REQUEST FOR APPROVAL

Check One: ☐ **Local Optional Scope of Practice** ☒ **Trial Study**

EMS Medical Director: Reza Vaezazizi, MD **Date:** 09/09/14

Local EMS Agency: Inland Counties EMS Agency (ICEMA)

Proposed Procedure or Medication: TXA Use in Trauma Patients by Paramedics in the Prehospital Setting.

Please provide the following information. For information provided, check "yes" and describe. For information not provided, check "no" and state the reason it is not provided.

Please see attached documents.

Yes	No	
☒	☐	**1. Description of the procedure or medication requested:**
☒	☐	**2. Description of the medical conditions for which the procedure/medication will be utilized:**
☒	☐	**3. Alternatives (Please describe any alternate therapy[ies] considered for the same conditions and any advantages and disadvantages):**
☒	☐	**4. An estimate of frequency of utilization:**
☐	☒	**5. Other factors or exceptional circumstances:**

Please attach the following documents. Check "yes" for each document attached; for documents not attached, check "no" and state the reason it is not attached.

Yes	No	
☒	☐	**6. Any supporting data, including relevant studies and medical literature.**
		7. Recommended policies/procedures to be instituted regarding:
☒	☐	**Use**
☒	☐	**Medical Control**
☒	☐	**Treatment Protocols**
☒	☐	**Quality assurance of the procedure or medication**
☒	☐	**8. Description of the training and competency testing required to implement the procedure or medication.**
☒	☐	**9. Copy of the local EMS System Evaluation and Quality Improvement Program plan for this request.**

REQUEST FOR APPROVAL
Form #EMSA-0391 **Revised 03/18/03**
Check One: □ Local Optional Scope of Practice **X Trial Study**
TXA Use in Trauma Patients by Paramedics in the Pre- Hospital Setting

1. **Description of the procedure or medication requested:**

Tranexamic acid – TXA (trade name Cyklokapron, Lysteda) is a synthetic derivative of the amino acid lysine. TXA blocks the formation of plasmin from plasminogen and, at high concentrations, noncompetitively inhibits plasmin. Plasmin is a molecule that triggers clot breakdown. TXA is excreted renally. The use of TXA as a supplement has been successful in the control of bleeding in hemophilia, preoperatively, gastric hemorrhage, menorrhagia, traumatic hyphema and in the treatment of hereditary angioedema. TXA is supplied in 1000mg ampules in 10mL normal saline.

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.

Administration and route:

- Administer 1 gram of TXA in 100 ml of 0.9% Normal Saline, intravenous or via interosseous device over 10 minutes as soon as possible but no later than three hours after injury (given by paramedics in the prehospital setting).
- Infuse a second gram of TXA IV or IO over 8 hours in 0.9% Normal Saline (given by RN's in the trauma centers). *See Attachment A.*
- TXA SHOULD NOT to be administered through same line as blood products, rfactor VIIa, or Hexend.
- DO NOT administer as IV push, may cause hypotension.
- Drug must be stored at 59-86 degrees Fahrenheit.

Patients who receive TXA will be clearly identified with an approved wristband prior to transporting to a regional trauma center participating in the study.

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

Patients must meet trauma triage criteria related to anatomic, physiologic, and mechanism of injury as established by ICEMA. Refer to ICEMA Reference #15030 - Trauma Triage Criteria And Destination Policy.

- Additionally, patient must be: at least 18 years or older, less than three hours post injury, and meet any of the criteria listed below:

  - Blunt or penetrating trauma to the torso with signs and symptoms of hemorrhagic shock including a systolic blood pressure (SBP) of less than 90 mmHg.
  - Major amputation of any extremity, proximal to the wrist and ankle.
  - Bleeding uncontrolled by direct pressure or tourniquet.
  - Estimated external blood loss (EBL) 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):**
Other antifibrinolytic agents are available; however, we do not believe any are superior to TXA for EMS use.

4. **An estimate of frequency of utilization:**
5-10 patients per month

5. **Other factors or exceptional circumstances:**
None.

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

7. **Recommended policies/procedures to be instituted regarding:**
TXA will be administered to blunt and trauma patients:
   - Blunt or penetrating trauma to the torso with signs and symptoms of hemorrhagic shock including a systolic blood pressure (SBP) of less than 90 mmHg.
   - Major amputation of any extremity, proximal to the wrist and ankle.
   - Bleeding uncontrolled by direct pressure or tourniquet.
   - Estimated external blood loss (EBL) of 500 ml or more in the field.

Medical Control:
Trauma Center base hospital will provide the medical control.

Treatment Protocols:
See Attachment C.

Quality assurance of the procedure or medication:

- All paramedic provider agencies participating in this study must use the ICEMA ePCR system.
- ICEMA will generate a daily list via ePCR and do the initial QA.
- Concurrently, paramedics participating in the TXA trial study will be required to notify the EMS Coordinator when TXA is administered upon completion of the incident. Each EMS coordinator will be required to QA the incident.
- Once a month the QA Leadership (EMS Coordinators, Principal Investigators, Trauma Medical Directors, ED Medical Directors, TPM's and EMS Agency) will meet and review all TXA administration cases, paying special attention to safety issues and fallouts.
- Severe adverse events (SAE) will be reported to EMSA and IRB within 24 hours of the incident.
- Adverse effects (AE) will be reported within 30 days.
- EMSA will receive a progress report at 6 months from the start of the trial and every 6 months until completion or as requested.
  See Attachment D.

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

A training video will be developed to distribute to the EMS providers, MICN's and nurses and MD's. The video will contain an overview of the TXA, inclusion criteria for the study, protocol information, documentation, data collection and reporting process. This educational offering will be *minimally* 1.5 hours long. A written post-test will be required. Participating EMS agencies will have a 3 month period to educate the EMS providers before the official start of the trial study. (Enclosed is a draft of the educational PowerPoint presentation, this will be developed into a training video.) *See Attachment E.*

9. **Copy of the local EMS System Evaluation and Quality Improvement Program plan for this request:**
   See Attachment D.

