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 intraosseous 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 Alameda County. The purpose of our pilot is to determine the following:

1. Are paramedics in Alameda 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?
REQUEST FOR APPROVAL  
Form #EMSA-0391
Application for Local Trial Study  
Use of Tranexamic Acid by Paramedics for Trauma Patients

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 Alameda 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 7-8 patients per month

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

None.

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 Alameda, with the goal of training for implementation by Fall of 2015.

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

3. Bleeding uncontrolled by direct pressure or tourniquet.  
4. Estimated external blood loss of 500 ml or more in the field

Medical Control:  
Highland Hospital (EMS base hospital and trauma center) will provide medical control.

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 for Alameda County EMS.  
2. We will link ePCR data to the Alameda County trauma registry to monitor outcomes and adverse events.  
3. We have letters of commitment from our Trauma Surgeons to report serious adverse events to Alameda County EMS within 48 hours.  
4. Once per month all TXA cases will be reviewed by EMS leadership to screen for safety or fallout issues.

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. And attachment E for the post-test.

8. Copy of the local EMS System Evaluation and Quality Improvement Program plan for this request:  
See Attachment C
REQUEST FOR APPROVAL
Form #EMSA-0391
Application for Local Trial Study
Use of Tranexamic Acid by Paramedics for Trauma Patients

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 effects 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 staff (site investigators and trial coordinating centre staff) 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. Every year, more than a million people die as a result of road traffic injuries around the world. Road traffic 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. Haemorrhage is responsible for about a third of in-hospital trauma deaths and can also contribute to deaths from multiorgan failure.

The haemostatic system helps to maintain circulation after severe vascular injury, whether traumatic or surgical in origin. 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 (hyperfibrinolysis) in some cases. 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.

Tranexamic acid is a synthetic derivative of the aminoacid lysine that inhibits fibrinolysis by blocking the lysine binding sites on plasminogen. A systematic review of the randomised trials of tranexamic acid in patients undergoing elective surgery identified 53 studies including 3836 participants. 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). Because the haemostatic responses to surgery and trauma are similar, 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. We assessed the effects 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 with 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 staff (site investigators and trial coordinating centre staff) 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, Cardiff, 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.10

We planned to report the effects 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 20000 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 99% CIs with 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 99% CIs with 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 99% CIs with two-sided p values for statistical significance.

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. 20 211 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 differed 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 20127 (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.

See Online for webappendix
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 effect 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 differ significantly in the tranexamic acid group versus the placebo group (table 2).

Vascular occlusive events (fatal or non-fatal) did not differ significantly, 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 VIIa (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 classified 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 prespecified that unless there was strong evidence (p<0.001) against homogeneity of effects, 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 prespecified 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 figures to round to specific digits) the number of patients in the early category (<1 h) was low and the subgroup estimate was imprecise. We therefore (post hoc) defined the early category as those treated less than or equal to 1 h from injury (figure 3).

