid Organ</th>
<th>Bones</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aorta</td>
<td>Spleen</td>
<td>Pelvis</td>
</tr>
<tr>
<td>Vena Cava</td>
<td>Liver</td>
<td>Femur</td>
</tr>
</tbody>
</table>
Blood loss from Fx

- Humerus 750 ml
- Tibia 750 ml
- Femur 1500 ml
- Pelvis > 3 L

Associated Soft Tissue Trauma
Release of Cytokines
- Increased permeability
- Magnify fluid loss
Confounding Factors

- Patients age
- Pre-existing disease / meds
- Severity of injury
- Access to care
- *Duration of shock*
- Amount prehospital fluid
- Presence of hypothermia
Hemorrhagic Shock

Pathophysiology
Heart Rate (beats/min) \times Stroke Volume (cc/beat) = Cardiac Output (L/min)

Preload \quad Myocardial Contractility \quad Afterload

Cardiac Output
Sympathetic Nervous System

Baroreceptor Reflex

1. Baroreceptors detect changes in arterial pressure
2. Signals sent to the medulla of the brain stem
3. Heart rate adjusted

Heart Rate Contractility Vasoconstriction
Sympathetic Nervous System

Progressive Vasoconstriction:
- Skin
- Muscle
Important Hormones in Shock

**Catecholamines: Epinephrine & Norepinephrine**
- Increased heart rate & contractility
- Vasoconstriction & narrowed pulse pressure

**Renin-Angiotensin Axis: Aldosterone and ADH**
- Water & sodium conservation & vasoconstriction
- Increase in blood volume and blood pressure
- Decreased urine output
Sympathetic Nervous System

- Increased shunting of blood to: **Heart & Brain**
Cellular Response to Shock

- Acidosis
- Blood Loss
- Inadequate Perfusion
- Cellular Hypoxia
- Cellular Edema
- Lactic Acid
- Anaerobic Metabolism
- Aerobic Metabolism
Hemorrhagic Shock

Assessment
Classic Signs & Symptoms of Shock

- Changing mentation
- Tachycardia
- Cool, clammy, skin
- Prolonged capillary refill
- Narrowed pulse pressure
- Decreased urine output
- Hypotension
Normal Vitals do not r/o Hypoperfusion
## ATLS Classification of Hemorrhagic Shock

<table>
<thead>
<tr>
<th></th>
<th>CLASS I</th>
<th>CLASS II</th>
<th>CLASS III</th>
<th>CLASS IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>BloodLoss (ml)</td>
<td>&lt;750 15%</td>
<td>750-1500 15%-30%</td>
<td>1500-2000 30%-40%</td>
<td>&gt;2000 &gt;40%</td>
</tr>
<tr>
<td>%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HR</td>
<td>&lt;100</td>
<td>&gt;100</td>
<td>&gt;120</td>
<td>&gt;140</td>
</tr>
<tr>
<td>BP</td>
<td>normal</td>
<td>normal</td>
<td>decrease</td>
<td>decrease</td>
</tr>
<tr>
<td>PP</td>
<td>normal</td>
<td>decrease</td>
<td>decrease</td>
<td>decrease</td>
</tr>
<tr>
<td>RR</td>
<td>14-20</td>
<td>20-30</td>
<td>30-40</td>
<td>&gt;35</td>
</tr>
<tr>
<td>UOP</td>
<td>&gt;30</td>
<td>20-30</td>
<td>5-15</td>
<td>negligible</td>
</tr>
<tr>
<td>CNS</td>
<td>slightly anxious</td>
<td>mildly anxious</td>
<td>anxious confused</td>
<td>confused lethargic</td>
</tr>
</tbody>
</table>
# Response Fluid Resuscitation

<table>
<thead>
<tr>
<th></th>
<th>Rapid Response</th>
<th>Transient Response</th>
<th>No Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vital Signs</td>
<td>Return to normal</td>
<td>Transient improvement</td>
<td>Remain abnormal</td>
</tr>
<tr>
<td>Estimated Blood Loss</td>
<td>Minimal (10-20%)</td>
<td>Moderate and ongoing (20-40%)</td>
<td>Severe (&gt;40%)</td>
</tr>
<tr>
<td>Need for more IV fluid</td>
<td>Low</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Need for Blood</td>
<td>Low</td>
<td>Moderate</td>
<td>Immediate</td>
</tr>
<tr>
<td>OR</td>
<td>Possibly</td>
<td>Likely</td>
<td>High</td>
</tr>
</tbody>
</table>
Value of Manual Vital Signs