ARROWHEAD REGIONAL MEDICAL CENTER
Administrative Operations Manual

SECTION: **PATIENT CARE** **SUB SECTION:** **BLOOD**

SUBJECT: **MASSIVE BLOOD TRANSFUSION (MASSIVE TRANSFUSION PROTOCOL)**

APPROVED BY: _____
Interim Chief Executive Officer

POLICY

I. The following criteria defines the patients that fall into this policy:

A. Any patient who requires transfusion replacing 70ml/kg e.g. ~5L blood loss in a 70 kg person.

B. Any patient with acute, ongoing blood loss whom the attending physician feels will require the initiation of the massive blood transfusion protocol (usually defined as anticipation for > 10 units packed red blood cells [PRBCs]).

C. The Blood Bank Technologist will call provider if four units or more of blood are transfused over a two-hour period to inquire whether to initiate the Massive Transfusion Protocol.

II. Once the Massive Transfusion Protocol has been activated, blood products will be provided in the following manner:

A. A Massive Transfusion Pack, consisting of six units of packed red blood cells (PRBC), three units (1200ml) of apheresis collected plasma (ACP) and one adult platelet pheresis which will be provided at each request.

B. Acquisition of Blood and Blood Products: Blood Administration. Please refer to Nursing Policy and Procedure Manual policy # 570.00.

III. Use of tranexamic acid (TXA) – all patients with potential requirement for blood products in the treatment of trauma related hemorrhage. Initiation must start as soon as possible prior to any surgery.

PROCEDURES:

I. The Massive Transfusion Protocol shall be initiated bya physician, by contacting the Blood Bank staff by telephone with a request for the "Massive Transfusion Pack".

II. The patient name and medical record number (M#) must be provided for identification.

III. TXA infusion will be infused in the following manner:

A. Infuse 1 gram of tranexamic acid in 100ml of 0.9% NS over 10 minutes intravenously in a separate IV line from any containing blood or blood products (more rapid injection has been reported to cause hypotension). Hextend should be avoided as a carrier fluid.

B. Infuse a second 1 gram dose intravenously over 8 hours infused with 0.9% NS.

IV. Laboratory personnel will deliver the "Massive Transfusion Pack" to the department when ready. The Blood Bank requires a physician's signature on the requisition for uncrossed matched blood form at the time of delivery.

V. Once the massive transfusion pack is dispensed, the treating physician (Surgery/Anesthesia) will indicate to the Blood Bank Technologist whether another pack should be prepared. If this is not clearly communicated then the technologist will obtain clarification from the physician.

VI. A hand delivered specimen must be submitted to the Blood Bank as soon as possible to determine the patient's ABO type.

VII. Fluid administration along with blood or blood products must be pre-warmed and or infused through fluid warmers.

VIII. All massively transfused patients should be placed onto a warming blanket, and in a warm environment.

IX. Humidified and warm gas should be used if the patient is on a ventilator.

X. All massive transfusion patients should be prepared for auto-transfusion via the chest tube system for hemothorax or the cell saver for hemoperitoneum unless contraindicated.

XI. Consider checking fibrinogen level and ionized calcium levels.

REFERENCES:

The American Society of Anesthesiologists Task Force on Perioperative Blood Transfusion and Adjuvant Therapies. (2006, July). Practice guidelines for perioperative transfusion and adjuvant therapies: an updated report by the American society of anesthesiologist's task force on perioperative blood transfusion and adjuvant therapies. *Anesthesiology, 105*(1), 198-208.

Como, J., Dutton, R., Scalea, T. Edelman, B. & Hess, J. (2004, June). Blood transfusion rates in the care of acute trauma. *Transfusion, 44*, 809-813.

Dutton, R., & Carson, J. (2006). Indications for early red blood cell transfusion. *The Journal of Trauma*, 60(6), s35-s40.

Dutton, R. (2007). Current concepts in hemorrhagic shock. *Anesthesiology Clinics, 25*, 23-34.

Nunez, TC, Young FP, Holcomb JB, Cotton BA (June 2010). Creation, Implementation, and Maturation of a Massive Transfusion Protocol for the exangumatry trauma patient. J. Trauma 68 (b): 1498-1505.

DEFINITIONS: N/A

ATTACHMENTS: N/A

APPROVAL DATE:

N/A	Policy, Procedure and Standards Committee
12/19/13	Trauma Committee Applicable Administrator, Hospital or Medical Committee
5/22/14	Michelle Sayre, Chief Nursing Officer Applicable Administrator, Hospital or Medical Committee
2/6/14	Quality Management Committee Applicable Administrator, Hospital or Medical Committee
2/20/14	Medical Executive Committee Applicable Administrator, Hospital or Medical Committee

REPLACES: Administrative Policy No. 660.03 Issue 1

EFFECTIVE: 07/06/12 **REVISED:** 11/07/13

REVIEWED: 06/21/13

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The importance of early treatment with tranexamic acid in bleeding trauma patients: an exploratory analysis of the CRASH-2 randomised controlled trial

*The CRASH-2 collaborators**

Summary

Background The aim of the CRASH-2 trial was to assess the effects of early administration of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage. Tranexamic acid significantly reduced all-cause mortality. Because tranexamic acid is thought to exert its effect through inhibition of fibrinolysis, we undertook exploratory analyses of its effect on death due to bleeding.