Table 1: Baseline data of participants

<table>
<thead>
<tr>
<th>Sex</th>
<th>Tranexamic acid (n=10093)</th>
<th>Placebo (n=10114)</th>
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</thead>
<tbody>
<tr>
<td>Men</td>
<td>8439 (83.5%)</td>
<td>8496 (84.0%)</td>
</tr>
<tr>
<td>Women</td>
<td>1654 (16.4%)</td>
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<th>Age (years)</th>
<th>Mean (SD)</th>
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<tr>
<td>&lt;25†</td>
<td>34.6 (14.1)</td>
<td>34.5 (14.4)</td>
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</tr>
<tr>
<td>25–34</td>
<td>3012 (29.8%)</td>
<td>3081 (30.5%)</td>
<td></td>
</tr>
<tr>
<td>35–44</td>
<td>1975 (19.6%)</td>
<td>1841 (18.2%)</td>
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</tr>
<tr>
<td>&gt;44</td>
<td>2321 (23.0%)</td>
<td>2335 (23.1%)</td>
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<tr>
<td>Not known</td>
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<th>Time since injury (h)</th>
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<td>&lt;1</td>
<td>2.8 (2.2)</td>
<td>2.9 (2.6)</td>
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<tr>
<td>1–3</td>
<td>3.75 (37.2%)</td>
<td>3.72 (38.6%)</td>
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<tr>
<td>&gt;3</td>
<td>3.045 (30.2%)</td>
<td>3.006 (29.7%)</td>
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<td>&gt;5</td>
<td>3.287 (32.6%)</td>
<td>3.380 (33.4%)</td>
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<tr>
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<td>6 (0.06%)</td>
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<th>Type of injury</th>
<th>Mean (SD)</th>
<th>Tranexamic acid (n=10093)</th>
<th>Placebo (n=10114)</th>
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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>
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<td>&lt;75</td>
<td>1566 (15.5%)</td>
<td>1608 (15.9%)</td>
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<tr>
<td>76–89</td>
<td>1615 (16.0%)</td>
<td>1697 (16.8%)</td>
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<td>90–109</td>
<td>6901 (68.4%)</td>
<td>6791 (67.1%)</td>
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<tr>
<td>Not known</td>
<td>11 (0.11%)</td>
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<th>Respiratory rate (per min)</th>
<th>Mean (SD)</th>
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<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>&gt;29</td>
<td>1491 (14.8%)</td>
<td>1429 (14.1%)</td>
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<tr>
<td>Not known</td>
<td>87 (0.86%)</td>
<td>100 (0.99%)</td>
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<th>Central capillary refill time (s)</th>
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<td>&lt;2</td>
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<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>
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</tr>
<tr>
<td>Not known</td>
<td>297 (2.9%)</td>
<td>314 (3.3%)</td>
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<tr>
<th>Heart rate (beats per min)</th>
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<td>&lt;77</td>
<td>875 (8.7%)</td>
<td>871 (8.6%)</td>
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<tr>
<td>78–91</td>
<td>1277 (17.1%)</td>
<td>1270 (17.5%)</td>
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<tr>
<td>92–107</td>
<td>2556 (25.3%)</td>
<td>2546 (25.2%)</td>
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</tr>
<tr>
<td>&gt;107</td>
<td>4872 (48.3%)</td>
<td>4853 (48.0%)</td>
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<tr>
<td>Not known</td>
<td>63 (0.62%)</td>
<td>74 (0.73%)</td>
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<th>Glasgow Coma Score (total)</th>
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<th>Placebo (n=10114)</th>
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<tbody>
<tr>
<td>Severe (3–8)</td>
<td>1799 (17.8%)</td>
<td>1839 (18.2%)</td>
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<tr>
<td>Moderate (9–12)</td>
<td>1353 (13.4%)</td>
<td>1351 (13.4%)</td>
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</tr>
<tr>
<td>Mild (13–15)</td>
<td>6934 (68.7%)</td>
<td>6908 (68.3%)</td>
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<tr>
<td>Not known</td>
<td>7 (0.07%)</td>
<td>16 (0.16%)</td>
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<table>
<thead>
<tr>
<th>Any protocol violation</th>
<th>Mean (SD)</th>
<th>Tranexamic acid (n=10093)</th>
<th>Placebo (n=10114)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;7</td>
<td>39 (0.4%)</td>
<td>39 (0.4%)</td>
<td></td>
</tr>
</tbody>
</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 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 with no apparent increase in fatal or non-fatal vascular occlusive events. All-cause mortality was significantly reduced with tranexamic acid.

Figure 2: Mortality by days from randomisation

Table 2: Death by cause

Data are number (%), unless otherwise indicated. RR=relative risk. *Includes myocardial infarction, stroke, and pulmonary embolism.

<table>
<thead>
<tr>
<th>Death by cause</th>
<th>Tranexamic acid (n=10 060)</th>
<th>Placebo (n=10 067)</th>
<th>RR (95% CI)</th>
<th>p value (two-sided)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any cause of death</td>
<td>1463 (14.5%)</td>
<td>1613 (16.0%)</td>
<td>0.91 (0.85–0.97)</td>
<td>0.0035</td>
</tr>
<tr>
<td>Bleeding</td>
<td>489 (4.9%)</td>
<td>574 (5.7%)</td>
<td>0.85 (0.76–0.96)</td>
<td>0.0077</td>
</tr>
<tr>
<td>Vascular occlusion*</td>
<td>33 (0.3%)</td>
<td>48 (0.5%)</td>
<td>0.69 (0.44–1.07)</td>
<td>0.096</td>
</tr>
<tr>
<td>Multiorgan failure</td>
<td>209 (2.1%)</td>
<td>233 (2.3%)</td>
<td>0.90 (0.75–1.08)</td>
<td>0.25</td>
</tr>
<tr>
<td>Head injury</td>
<td>603 (6.0%)</td>
<td>621 (6.2%)</td>
<td>0.97 (0.87–1.08)</td>
<td>0.60</td>
</tr>
<tr>
<td>Other causes</td>
<td>129 (1.3%)</td>
<td>137 (1.4%)</td>
<td>0.94 (0.74–1.20)</td>
<td>0.61</td>
</tr>
</tbody>
</table>

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 difficulty of accurate 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...
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.