Most Predictive for Need of Life Saving Interventions
BP Estimation from Pulse

• If you can palpate this pulse, you know the SBP is roughly this number
Occult Hypoperfusion

State of ↓ O2 delivery in the setting of grossly normal physiologic criteria

Patients don’t suddenly deteriorate, rather we suddenly notice…
Changing Mentation

• Indicator of perfusion
• Affected by drugs & alcohol
• Hypoxia/Head Injury
  • Until proven otherwise
Skin Perfusion

- Pale, cool, mottled
  - Vasoconstriction
- Most sensitive in pediatrics
  - Starts distal extremities
  - Ascends towards trunk
- Capillary Refill
  - Unreliable to measure
  - Normal < 2 seconds
Blood Pressure

- BP response to volume loss
  - Non-linear due to compensatory mechanisms
  - Insensitive sign of early shock

- NTDB study
  - SBP did not decrease < 90
  - Until base deficit was > 20

- Infrequently & or inadequately monitored
  - First BP should always be manual
  - Automated BP overestimated by 10 mm Hg
Blood Pressure

- Systolic BP drop a late sign
- Systolic BP does not fall until:
  - Adults 30% blood loss
  - Pediatrics 40-45% blood loss
- SBP $\leq$ 90 mm Hg: mortality approaches 65%
Pulse Pressure

- Narrowed pulse pressure suggests significant blood loss

- Result of increasing diastolic pressure from compensatory catecholamine release

100/66  100/74  100/77  100/84
Lacks specificity alone
Age dependent
Affected by:
- Emotion
- Fever
- Pain
- Drugs
Pulse & character together more reliable
Trended over time may have sensitivity
When to be concerned?
80 90 100 110 > 120

Any patient who is cool & tachycardic is in shock until proven otherwise
Relative Bradycardia (Paradoxical Bradycardia)

- Defined as Pulse < 90 with SBP < 90
- Occurs in up to 45% of all hypotensive trauma
- Cause remains unclear:
  - Sign of rapid & severe internal bleeding?
  - Increased vagal tone from blood in abd cavity?
  - Protective reflex designed to increase diastolic filing in the presence of severe hypovolemia?
Hemorrhagic Shock

Treatment
airway... breathing... circulation...
Is There a Shock Position?

- Dr. Friedrich Trendelenburg 1800’s
- To improve surgical exposure - pelvic organs

No Benefit in Shock
Stopping Hemorrhage

**Pelvic Binders**
- Reduce pelvis volume
- Tamponade effect

**Tourniquets**
- Studied extensively in war
- Good outcomes
- Safe and effective
Stopping Hemorrhage

Hemostatic Dressings

- Actions:
  - Direct compression
  - Activation of clotting
  - Adhesion
- Utility
  - Speed of application (under fire)
  - Pliable, Z Fold conformation
IV Access Principles in Shock

- Fastest, simplest route best (antecubital)
- Large bore, short length (14-16 gauge, 2 inch length)
- Flow limited by IV gauge & length *not size of vein*

**Optimally**
- Two different sites
- Two to three sites required per major trauma
- Consider Intraosseous (IO) *early* as rescue device
Avoid IV Access

- Injured limb
- Distal to possible vascular wound
Intraosseous Devices

- Temporary access
- Children & adults
- Insert within 1 minute
- Manual or power drill
- Prox tibia/humerus/sternum
- Avoid fracture /injury sites
- Good for fluid/blood/meds
- Flow rates up to 125 mL/min w pressure bag
- Risk: extravasation → compartment syndrome
IV Placement

- No evidence to support IV placement at scene
- Enroute OK
- Limit 2 attempts → I.O.
- Saline lock/Keep open
- Avoid continuous IV
- Use small boluses (250cc)
- Titrate to palpable radial
Fluid Administration Balance

- **Too little...**
  - Ongoing shock
  - Continued acidosis
  - Coagulopathy
  - Myocardial dysfunction
  - Renal failure
  - Death

- **Too much...**
  - Increased bleeding
  - Clot disruption
  - Dilution coagulation factors
  - Compartment syndromes
  - Transfusion concerns
    - Inflammation
    - Immunosuppression
    - Transfusion Related Acute Lung Injury (TRALI)
If it doesn’t carry oxygen or it doesn’t clot!