Methods The CRASH-2 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 followed by infusion of 1 g over 8 h) or placebo. Patients were randomly assigned by selection of the lowest numbered treatment pack from a box containing eight numbered packs that were identical apart from the pack number. Both participants and study staff (site investigators and trial coordinating centre staff) were masked to treatment allocation. We examined the effect of tranexamic acid on death due to bleeding according to time to treatment, severity of haemorrhage as assessed by systolic blood pressure, Glasgow coma score (GCS), and type of injury. All analyses were by intention to treat. The trial is registered as ISRCTN86750102, ClinicalTrials.gov NCT00375258, and South African Clinical Trial Register/Department of Health 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. 1063 deaths (35%) were due to bleeding. We recorded strong evidence that the effect of tranexamic acid on death due to bleeding varied according to the time from injury to treatment (test for interaction p<0·0001). Early treatment (≤1 h from injury) significantly reduced the risk of death due to bleeding (198/3747 [5·3%] events in tranexamic acid group *vs* 286/3704 [7·7%] in placebo group; relative risk [RR] 0·68, 95% CI 0·57–0·82; p<0·0001). Treatment given between 1 and 3 h also reduced the risk of death due to bleeding (147/3037 [4·8%] *vs* 184/2996 [6·1%]; RR 0·79, 0·64–0·97; p=0·03). Treatment given after 3 h seemed to increase the risk of death due to bleeding (144/3272 [4·4%] *vs* 103/3362 [3·1%]; RR 1·44, 1·12–1·84; p=0·004). We recorded no evidence that the effect of tranexamic acid on death due to bleeding varied by systolic blood pressure, Glasgow coma score, or type of injury.

Interpretation Tranexamic acid should be given as early as possible to bleeding trauma patients. For trauma patients admitted late after injury, tranexamic acid is less effective and could be harmful.

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

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See Online/Comment DOI:10.1016/S0140-6736(11)60396-6

See Online/Correspondence DOI:10.1016/S0140-6736(11)60317-6

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Introduction

The CRASH-2 trial showed that administration of tranexamic acid to adult trauma patients with, or at risk of, significant haemorrhage, within 8 h of injury, significantly reduces all-cause mortality (relative risk [RR] 0·91, 95% CI 0·85–0·97; p=0·0035) with no apparent increase in vascular occlusive events.[1] As a consequence of this trial, tranexamic acid has been incorporated into trauma treatment protocols worldwide.

Results from the CRASH-2 trial raise some important questions. The trial was motivated by the evidence that tranexamic acid reduces bleeding in patients undergoing elective surgery, and the hypothesised mechanism was inhibition of fibrinolysis leading to improved effectiveness of haemostasis.[2] However, no significant difference was recorded in transfusion requirements between the tranexamic acid and placebo groups, and the CRASH-2 trial did not measure the effect of this drug on fibrinolytic assays. Thus an alternative hypothesis is that tranexamic acid might act by reducing the pro-inflammatory effects of plasmin, rather than by improving haemostasis.[3]

There has also been discussion about which trauma patients should be treated with tranexamic acid. The CRASH-2 trial[1] reported the few subgroup analyses that were prespecified in the statistical analysis plan. These analyses assessed the effect of tranexamic acid on the primary endpoint of all-cause mortality, according to time since injury, systolic blood pressure, Glasgow coma score, and type of injury. No strong evidence of

heterogeneity was recorded for any of these analyses, suggesting that tranexamic acid is likely to be equally effective in all the subgroups examined.

The focus on all-cause mortality was appropriate because it is an outcome that matters to patients and one that is not affected by the methodological problem of competing risks.[4] However, the effect of the trial treatment on the biologically relevant outcome could have been diluted by outcomes on which tranexamic acid might have little or no effect. In response to these concerns, we undertook exploratory analyses of the effect of tranexamic acid on mortality due to bleeding. We report the same prespecified subgroup analyses but for the outcome that we hypothesise would be most affected by this drug, specifically mortality due to bleeding.

	N	All causes of death	Bleeding death	Non-bleeding death
Overall	20127	0·91 (0·85–0·97); p=0·0035	0·85 (0·76–0·96); p=0·0077	0·94 (0·86–1·02); p=0·13
Time to treatment (h)				
≤1	7451	0·87 (0·76–0·97)	0·68 (0·57–0·82)	1·04 (0·89–1·21)
>1–3	6033	0·87 (0·77–0·97)	0·79 (0·64–0·97)	0·91 (0·78–1·05)
>3	6634	1·00 (0·90–1·13)	1·44 (1·12–1·84)	0·89 (0·78–1·02)
χ^2 test of homogeneity	..	4·411 (p=0·11)	23·516 (p=0·0000)	2·537 (p=0·28)

Table 1: Relative risk (95% CI) of death with tranexamic acid, overall and by time to treatment

	≤1 h (n=7451)	>1–3 h (n=6033)	>3 h (n=6634)
Age (years)			
Mean (SD)	33·4 (13·9)	35·0 (14·0)	35·5 (14·8)
<25	2283 (30·6%)	1557 (25·8%)	1773 (26·7%)
25–34	2360 (31·7%)	1832 (30·4%)	1882 (28·4%)
35–44	1356 (18·2%)	1177 (19·5%)	1262 (19·0%)
>44	1452 (19·5%)	1467 (24·3%)	1716 (25·9%)
Systolic blood pressure (mm Hg)			
≤75	1380 (18·5%)	1012 (16·8%)	768 (11·6%)
76–89	1203 (16·1%)	1064 (17·6%)	1029 (15·5%)
>89	4857 (65·2%)	3955 (65·6%)	4821 (72·7%)
Heart rate (beats per min)			
<77	681 (9·1%)	450 (7·5%)	603 (9·1%)
77–91	1189 (16·0%)	971 (16·1%)	1326 (20·0%)
92–107	1888 (25·3%)	1562 (25·9%)	1625 (24·5%)
>107	3637 (48·8%)	2990 (49·6%)	3059 (46·1%)
Respiratory rate (breaths per min)			
<10	149 (2·0%)	82 (1·4%)	77 (1·2%)
10–29	6144 (82·5%)	4992 (82·7%)	5590 (84·3%)
>29	1077 (14·5%)	901 (14·9%)	923 (13·9%)
Capillary refill time (s)			
≤2	2450 (32·9%)	2140 (35·5%)	2217 (33·4%)
3–4	3472 (46·6%)	2773 (46·0%)	3110 (46·9%)
>4	1131 (15·2%)	963 (16·0%)	1257 (19·0%)
Glasgow coma score			
Severe (3–8)	1000 (13·4%)	1124 (18·6%)	1494 (22·5%)
Moderate (9–12)	868 (11·7%)	915 (15·2%)	909 (13·7%)
Mild (13–15)	5577 (74·9%)	3994 (66·2%)	4214 (63·5%)
Continents			
Asia	1213 (16·3%)	2475 (41·0%)	3656 (55·1%)
Africa	2490 (33·4%)	1437 (23·8%)	872 (13·1%)
Central and South America	2453 (32·9%)	1456 (24·1%)	1355 (20·4%)
North America, Europe, and Oceania	1295 (17·4 %)	665 (11·0%)	751 (11·3%)

Data are number (%), unless otherwise stated.