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. 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. 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. 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
haemorrhage is a leading cause of maternal mortality, accounting for about 100,000 maternal deaths every year. 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 effect of tranexamic acid on endpoints that are important to women. A large trial is being undertaken to assess the effect of tranexamic acid on the risk of death and hysterectomy in women with post-partum haemorrhage.

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.

CRASH-2 trial collaboration

**CRASH-2 trial coordination**

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Articles

2 Gosselin RA, Spiegel DA, Coughlin R, Zirkled LG. Injuries: the references those of the authors and do not necessarily reflect those of the Department of Health.

References


Online First

Military Application of Tranexamic 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 tranexamic 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; \(P=0.03\)) 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.1,2 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.3-5 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.6 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.7 Tranexamic acid is a lysine analog that occupies binding sites on the plasminogen molecule, inhibiting fibrinolysis. It has an established safety and efficacy profile,8-12 and its primary effect of inhibition of clot breakdown portends a favorable effect on patients with hemorrhage from vascular disruption.7,13 Because plasmin is known to have proinflammatory effects, other beneficial effects have been suggested.14-16 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>
<thead>
<tr>
<th>Table 1. Demographic Data, Mechanism of Injury, Injury Severity, Physiology, and Transfusion Requirement for Overall and Massive Transfusion Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Variable</strong></td>
</tr>
<tr>
<td><strong>TXA</strong> (&lt;n=293&gt;)</td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td>Demographic data</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
</tr>
<tr>
<td>Male, %</td>
</tr>
<tr>
<td>Host national, No. (%)</td>
</tr>
<tr>
<td>NATO military</td>
</tr>
<tr>
<td>Mechanism of injury, %</td>
</tr>
<tr>
<td>GSW</td>
</tr>
<tr>
<td>Explosion</td>
</tr>
<tr>
<td>Injury severity</td>
</tr>
<tr>
<td>ISS, mean (SD)</td>
</tr>
<tr>
<td>AIS score ≥3, %</td>
</tr>
<tr>
<td>Head</td>
</tr>
<tr>
<td>Chest</td>
</tr>
<tr>
<td>Abdomen</td>
</tr>
<tr>
<td>Extremity</td>
</tr>
<tr>
<td>RTS, mean (SD)</td>
</tr>
<tr>
<td>Admission physiology, %</td>
</tr>
<tr>
<td>GCS score ≤8</td>
</tr>
<tr>
<td>SBP ≤90 mm Hg</td>
</tr>
<tr>
<td>24-h Transfusion, mean (SD), units</td>
</tr>
<tr>
<td>PRBCs</td>
</tr>
<tr>
<td>FFP</td>
</tr>
<tr>
<td>Platelets</td>
</tr>
<tr>
<td>Cryoprecipitate</td>
</tr>
<tr>
<td>Miscellaneous</td>
</tr>
<tr>
<td>Time in ED, mean (SD), min</td>
</tr>
<tr>
<td>Time in OR, mean (SD), min</td>
</tr>
<tr>
<td>Lowest body temperature, mean (SD), °C</td>
</tr>
<tr>
<td>Pulmonary embolism, No. (%)</td>
</tr>
<tr>
<td>Deep venous thrombosis, No. (%)</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 as 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 admission (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 \( \chi^2 \) 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 (\( \leq 8 \) vs >8), SBP (\( \leq 90 \) vs >90 mm Hg), ISS (\( >15 \) vs \( \leq 15 \)), and body region AIS scores (\( \geq 3 \) vs <3). The following parameters were analyzed with univariate analysis for inhospital mortality: sex, nation 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 (\( P < .15 \)) 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 \( P < .05 \) 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\(^{MT} \) vs no-TXA\(^{MT} \)) 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\(^{MT} \) 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\(^{MT} \) 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\(^{MT} \) and no-TXA\(^{MT} \) groups with the exception of cryoprecipitate. The PRBC:FFP ratio in the TXA\(^{MT} \) and no-TXA\(^{MT} \) groups 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\(^{MT} \) group had a higher rate of PTE compared with the no-TXA\(^{MT} \) 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-
creased 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*MT 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 = .02), abdominal 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), 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).