Don’t give it to me!
How Does Bleeding Stop?

Three processes occur to stop bleeding:

1. Vasoconstriction
2. Platelet Adhesion
3. Fibrin Clot
Fibrin Clot

Image from www.daviddarling.info
Coagulation

• The process is sometimes characterized as a cascade, because one event prompts the next as in a multi-level waterfall.

• The result is the production of a gelatinous but robust clot made up of a mesh of Fibrin-\textit{a n} insoluble filamentous protein derived from fibrinogen, the plasma protein introduced earlier-in which platelets and blood cells are trapped.
In the coagulation cascade, chemicals called *clotting factors* prompt reactions that activate still more coagulation factors. The process is complex, but is initiated along two basic pathways:

- **The extrinsic pathway**, which normally is triggered by trauma.
- **The intrinsic pathway**, which begins in the bloodstream and is triggered by internal damage to the wall of the vessel.
- Both of these merge into a third pathway, referred to as the **common pathway**.
The three pathways that make up the classical blood coagulation pathway

**Intrinsic**
- surface contact
  - XII → XIIₐ
  - XI → XIₐ
  - IX → IXₐ
- (VIII, PL, Ca++)
  - X → Xₐ
- (V, PL, Ca++)
  - prothrombin → thrombin (serine protease)

**Extrinsic**
- TF: VIIₐ → tissue damage

**Common**
- XII – Hageman factor, a serine protease
- XI – Plasma thromboplastin, antecedent serine protease
- IX – Christmas factor, serine protease
- VII – Stable factor, serine protease
- XIII – Fibrin stabilising factor, a transglutaminase
- PL – Platelet membrane phospholipid
- Ca++ – Calcium ions
- TF – Tissue Factor
  \[ \text{TF} \rightarrow \text{TF:VII}_a \]

- fibrinogen → fibrin
- XIII → XIIIₐ
- stable fibrin clot
Activation of fibrinolysis

- t-PA
- Plasminogen
- Lysine binding site
- Fibrin
- t-PA
- Plasmin

Fibrin degradation products

Panel A

Inhibition of fibrinolysis

- t-PA
- Plasminogen
- Tranexamic acid
- Fibrin
- t-PA
- Plasmin

Panel B
Trauma Associated Hyperfibrinolysis

- Depletion of coagulation factors secondary to blood loss, and consumption
- Dilution due to fluid infusion, >1000ml
- Dysfunction of the remaining coagulation factors due to hypothermia and acidosis
- Severe shock and major tissue trauma are the main drivers of this HF.
- According to visco-elastic testing of trauma patients upon emergency room admission, HF is present in approximately 2.5-7% of all trauma patients.
- Visco-elastic tests provide information on severe forms of HF.
Tissue & Endothelial Injury

T-PA (tissue plasminogen activator)
PAI-1 (plasminogen activator inhibitor)

Antifibrinolytics
Fibrinogen cone.
Cryoprecipitate

In Initial Phase t-PA > PAI-1

Hyperfibrinolysis and Hemorrhagic Shock
Trauma & Trauma Care

- Trauma is one of the leading causes of death amongst people 16-35
  - Roughly 1.3 of trauma related deaths are causes by bleeding
  - Unit now our treatment for trauma patients has been limited
    - Tourniquets
    - Patient position
    - Two IV’s
    - Fluid bolus
Antifibrinolytics

These agents enhance hemostasis when fibrinolysis contributes to bleeding

Lysine analogs

- EACA (e-AminoCaproic acid)
- TXA (Tranexamic acid)
- Aprotinin (No marking since 2007)
What is Tranexamic Acid?