Table 2: Patient characteristics by time to treatment

Methods

Study design and patients

The background to the trial, methods, and baseline characteristics of the randomised patients have been previously reported.[1] Briefly, we randomly allocated 20 211 adult trauma patients with, or at risk of, significant bleeding who were within 8 h of injury to either tranexamic acid (loading dose 1 g over 10 min followed by infusion of 1 g over 8 h) or matching placebo, with 99·6% follow-up. In most hospitals we used a local pack system for randomisation. After eligibility had been confirmed and the locally approved consent procedures had been completed, patients were randomly assigned by selection of 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 Trial Coordinating Centre in London, UK. Hospitals with telephone access used a telephone randomisation service. Both participants and study staff (site investigators and trial coordinating centre staff) were masked to treatment allocation.

Statistical analysis

The primary outcome was death in hospital within 4 weeks of injury, with cause of death 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. We examined the effect of the trial treatment on death due to bleeding subdivided by four baseline characteristics: (1) time from injury to treatment (≤1, >1–3, >3 h); (2) severity of haemorrhage as assessed by systolic blood pressure (≤75, 76–89, >89 mm Hg); (3) Glasgow coma score (severe 3–8, moderate 9–12, mild 13–15); and (4) type of injury (penetrating only, blunt plus blunt and penetrating). These were the same subgroup analyses that were reported previously, but for the outcome of death due to bleeding rather than for all-cause mortality.

Heterogeneity in treatment effects across subgroups was assessed by a χ^2 test. We had prespecified that unless there was strong evidence against the null hypothesis of homogeneity of effects (ie, p<0·001), the overall RR would be considered the most reliable guide to the approximate RRs in all subgroups. To test the

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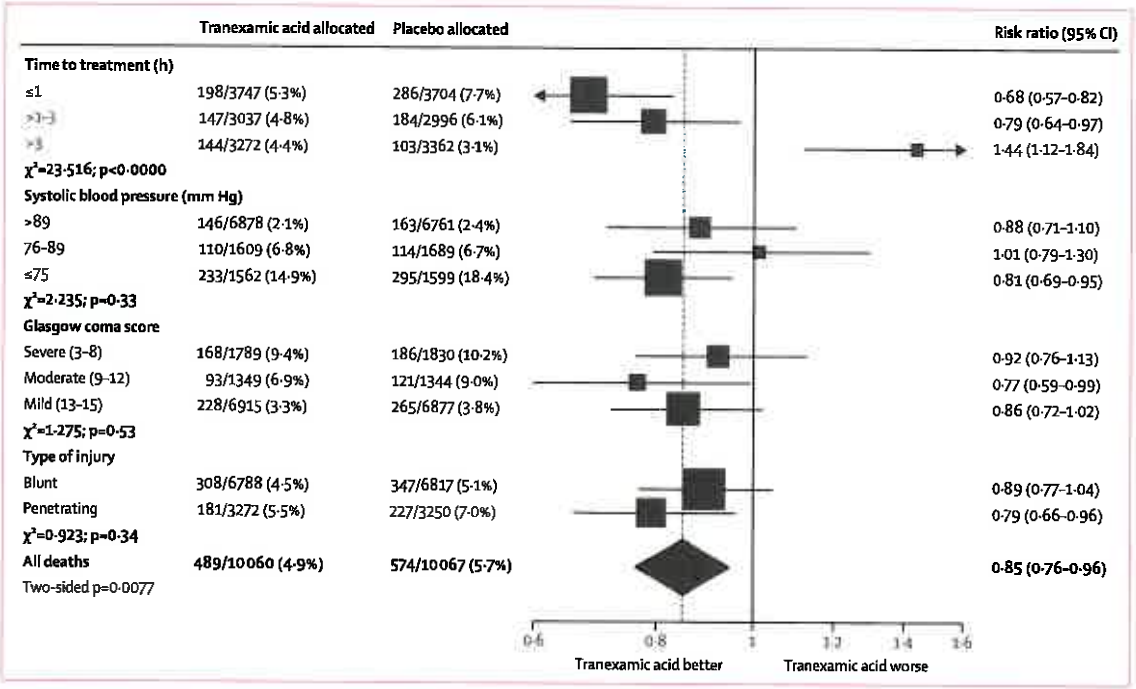

Figure 1: **Mortality due to bleeding by subgroups**

independence of any observed treatment interactions we ran a logistic model including all possible interactions in the four prespecified baseline characteristics and treatment subgroups.

A logistic regression was estimated with death due to bleeding as the dependent variable and treatment group and time to treatment as explanatory factors. We included an interaction parameter to allow for a proportional change in the odds ratio (OR) as time to treatment increases. ORs and 95% CIs were estimated for different times to treatment. CIs were calculated with a logistic model with time as a continuous term and an interaction term between time and tranexamic acid. We also ran a model with an interaction term for time to treatment squared to allow for a non-constant proportional change in the OR.

The trial is registered as ISRCTN86750102, ClinicalTrials.gov NCT00375258, and South African Clinical Trial Register/Department of Health DOH-27-0607-1919.

Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author (IR) had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Of the 3076 deaths from all causes, death due to bleeding accounted for 1063 (35%). The risk of death due to bleeding was significantly reduced with tranexamic acid. 489 of 10 060 (4·9%) patients died because of bleeding in the tranexamic acid group versus 574 of 10 067 (5·7%) in the placebo group (RR 0·85, 95% CI 0·76–0·96; p=0·0077). We noted no significant effect on the risk of death for all other (non-bleeding) causes combined (table 1).

Table 2 shows the baseline characteristics of patients according to time to treatment. Figure 1 shows the results of the subgroup analyses for death due to bleeding. Time to treatment was unknown in nine participants. Treatment given 1 h or less from injury significantly reduced the risk of death due to bleeding (198/3747 [5·3%] in tranexamic acid group *vs* 286/3704 [7·7%] in placebo group; RR 0·68, 95% CI 0·57–0·82; p<0·0001). Treatment given between 1 and 3 h also reduced the risk of death due to bleeding (147/3037 [4·8%] *vs* 184/2996 [6·1%]; RR 0·79, 0·64–0·97; p=0·03). Treatment given more than 3 h after injury significantly increased the risk of death due to bleeding (144/3272 [4·4%] *vs* 103/3362 [3·1%]; RR 1·44, 1·12–1·84; p=0·004). We recorded strong evidence that the effect of tranexamic acid on death due to bleeding varied according to time from injury to treatment (p<0·0001). The evidence for interaction remained strong even after adjustment for interactions between the other prespecified baseline characteristics and treatment (p<0·0001; data not shown).

The estimated OR of tranexamic acid on death due to bleeding when given immediately after injury was 0·61

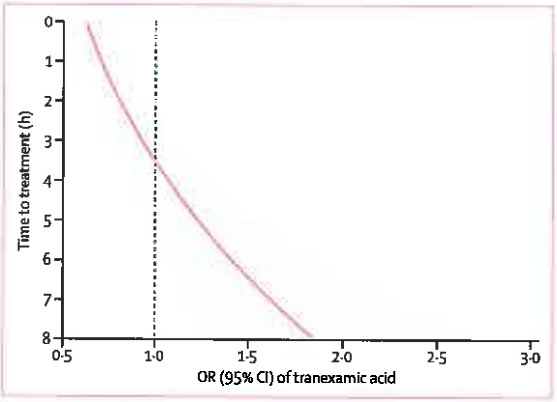

Figure 2: **Effect of tranexamic acid on death due to bleeding by time to treatment**
Shaded area shows 95% CI. OR=odds ratio.

(95% CI 0·50–0·74). We estimated that this OR is multiplied by 1·15 (95% CI 1·08–1·23) for every hour that passes since the injury. Figure 2 shows how the OR and 95% CIs vary with time to treatment. The interaction term for time to treatment squared was not significant (OR=0·99; p=0·38).

We recorded no evidence of heterogeneity for the subgroup analyses according to systolic blood pressure, Glasgow coma score at randomisation, or type of injury (figure 1). We detected no evidence of heterogeneity in the effect of tranexamic acid on the risk of non-bleeding deaths (table 1).

Discussion

The effect of tranexamic acid on death due to bleeding depends on the time between injury and onset of treatment. Early treatment with this drug seems to be much more effective than does late treatment. These results also raise the possibility that late treatment with tranexamic acid might increase the risk of death due to bleeding, although there was no evidence of any increase in all-cause mortality in patients treated after 3 h (table 1). This finding might indicate that patients treated with tranexamic acid beyond 3 h who died from bleeding might otherwise have died from some other non-bleeding cause (competing risks). If late administration does cause harm, this finding would be important since many bleeding trauma patients in low-income and middle-income countries have long prehospital times. Indeed, about a third of trauma patients in the CRASH-2 trial were treated more than 3 h after the injury.

The inclusion criteria in the CRASH-2 trial were entirely clinical, and reflect the situation that doctors are faced with in clinical practice. Patients were enrolled if the treating physician judged them to have ongoing significant haemorrhage, as evidenced by hypotension or tachycardia, or if they were considered to be at risk of significant haemorrhage. Some of the included patients might not have been actively bleeding. Any such misdiagnosis would have reduced the power of the trial to show an effect of tranexamic acid on mortality from bleeding, in which case the large and highly significant reduction in bleeding mortality in patients treated with this drug within 1 h of injury is particularly noteworthy.

Because patients were randomly assigned soon after hospital admission, before the precise anatomical location of bleeding and other injury was known, we were unable to do a stratified analysis based on an anatomical assessment of injury severity. We acknowledge that this omission is a methodological weakness, since such an analysis might provide insight into the mechanism of action of tranexamic acid. However, since this information would not normally be available to treating clinicians, especially in view of the importance of early treatment, the clinical value of a stratified analysis based on anatomical injury severity is small.

Data for the time between injury and treatment were available for all but nine trial participants. Because in some cases the injury would not have been witnessed, this interval sometimes had to be estimated and might therefore be inaccurate. However, any inaccuracy would be independent of the trial treatment and therefore should not bias the results. The ascertainment of a death as a bleeding death might also have been inaccurate, but similarly any inaccuracy should be independent of the trial treatment.

In clinical trials, a treatment is not often beneficial in one subgroup but harmful in another (qualitative interaction), and some trialists recommend that qualitative interactions should generally be disbelieved.[5] The results of our analysis of the effect of tranexamic acid on death due to bleeding do, however, satisfy most of the criteria against which the credibility of subgroup results should be judged:[6] time from injury was measured at baseline; the hypothesis that early treatment with tranexamic acid might be more effective was prespecified in the trial protocol; the interaction suggests a very low likelihood that chance explains the findings; the interaction remained significant after controlling for the non-significant interactions between treatment and the other prespecified baseline prognostic factors; the subgroup effect is large; and a biological rationale supports the interaction. Although this clinical trial was not powered to examine subgroup effects, the interaction recorded is large and highly significant.[7]

Nevertheless, we prespecified in our trial protocol that the main subgroup analyses would be undertaken for all-cause mortality, and not for mortality due to bleeding. Even though we postulated that tranexamic acid would act by reducing bleeding, we focused on all-cause mortality because overall survival is most important to patients. However, in view of the significant reduction in all-cause mortality, most of which was attributable to the effect of tranexamic acid on death due to bleeding, and the biological rationale that this drug would act by

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improving haemostasis, our analyses, although not prespecified, would seem justified.