Table 2. All-Cause Mortality of Overall and Massive Transfusion Groups Within 24 Hours, Within 48 Hours, and In-Hospital Mortality

<table>
<thead>
<tr>
<th>End Point</th>
<th>Total No. of Patients in Follow-up (Mortality, %)</th>
<th>TXA</th>
<th>No TXA</th>
<th>P Value&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;24 h</td>
<td></td>
<td>293</td>
<td>603</td>
<td>12.4 (9.6)</td>
</tr>
<tr>
<td>&lt;48 h</td>
<td></td>
<td>264</td>
<td>507</td>
<td>18.9 (11.3)</td>
</tr>
<tr>
<td>In-hospital mortality&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td>264</td>
<td>603</td>
<td>23.9 (17.4)</td>
</tr>
<tr>
<td>Massive transfusion</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;24 h</td>
<td></td>
<td>125</td>
<td>196</td>
<td>14.8 (9.6)</td>
</tr>
<tr>
<td>&lt;48 h</td>
<td></td>
<td>112</td>
<td>160</td>
<td>23.5 (10.4)</td>
</tr>
<tr>
<td>In-hospital mortality&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td>125</td>
<td>196</td>
<td>28.1 (14.4)</td>
</tr>
</tbody>
</table>

Abbreviation: TXA, tranexamic acid.
<sup>a</sup>Statistically significant values (P < .05) are bold.
<sup>b</sup>Mean (SD) follow-up, 15 (13) days.
<sup>c</sup>Mean (SD) follow-up, 16 (13) days.

Table 3. Factors Associated With Survival Following Multivariate Analysis of the Overall Group and the Massive Transfusion Group

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Odds Ratio (95% CI)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>P Value&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GCS score ≤ 8</td>
<td>0.304 (0.108-0.860)</td>
<td>.02</td>
</tr>
<tr>
<td>Hypotension</td>
<td>0.303 (0.107-0.855)</td>
<td>.02</td>
</tr>
<tr>
<td>Coagulopathy at admission</td>
<td>0.291 (0.113-0.749)</td>
<td>.01</td>
</tr>
<tr>
<td>Massive transfusion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GCS score ≤ 8</td>
<td>0.027 (0.008-0.085)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>ISS &gt; 15</td>
<td>0.359 (0.123-1.053)</td>
<td>.06</td>
</tr>
<tr>
<td>TXA</td>
<td>7.228 (3.016-17.322)</td>
<td>&lt; .001</td>
</tr>
</tbody>
</table>

Abbreviations: GCS, Glasgow Coma Scale; ISS, Injury Severity Score; TXA, tranexamic acid.
<sup>a</sup>Wald 95% CIs for odds ratios are used.
<sup>b</sup>Statistically significant values (P < .05) are bold.

Figure 3. Kaplan-Meier survival curve of the overall cohort, including patients receiving tranexamic acid (TXA) vs no TXA. P = .006, Mantel-Cox log-rank test.
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.\(^7\) 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.\(^7\) 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.

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.\(^7\)

The timing and magnitude of survival benefit of TXA in 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 primary 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\(^{15}\) 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.\(^15\) As one of several studies that have shown reduced bleeding and transfusion requirements with TXA in cardiac surgery,\(^{21-23}\) Casati et al\(^{13}\) 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.\(^24-27\) 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.
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. This benefit is present in all who receive blood transfusions following combat injury at a combat support hospital. J Trauma. 2007;63(4):805-813.


Development, Concepts and Doctrine Centre. Transfusion medicine leaflet 2-24-1:

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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


15. Development, Concepts and Doctrine Centre. Transfusion medicine leaflet 2-24-1:

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 exploratory analysis of the CRASH-2 randomised controlled trial 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 randomisation. Despite these challenges, the study successfully highlighted the lack of standardized indications and dosing used during 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.

Kenji Inaba, MD

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Financial Disclosure: None reported.


18. Fresh-Frozen Plasma, Cryoprecipitate, and Platelets Administration Practice Guide-
ATTACHMENT B – DRAFT PROTOCOLS
TRAUMA PATIENT CARE

• **Routine Medical Care**
  - Control major external hemorrhage (see page 126)
  - Control the Airway - Consider **endotracheal intubation or supraglottic airway device if indicated** (See below for patients with closed head trauma)
  - Determine patient severity (see “Trauma Patient Criteria” - see page 24):
    - Meets Physiologic and/or Anatomic Factors
    - Meets Mechanism of Injury Criteria

<table>
<thead>
<tr>
<th></th>
<th>Meets Physiologic and/or Anatomic Factors</th>
<th>Meets Mechanism of Injury Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>➤ Transport to the Trauma Center</td>
<td>➤ Transport to the Trauma Center Code 2.</td>
<td>➤ ADULT/PEDIATRIC - Establish one (1) large bore IV/IO with Normal Saline (NS) or Saline Lock (SL).</td>
</tr>
<tr>
<td>➤ ADULT - Establish one (1) large bore IV/IO with Normal Saline (NS) or Saline Lock (SL). Establish 2nd IV if appropriate.</td>
<td>➤ ADULT/PEDIATRIC - Establish one (1) large bore IV/IO with Normal Saline (NS) or Saline Lock (SL).</td>
<td></td>
</tr>
<tr>
<td>➤ PEDIATRIC - Establish one (1) appropriate large bore IV/IO with Normal Saline (NS) or Saline Lock (SL).</td>
<td>➤ PEDIATRIC - Establish one (1) appropriate large bore IV/IO with Normal Saline (NS) or Saline Lock (SL).</td>
<td></td>
</tr>
</tbody>
</table>