- TXA was created in the 1950’s in Japan by scientists Shosuke and Utako Okamoto.
- TXA is a synthetic derivative of the amino acid lysine.
- TXA is an anti-fibrinolytic that competitively inhibits the activation of plasminogen to plasmin. Plasmin breaks down fibrin.
- TXA may reduce the pro-inflammatory effects of plasmin.
FIBRINOLYSIS

Intact fibrin clot

Fibrin clot exposed to plasmin
TXA in Elective Surgery

- **TXA in elective surgical patients has shown to:**
  - Reduce number patients receiving transfusion by ~1/3
  - Reduce volume of blood transfused by 1 unit
  - Decrease the need for further surgery to control bleeding by 50%

- These results helped lead to the CRASH 2 study.
Bleeding to Death

There are millions of trauma deaths each year. Many patients survive to reach hospital. This slide shows the causes of *in-hospital* trauma deaths.

- **Bleeding**: 45%
- **CNS injury**: 41%
- **Organ failure**: 10%
- **Other**: 4%
Methods

- Over 20,000 bleeding trauma patients were randomly allocated to get tranexamic acid or matching placebo
- Included all adult trauma patients who were within 8 hours of their injury, if their doctor thought that they had or could have significant hemorrhage
- Collected data on death in hospital within 4 weeks of injury and all important side effects
## Trial Dose

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Tranexamic acid dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Loading</strong></td>
<td>1 gram over 10 minutes (by slow intravenous injection or an isotonic intravenous infusion)</td>
</tr>
<tr>
<td><strong>Maintenance</strong></td>
<td>1 gram over 8 hours (in an isotonic intravenous infusion)</td>
</tr>
</tbody>
</table>
Patient enrollment

- 20,211 patients
- from 274 hospitals
- in 40 countries

Randomised many trauma patients
CRASH-2

20,211 randomised

10,096 allocated TXA
3 consent withdrawn
10,093 baseline data
33 lost to follow-up
Followed up = 10,060 (99.7%)

10,115 allocated placebo
1 consent withdrawn
10,114 baseline data
47 lost to follow-up
Followed up = 10,067 (99.5%)
### This is what was found

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>TXA 10,060</th>
<th>Placebo 10,067</th>
<th>Risk of death</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleeding</td>
<td>489</td>
<td>574</td>
<td>0.85 (0.76–0.96)</td>
<td>0.0077</td>
</tr>
<tr>
<td>Thrombosis</td>
<td>33</td>
<td>48</td>
<td>0.69 (0.44–1.07)</td>
<td>0.096</td>
</tr>
<tr>
<td>Organ failure</td>
<td>209</td>
<td>233</td>
<td>0.90 (0.75–1.08)</td>
<td>0.25</td>
</tr>
<tr>
<td>Head injury</td>
<td>603</td>
<td>621</td>
<td>0.97 (0.87–1.08)</td>
<td>0.60</td>
</tr>
<tr>
<td>Other</td>
<td>129</td>
<td>137</td>
<td>0.94 (0.74–1.20)</td>
<td>0.63</td>
</tr>
<tr>
<td>Any Death</td>
<td>1463</td>
<td>1613</td>
<td>0.91 (0.85–0.97)</td>
<td>0.0035</td>
</tr>
</tbody>
</table>
Further Review of Data Showed…

- Acute severe trauma is associated with increased fibrinolysis, leading to early coagulopathy and increased mortality.
- The earlier TXA is given the better, preferably within 3 hours of injury.
- TXA given <1 hr of injury had greatest benefit – 32% reduction in deaths caused by bleeding (5.3% vs 7.7%)
- TXA after 3 hr of injury associated with increased risk of death caused by bleeding (4.4% vs 3.1%): DIC?
Conclusion

- Tranexamic acid…
  - Shown to reduce mortality in bleeding trauma patients
  - Needs to be given within 3 hr of injury; most benefit within 1st hour
  - Easy to administer
  - Is cheap - One dose of TXA ~$40 - $65
  - Is being used in military and civilian mass transfusion protocols
  - Added to the WHO List of Essential Medicines
  - Approved by Jehovah’s Witnesses for use
TXA Indications

- Suspected hemorrhagic shock in a trauma patient with mechanism, AND
  - Adults (Age 18 or greater) with hemorrhagic shock from trauma.
  - Estimated blood loss of 500 mL.
  - Patients who considered to be high risk for significant hemorrhage.
  - Must have obvious bleeding external wounds neck to mid-thigh or suspected severe internal injuries from blunt or penetrating trauma.
  - Trauma occurred within last 3 hours.
  - Must have sustained tachycardia 110 beats per minute and/or sustained hypotension with systolic blood pressure 90 mmHg or less.