Acute severe trauma is associated with increased fibrinolysis that contributes to an early coagulopathy and increased mortality.[8,9] Fibrinolysis can be assessed by measurement of fibrin degradation products, which include small protein fragments called D-dimers. Brohi and colleagues[8] showed that D-dimer concentrations are raised in trauma patients at the time of hospital admission (median prehospital time 28 min), with the highest concentrations measured in the most severely injured patients.[8] Similar results were recorded in a 2009 study from Japan that measured fibrin degradation product and D-dimers in 314 severe trauma patients.[10] If this early increased fibrinolysis exacerbates bleeding and increases the risk of death, then we might expect that an antifibrinolytic drug such as tranexamic acid would be most effective in this period.

Although we had anticipated that early treatment with tranexamic acid might be most effective, the apparent increase in the risk of death due to bleeding in patients treated more than 3 h after the injury is unexpected and cannot readily be explained. It could be a chance finding and there might be no real biological effect. However, patients in the late phase of trauma can develop thrombotic disseminated intravascular coagulation, and antifibrinolytics could be contraindicated in this period.[10,11] Although disseminated intravascular coagulation is characterised by fibrin formation and coagulation, the rapid consumption of coagulation proteins can lead to their exhaustion, resulting in uncontrolled bleeding. The need to avoid giving an antifibrinolytic in this late phase was why we restricted trial inclusion to patients who were within 8 h of injury. The possibility that the change to a prothrombotic state might occur sooner than was previously expected is open to debate and needs further research. We should also bear in mind that patients who arrive at hospital many hours after injury are likely to differ from those who arrive early. For example, there could be an increased prevalence of hypothermia and acidosis. These or other differences could explain the decreased efficacy of tranexamic acid administration when given late.

A 2011 systematic review of randomised controlled trials concluded that tranexamic acid safely reduces mortality in bleeding trauma patients.[12] Our results strongly endorse the importance of early administration of tranexamic acid in bleeding trauma patients and suggest that trauma systems should be configured to facilitate this recommendation (panel). In patients presenting late (several hours after injury) the clinician should be more cautious and make an assessment of the individual benefits and risks of this treatment, since the drug is likely to be much less effective and possibly even harmful. To the extent that our subgroup analyses are consistent with the results of studies showing an early increased fibrinolytic coagulopathy, they support the hypothesis that tranexamic acid acts through the inhibition of fibrinolysis with improved haemostasis.

Future research using the CRASH-2 trial data will develop a prognostic model to predict death due to bleeding.[13] This model will facilitate further analysis of the effect of tranexamic acid according to baseline risk of haemorrhage death.

Panel: Research in context

Systematic review

A 2011 Cochrane systematic review[12] of antifibrinolytic drugs for acute traumatic injury identified two randomised trials of tranexamic acid in bleeding trauma patients, involving 20 451 patients. The review concluded that tranexamic acid safely reduces mortality in bleeding trauma patients without increasing the risk of adverse events.

Interpretation

Our results emphasise the importance of early administration of tranexamic acid and the need for caution in patients presenting several hours after the injury.

Contributors

All members of the Writing Committee, apart from AA and GG, attended a 2-day meeting in London, UK, at which the subgroup analyses were presented and discussed and the report was drafted. Both AA and GG contributed to the discussions and drafting by phone and in correspondence.

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Conflicts of interest

Members of the Writing Committee declare that they have no conflicts of interest.

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

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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; $P=.03$) 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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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.

See Invited Critique at end of article

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-

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

Variable	Overall (N=896)			Massive Transfusion (n=231)		
	TXA (n=293)	No TXA (n=603)	*P* Value[a]	TXA (n=125)	No TXA (n=196)	*P* Value[a]
Demographic data						
Age, mean (SD), y	24.9 (9.6)	23 1 (10 1)	.12	23.8 (7 7)	22 9 (9.2)	.46
Male, %	97 3	94 2	**.04**	98 4	96.9	.49
Host national, No. (%)	116 (39.6)	261 (43.3)	.29	39 (31 2)	65 (33.2)	.71
NATO military	177 (60.4)	342 (56 7)		86 (68.8)	131 (66.8)	
Mechanism of injury, %						
GSW	25.3	36 7	**<.001**	24.0	32 1	.14
Explosion	74.7	62 4		76.0	66.8	
Injury severity						
ISS, mean (SD)	25.2 (16.6)	22 5 (18.5)	**<.001**	26.1 (17 1)	25.2 (20.5)	11
AIS score ≥3, %						
Head	9.9	13 4	**13**	9.6	13.8	.26
Chest	22.2	22 2	.99	21 6	23.0	78
Abdomen	14 7	16 4	.50	13 6	21 0	.06
Extremity	66.6	47 3	**< 001**	68.0	51 0	**.003**
RTS, mean (SD)	5 53 (2 14)	6.04 (2 69)	**.01**	5.58 (2 21)	5.74 (2.88)	21
Admission physiology, %						
GCS score ≤8	63 3	35.6	**<.001**	64 1	39.3	**< 001**
SBP ≤90 mm Hg	22.8	13 8	**.003**	20.4	18.2	.67
24-h Transfusion, mean (SD), units						
PRBCs	11 8 (12 1)	9 8 (13 1)	**<.001**	21 0 (12 8)	22.5 (15 9)	47
FFP	10 3 (10.8)	8 6 (11 7)	**<.001**	18 4 (11 5)	19.6 (14.3)	.67
Platelets	1 6 (2.2)	1 4 (2 7)	**001**	3 2 (2 4)	3 6 (3 6)	.84
Cryoprecipitate	1 6 (2.7)	0 5 (1 3)	**<.001**	1 6 (2 6)	0 7 (1 6)	**< 001**
Miscellaneous						
Time in ED, mean (SD), min	36 (25)	56 (55)	**< 001**	39 (27)	52 (57)	39
Time in OR, mean (SD), min	170 (121)	115 (74)	**< 001**	180 (126)	113 (74)	**< 001**
Lowest body temperature, mean (SD), °C	36 1 (1 1)	36 4 (0.9)	**04**	36 5 (0 8)	36 3 (0 9)	28
Pulmonary embolism, No. (%)	8 (2 7)	2 (0 3)	**.001**	4 (3.2)	0	**.01**
Deep venous thrombosis, No. (%)	7 (2 4)	1 (0 2)	**.001**	2 (1 6)	1 (0.5)	32

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.