Do NOT delay transport to establish IV/IO access
See “Trauma Patient Criteria” (page 24) for additional judgment decisions on code 2 transports

• Consider spinal motion restriction (SMR) for blunt trauma (see page 136)
• Administer **Oxygen** - Titrate SpO₂ to 94-99%
• **IV fluid resuscitation:**
  - SBP < 90 mmHg, Consider TXA - 1gm (see page xxx) NS IV/IO 250 – 500ml bolus
  - > 90 mmHg, IV/IO TKO or Saline Lock
  - Reassess BP q 5 minutes

• **Care of the patient with a closed head injury** (GCS < 8):
  - **Advanced airway (ETT or King-LTD)**
  - End-tidal CO₂ should be between 30-35 mmHg
  - Track respirations or ventilate to a rate of approx 12 times/minute with 100% O₂ (AVOID HYPERVENTILATION)
  - **IV/IO** NS in 500 mL increments to **maintain mean arterial pressure (MAP) of at least 80 mmHg**. Reassess BP q 5 minutes

**IMPORTANT CONSIDERATIONS**
- Contact the Base Hospital, if appropriate
- Contact the Trauma Center, as soon as possible
- Consider pain management when appropriate
- Splint fractures and dress wounds ONLY if time permits

FORMULA FOR ESTIMATING MAP

\[
\text{MAP} = \text{diastolic} + \frac{(\text{systolic} - \text{diastolic})}{3}
\]
TRANEXAMIC ACID

1. INTRODUCTION: Tranexamic Acid (TXA) 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.

2. INDICATIONS:

2.1 Adults, age > 15 years old

2.2 Patient meets one or more of the following criteria:
   - Blunt or penetrating trauma with signs and symptoms of hemorrhagic shock including SBP < 90 mmHg
   - Major amputation of any extremity, proximal to wrist or ankle.
   - Bleeding uncontrolled by direct pressure or tourniquet.
   - Estimated external blood loss of 500 ml or more in the field

2.3 < 3 hours from time of injury

3. CONTRAINDICATIONS:

3.1 Age ≤ 14 years old

3.2 Time of injury > 3 hours prior to administration (If time of injury is uncertain but not likely to be much more than 3 hours it is appropriate to administer TXA.)

3.3 Known hypersensitivity to TXA

4. ADMINISTRATION:

4.1 Administer TXA 1 gram in 100ml NS IV/IO over 10 minutes (NOT IV push)

4.2 Follow IV fluid resuscitation guidelines on page 23, “Trauma Patient Care”

5. ADVERSE EFFECTS

5.1 Thromboembolism (DVT and pulmonary embolism)

5.2 Gastrointestinal effects including nausea, vomiting, diarrhea

5.3 Headache

5.4 Fatigue

5.5 Dizziness

5.6 Visual Disturbance
ATTACHMENT C – EMS QI PLAN AND LETTERS OF SUPPORT
EMS CQI Plan

Study Participants and QI Leaders

1. Alameda County EMS
   • Karl Sporer, MD, Medical Director
   • Michelle Voos, EMT-P, Trauma Coordinator
   • Joshua English, EMT-P, PHCC
   • Brian Savino, MD, EMS Fellow

2. Oakland Fire Department
   • Gene Hern, MD, Medical Director

3. Highland Hospital
   • Gregory Victorino, MD, Trauma Director

4. Eden Hospital
   • Saba Azimi, MD, Trauma Director

5. Paramedics Plus, Alameda County
   • Senai Kidane, MD, Medical Director

Description of Study Participant Roles:

1. Alameda County EMS along with Gene Hern, Oakland Fire: Will form a TXA committee that will meet monthly to review all cases in Alameda County. This committee will compile a formal report to give to the EMS Commission 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. Paramedics plus 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. Alameda 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
EMS CQI Plan

- 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 Alameda County and continually monitored by Alameda 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 and linked data with the county wide trauma registry.