*TXA does require a specific set of parameters for use but don't forget to look for early/other signs and symptoms of shock:
  - Poor skin signs
  - Altered level of consciousness
  - Sustained tachycardia

Patients displaying these symptoms could fall into the TXA parameters rather quickly.
Dosing & Storage

- TXA (Cyklokapron) - 1 gm in 100cc/NSS given over 10 minutes (loading dose)

- Followed by 1 gm in 100 cc/NSS over 8 hrs (in the ED)

- Can be mixed with just about any available solution

- Not to be administered in the same line as blood or blood products or in a line used for rFVIIa or Penicillin

- Should be stored between 15-30C or 56-86F
Side Effects

- Acute gastrointestinal disturbances (nausea, vomiting and diarrhea; generally dose-related).
- Visual disturbances (blurry vision and changes in color perception, especially with prolonged use).
- Thromboembolic events (deep venous thrombosis, pulmonary embolism).
- Dizziness, fatigue, headache, and hypersensitivity reaction.
- Seizure
Contraindications

- Non-hemorrhagic shock.
- Any patients under the age of 18 years of age.
- Traumatic arrest with greater than five minutes of CPR, without return of vital signs.
- Penetrating cranial injury.
- Traumatic brain injury with brain matter exposed.
- Isolated drowning or hanging victims.
- Documented cervical cord injury with motor deficit.
- Non-traumatic hemorrhagic shock.
- Hemorrhagic shock stabilized with other hemostatic agents/measures.
- Time since injury exceeds 3 hours.
- Isolated Traumatic Brain injury.
TXA Procedure

- TXA Bolus (IV/IO): Mix 1 gram in 100ml of NS and infuse over 10 minutes before other IV fluids if possible.

- Best if administered in FIRST hour. CONTRAINDIQUATED after 3 hours.

- Document any noted side effects.

- Document time, dose, amount of medication, route of administration and indication for use.

- Document any change in patient physical assessment, clinical presentation and vital signs.
Hemorrhagic Shock

QI
Data Collection - EMS

Each patient who receives TXA will need to have a trailing document completed in addition to our normal PCR's.

The document will be a form of data collection and must contain some baseline characteristics:

- Time of Injury
- Time of first (EMS) of TXA
- Demographics: age, gender, race
- Vital signs:
  - Pre TXA dose, during first dose, post the dose, and every five minutes thereafter until arrival at the hospital
- Heart rate, respiratory rate, body temperature, blood pressure, cap refill
- Glasgow coma scale
- Mechanism of injury
- Area of Injury
- Estimated blood loss
- 12 Lead EKG prior and post infusion (do not delay transport)
YEMSA will collect the following data from the hospitals:

- Time of Second dose
- GCS @ 25hrs & 48hrs
- Estimated blood loss at hospital
- Number of transfused blood products
- Length of stay at hospital
- Use of ventilator
- OR
- Adverse side effects from TXA
- Deceased or discharged
QI

YEMSA will QI 100% all TXA PCR’s

Collect data

- We will gauge morality rate at 24hr, 48hr and 28 days of TXA trauma patients vs. all other trauma patients
- Measuring total amounts of blood products transfused and total blood loss in TXA patients versus all other trauma patients
- Number of adverse events (pulmonary embolism, deep vein thrombosis, seizure)
- PCR data will be linked with the trauma data from the hospitals to monitor outcome

All QI will be presented at the Physician Advisory Committee
Goals

- Prevent hemorrhagic shock
- Prevention of coagulopathy
- Reduction of critical patients in the operating room leading to less surgical intervention
- Reduction of length of stay at the hospital
- Prevention of death due to blood loss