[a]Statistically significant values ($P<.05$) are bold.

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[17] 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,[17] 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

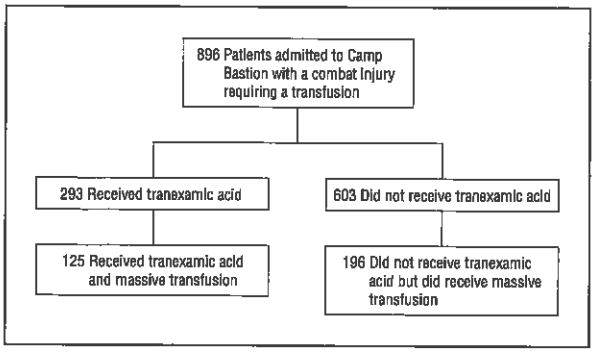

Figure 1. Study profile illustrating the overall cohort and study groups.

24 hours were identified as the massive transfusion (MT) cohort and assigned to treatment (TXA^{MT}) and nontreatment (no-TXA^{MT}) groups (**Figure 1**).

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).[18] 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.[19] 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).[20] 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 χ^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 (≤8 vs >8), SBP (≤90 vs >90 mm Hg), ISS (>15 vs ≤15), and body region AIS scores (≥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-

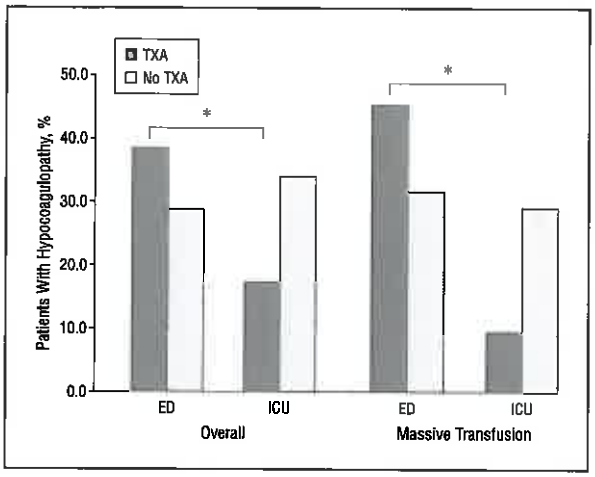

Figure 2. Percentage of patients with hypocoagulopathy on admission to the emergency department (ED) and then the intensive care unit (ICU) following the initial operation. Coagulation data were available for 462 patients in the overall cohort and 155 patients in the groups that received massive transfusion. TXA indicates tranexamic acid. *$P<.05$.

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

End Point	Total No. of Patients in Follow-up (Mortality, %)		
	TXA	No TXA	*P* Value[a]
Overall			
<24 h	293 (9 6)	603 (12 4)	20
<48 h	264 (11 3)	507 (18.9)	**.004**
In-hospital mortality[b]	264 (17 4)	603 (23 9)	**03**
Massive transfusion			
<24 h	125 (9 6)	196 (14 8)	17
<48 h	112 (10 4)	160 (23 5)	**.003**
In-hospital mortality[c]	125 (14 4)	196 (28 1)	**.004**

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

crease in the percentage of patients in the TXA groups with hypocoagulopathy between these 2 points. **Table 2** illustrates mortality in the 2 cohorts. In the overall cohort, the absolute reduction in in-hospital mortality for the TXA group was 6.5%, while the absolute reduction in the TXA^{MT} group was 13.7% (relative reduction of 49%).

The following parameters had $P\leq.15$ 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 $P\leq.15$ 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

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

Cohort	Odds Ratio (95% CI)[a]	*P* Value[b]
Overall		
GCS score ≤8	0.304 (0 108-0 860)	**.02**
Hypotension	0.303 (0 107-0.855)	**.02**
Coagulopathy at admission	0.291 (0 113-0.749)	**.01**
Massive transfusion		
GCS score ≤8	0.027 (0.008-0.085)	**<.001**
ISS >15	0.359 (0 123-1 053)	.06
TXA	7 228 (3.016-17.322)	**< 001**

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

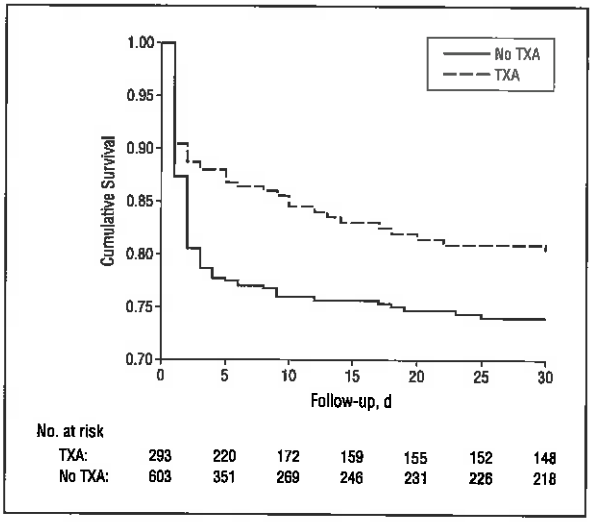

Figure 3. Kaplan-Meier survival curve of the overall cohort, including patients receiving tranexamic acid (TXA) vs no TXA. $P=.006$, Mantel-Cox log-rank test.