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.
EMS CQI Plan

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 Alameda 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 Alameda 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 Alameda County EMS
November 14, 2014

Karl Sporer, MD
EMS Medical Director
Alameda County
Emergency Medical Services
1000 San Leandro Blvd, Suite 200
San Leandro, CA 94577

Dear Dr. Sporer and Members of the Scope of Practice Committee:

As a Trauma surgeon and Trauma Director in Alameda County, I am writing to affirm my support for the implementation of prehospital use of tranexamic acid, (TXA) in severely injured trauma patients in our county. We are committed to providing state of the art care to our patients and recent large, multi-center trials have shown a mortality benefit with early administration of this medication. This makes TXA an ideal candidate for prehospital use.

For my part, I am committing our institution to continue the administration of TXA when trauma patients arrive at our facility if it is determined that it is indicated. I am also committed to reporting any severe adverse events that could possibly be associated with this medication to Alameda County EMS agency within 48 hours of occurrence.

I am looking forward to working closely with Alameda County EMS in implementing this potentially lifesaving new medication protocol.

Sincerely,

[Signature]

Gregory P Victorino, MD
UCSF – East Bay, Department of Surgery
Associate Professor of Surgery
Chief, Division of Trauma
Alameda Health System-Highland Hospital
Nov 14, 2014

Ken Miller, MD, PhD
Chair, EMDAC Scope of Practice Committee
405 West Fifth Street #301A
Santa Ana, CA 92701

Dear Dr. Miller and Members of the Scope of Practice Committee,

As a Trauma surgeon and Trauma Director at Eden Hospital, a Level 2 Trauma Center, I am writing to affirm my support for the implementation of prehospital use of tranexamic acid, or TXA, in severely injured trauma patients in our county. We are committed to providing state of the art care to our patients and recent large, multi-center trials have shown a mortality benefit with early administration of this medication. This makes TXA an ideal candidate for prehospital use.

For my part, I am committing our institution to continue the infusion of TXA when trauma patients arrive at our facility and it is determined that the patient meets criteria. I am also committed to reporting any severe adverse events that could possibly be associated with this medication to Alameda County EMS agency within 48 hours of occurrence.

I am looking forward to working closely with Alameda County EMS in implementing this potentially lifesaving new medication protocol.

Sincerely,

Moor Saba Azimi MD, FACS
Director of Trauma and Acute Care Surgery
Eden Medical Center
ATTACHMENT D – TRAINING MATERIALS
TXA Trial Study

Education
December 15, 2014
Acknowledgment

- Thank you to ICEMA for sharing training materials
Goals & Objectives

At the end of this presentation, participants will be able to:

• Discuss basic clotting physiology
• Tranexamic Acid (TXA), Evidence-based medicine
• State the indications for the TXA administration.
• State the contraindications to TXA administration
• State the EMS ePCR documentation requirements
Coagulopathy that is frequently encountered in hemorrhagic shock has been shown to be an independent risk factor for death after trauma.

Platelets In Fibrin Mesh
Three steps to achieve Hemostasis

- Vascular Spasm
- Formation of the Platelet Plug
- Coagulation – Our Focus
Primary hemostasis: Vasoconstriction & Plug Formation

1. Exposed collagen binds and activates platelets.
2. Release of platelet factors
3. Attracts more platelets
4. Aggregate into platelet plug

Diagram:
- Lumen of blood vessel
- Intact endothelium
- Smooth muscle cells
- Collagen in subendothelial layer
- Exposed collagen in damaged blood vessel wall
- Prevents platelet adhesion
- Releases prostacyclin and NO
- EGF
1. Injury to lining of blood vessel exposes connective tissue; platelets adhere

2. Platelet plug forms

3. Fibrin clot with trapped cells

Collagen fibers

Platelet releases chemicals that make nearby platelets sticky

Platelet plug

Fibrin

Clotting factors from:
- Platelets
- Damaged cells
- Plasma (factors include calcium, vitamin K)

Prothrombin → Thrombin

Fibrinogen → Fibrin
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—an insoluble filamentous protein derived from fibrinogen, the plasma protein introduced earlier—in which platelets and blood cells are trapped.
Clotting Factors Involved in Coagulation

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**.
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 only.
Hyperfibrinolysis at admission is an uncommon but highly lethal event associated with shock and prehospital fluid administration.

Tissue & Endothelial injury

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

Antifibrinolytics
Fibrinogen conc.
Cryoprecipitate

In Initial Phase t-PA > PAI-1

Hyperfibrinolysis and Hemorrhagic Shock
Antifibrinolytics

- These agents enhance hemostasis when fibrinolysis contributes to bleeding
- Lysine analogs
  * EACA (e-AminoCaproic acid)
  * TXA (Tranexamic acid)
  * Aprotinin (No marking since 2007)
Mechanism of Action

• A synthetic derivative of lysine that inhibits fibrinolysis by blocking the lysine binding sites on plasminogen
• Inhibits both Plasminogen activation and Plasmin activity thus preventing clot breakdown.
• 10x more potent than Aminocaproic acid in vitro.
TXA

Prothrombin → Thrombin → Fibrin monomers → Fibrin polymers → Factor XIII → Factor XIIIa → Cross-linked Fibrin (Stable Clot) → Plasminogen → Plasmin → Fibrin degradation products
TXA

- Is useful in a wide range of hemorrhagic conditions.
- In large, randomized controlled trials, significantly reduced perioperative blood loss compared with placebo in a variety of surgical procedures, including cardiac surgery with or without cardiopulmonary bypass, total hip and knee replacement and prostatectomy, gynecological procedures.
FIBRINOLYSIS

Intact fibrin clot

Fibrin clot exposed to plasmin
Dosing/Storage

- TXA (Cyklokapron) – 1gm in 100cc/NSS given over 10 minutes (loading dose)
  - Followed by 1gm in 100cc/NSS over 8 hrs
- 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

- Acquired defective color vision
- SAH
- Active intravascular clotting
- Hypersensitivity to TXA
Jehovahs Witnesses – approved

- Desmopressin (DDAVP)
- e-aminocaproic acid (Amicar)
- **Tranexamic acid (Cyklokapron)**
- Vasopressin (Pitressin)
- Aprotinin (Trasylol)
- Vincristine (Oncovin)
- Conjugated estrogens
- Vitamin K (Phylonadione)
- Recombinant Factor VIIa (NiaStase)
- Recombinant Factor IX (BeneFIX)
Oakland Fire Dept and Alameda City in conjunction with Alameda County EMS will be involved in a trial study in preparation for county wide implementation of prehospital TXA administration.
### Trauma and Trauma Care

- Trauma is one of the leading causes of death amongst people 16–35.
- Roughly 1/3 of all trauma related deaths are caused by bleeding

- Until now our treatment for trauma patients has been limited.
  - Tourniquets
  - Patient positioning
  - Direct pressure
  - Two IV’s with boluses of LR or NS.
Ineffectiveness in trauma care:

- All trauma patients get two large bore IV’s and fluid resuscitation!!!
  - Why?
  - Too much fluid can dilute coagulation factors.
  - It increases mean arterial pressure which can dislodge clots and cause hypothermia.
  - Fluid resuscitation is inefficient and dangerous for the patient.
- And what about those patients with internal hemorrhage?
  - We don’t carry a tourniquet for that.
What is the next step in Trauma care?

- Tranexamic Acid or TXA
- TXA is a medication introduced in the 1970’s which promotes vascular clotting.
- Studies show that early administration of TXA increases the patients survivability rate by reducing blood loss along with decreasing the amount of transfused blood products in trauma patients.
TXA Trial Study

Study Drug:

- Tranexamic acid
Tranexamic Acid or TXA is an antifibrinolytic that competitively inhibits the activation of plasminogen to plasmin. Plasmin is a molecule responsible for the degradation of fibrin, the protein that forms the framework of blood clots.

TXA is a synthetic medication void of any blood products. i.e. should have no religious objections to use.
Common Uses

- Hospital Settings to minimize blood loss.
- Dental Offices to control oral bleeding
- Treatment via oral tablet for heavy menstrual periods.
- Surgeries with high risk of blood loss such as cardiac, liver, vascular and large orthopedic procedures.
New Studies
CRASH2 and MATTERS

- CRASH2: Clinical Randomization of Antifibrinolytic in Significant Hemorrhage–2
  - CRASH2 is a study introduced in 40 countries and 274 hospitals around the world
    - It involved 20,000 randomized trauma patients considered hemodynamically unstable
    - Determined by GCS, Systolic BP below 90 and type of injury
Half of the 20,000 were treated with TXA
The TXA patients showed a 32% decrease in mortality Rate due to death by bleeding when given under 1 hour from time of trauma
TXA showed a 21% decrease in mortality when given to patients in under 3 hours
Adversely, there is a 30% increase in mortality when the medication is given after the 3 hour mark
MATTERS: Military Application of Tranexamic Acid in Trauma Emergency Resuscitation

- Matters was a military study done on 1,000 patients injured in combat.
  - Just as in the CRASH2 half the patients were administered TXA at random.
  - The results were roughly the same. The TXA patients showed a 30% decrease in mortality rate.
  - In patients who received a large volume blood transfusion (10 units or more,) the mortality rate decreased by 50%.
The military currently uses TXA to treat combat patients.
The military considers TXA a class 1a drug and uses it prior to fluids.

Final Conclusion?
Both studies showed the EARLIER you give TXA the greater the survivability rate becomes.

TXA SAVES LIVES!
Alameda County and the State of California have approved a trial study for TXA in the anticipation of likely county-wide implementation.

We will be administering TXA in the pre-hospital setting to trauma patients meeting a specific criteria

Other counties are also implementing new trauma protocols that include TXA.
What do we hope to accomplish?

- The prevention of 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
What is the criteria for administering TXA?
- Adults, age > 15 years old
- < 3 hours from time of injury
- TXA should be considered for any trauma patient exhibiting signs and symptoms of hemorrhagic shock:
  - Blunt or penetrating trauma with signs and symptoms of hemorrhagic shock including systolic blood pressure less than 90mmHG.
  - Estimated blood loss of 500 milliliters in the field.
  - Bleeding not controlled by direct pressure or tourniquet.
  - Major amputation of any extremity, proximal to wrist or ankle.
Paramedic considerations:

- 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.
What would exclude patients from receiving TXA?

- Any Patient under 15 years of age.
- Any patient with an active thromboembolic event (within the last 24 hours ) – i.e. active stroke, myocardial infarction or pulmonary embolism.
- Any patient with a hypersensitivity anaphylactic reaction to TXA
- Any patient more than three hours post injury
TXA Procedure

- TXA administration and route
  - TXA is typically given twice – once as a loading dose and then as a sustained infusion.
  - Our focus is the first, loading dose, which will be given by the pre-hospital providers.
  - The first dose by the EMS (1gm in 100cc’s of NS)
  - The first dose should be given as soon as possible but no later than three hours after injury!
  - The second dose will be given by the trauma surgeons at either Highland or Eden hospitals.
TXA administration continued

- TXA is supplied in 1000mg ampoules in 10mL of normal saline.
- TXA will be administered via IV or IO.
- The first dose: 1gm mixed in a 100mL bag of NS and administered as a drip over 10 minutes.
- Any patient with a GCS of 15 requires verbal consent, all patients with GCS of ≤14 shall fall under implied consent
TXA Procedure

- TXA administration continued
  - It should not be administered through same line as blood products.
  - DO NOT administer as IV push, this could cause hypotension.
  - The drug must be stored at 59–86 degrees Fahrenheit
  - All TXA patients must be transported to a designated trauma center.
  - It MUST be reported to the receiving TRAUMA SURGEON OR ER ATTENDING that the patient received TXA in the field.
Data Collection:

- 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) and second (ARMC) dose of TXA
  - Demographics: age, gender, race
  - Vital signs: five sets (pre-hospital, during first dose, post drip, during second dose, post second dose.)
    - Heart rate, respiratory rate, body temperature, blood pressure, cap refill
Data Collection Continued:

- Baseline characteristics continued:
  - Glasgow coma scale (pre treatment, 24 hours, 48 hours)
    - \( \leq 8, 9-12, 13-15 \)
  - Mechanism of injury
  - Area of Injury
  - Estimated blood loss
    - This will be a combination of EMS and Hospital tallied blood loss
Data collection continued:

- 12 lead EKG prior and post first infusion. (Do not delay transport or infusion due to 12 lead)
- Number of transfused blood products
- Length of stay at hospital, use of ventilator?
- Adverse side effects i.e. deep vein thrombosis, pulmonary embolisms, seizures
Statistical Analysis:

- Once implemented in Oakland and Alameda City, we expect to administer TXA 7–8 times per month, with the number increasing significantly with county wide roll out.
- We will gauge the mortality rate at 24hrs, 48hrs and 28 days of TXA trauma patients verses all other trauma patients.
- We will also be measuring total amount of blood products transfused and total blood loss in TXA patients verses all other trauma patients.
- Analysis will also include the number of adverse events occurred. i.e. pulmonary embolisms, deep vein thrombosis.
Quality Improvement:

- 100% completion of documentation is necessary for this study to be effective.
- Our QI team will follow up with every patient involved in the TXA study and review every document submitted.
- We must maintain 100% compliance to garner the best and most true results.
- ePCR data will be linked with the trauma registry to monitor outcome data.
REQUIRED DATA ELEMENTS TO BE ENTERED IN THE FIELD
Data Collection

- The success of this trial study depends on the accuracy of pre-hospital and hospital data collection. The following are REQUIRED data elements that are necessary for outcome tracking.
Pre–Hospital Data Collection

- Date and Time of Incident
- Incident Number
- Primary Impression
- Mechanism of Injury
- Patient Age
- Weight
- Gender
Pre-Hospital Data Collection

- Time of Injury
- Dose and Time of TXA administration
- Pre and Post TXA vital signs
- Narrative Details