($P<.001$), 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 ($P\leq.15$). 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 ($P=.006$).

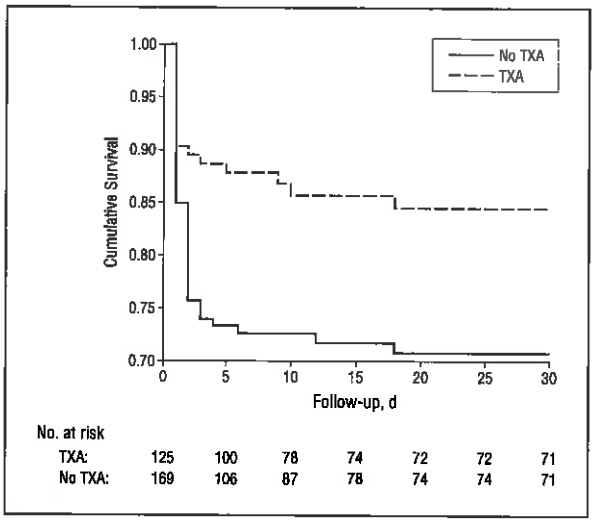

Figure 4. Kaplan-Meier survival curve of the massive transfusion group receiving tranexamic acid (TXA) or no TXA. *P*=.004, Mantel-Cox log-rank test.

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

COMMENT

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[23] 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. On the basis of these findings, early administration of TXA following severe wartime vascular disruption with hemorrhage should be implemented into clinical practice.

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INVITED CRITIQUE

ONLINE FIRST

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.[1] Despite a subtle but significant outcome benefit, direct application of these results to clinical practice was made challenging by several factors, including the inclusion criteria that effectively diluted out those patients who were actually bleeding. These results became even more difficult to interpret when an analysis of the time from injury to treatment demonstrated an *increase* in the risk of death due to bleeding[2] if the antifibrinolytic was administered beyond 3 hours.

The MATTERs Study,[3] however, specifically targeted the cohort of patients who were actively bleeding and demonstrated a strong association with improved survival. It is a retrospective study and as such does have its limitations. Its data predate and cross over the CRASH-2 release date, highlighting the lack of standardized indications and dosing used throughout the study period. Like the studies before it, the MATTERs Study also failed to quantitate the degree of hyperfibrinolysis or its response to treatment. In addition, a detailed analysis of the timing of treatment, a critical factor emphasized by the CRASH-2 trial, could not be performed.

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

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

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Do all trauma patients benefit from tranexamic acid?

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BACKGROUND: This study tested the hypothesis that early routine use of tranexamic acid (TXA) reduces mortality in a subset of the most critically injured trauma intensive care unit patients.

METHODS: Consecutive trauma patients (n = 1,217) who required emergency surgery (OR) and/or transfusions from August 2009 to January 2013 were reviewed. At surgeon discretion, TXA was administered at a median of 97 minutes (1-g bolus then 1-g over 8 hours) to 150 patients deemed high risk for hemorrhagic death. With the use of propensity scores based on age, sex, traumatic brain injury (TBI), mechanism of injury, systolic blood pressure, transfusion requirements, and Injury Severity Score (ISS), these patients were matched to 150 non-TXA patients.

RESULTS: The study population was 43 years old, 86% male, 54% penetrating mechanism of injury, 25% TBI, 28 ISS, with 22% mortality. OR was required in 78% at 86 minutes, transfusion was required in 97% at 36 minutes, and 75% received both. For TXA versus no TXA, more packed red blood cells and total fluid were required, and mortality was 27% versus 17% (all $p < 0.05$). The effects of TXA were similar in those with or without TBI, although ISS, fluid, and mortality were all higher in the TBI group. Mortality associated with TXA was influenced by the timing of administration ($p < 0.05$), but any benefit was eliminated in those who required more than 2,000-mL packed red blood cells, who presented with systolic blood pressure of less than 120 mm Hg or who required OR (all $p < 0.05$).

CONCLUSION: For the highest injury acuity patients, TXA was associated with increased, rather than reduced, mortality, no matter what time it was administered. This lack of benefit can probably be attributed to the rapid availability of fluids and emergency OR at this trauma center. Prospective studies are needed to further identify conditions that may override the benefits from TXA. (*J Trauma Acute Care Surg.* 2014;76: 1373–1378. Copyright © 2014 by Lippincott Williams & Wilkins)

LEVEL OF EVIDENCE: Therapeutic study, level IV.

KEY WORDS: Hemostasis; resuscitation; transfusion.

Tranexamic acid (TXA) is a synthetic derivative of the amino acid lysine that has hemostatic properties. It is an antifibrinolytic that competitively inhibits the activation of plasminogen to plasmin. CRASH-2 was a multicenter randomized controlled civilian trial in 20,000 patients which showed that TXA reduced all-cause mortality versus placebo (14.5% vs. 16.0%).[1] The risk of death caused by bleeding was also reduced (4.9% vs. 5.7%).[1] This was confirmed in the retrospective MATTERS study and rapidly incorporated into military practice guidelines[2] and subsequently for civilians worldwide.[3–5] CRASH-2 also suggested that TXA was less effective and could even be harmful if treatment was delayed more than 3 hours after admission.[3]

On March 26, 2011, TXA was used for the first time at the Ryder Trauma Center. It is now frequently (but not universally) used for our most severely injured patients, at surgeon discretion. Originally, we intended to evaluate the impact of TXA in our hands on the quality of care because there are several distinctions between our practice and CRASH-2, including shorter transport times, higher percentage of older patients, earlier operative intervention (OR), and earlier use of fluid and blood products (Table 1).

As the data were collected, the question evolved, based, in part, on the growing evidence in this rapidly changing field; for example, new evidence suggests that TXA is safest and most effective only in those with hyperfibrinolysis.[6] This is important because early detection of fibrinolysis generally requires point-of-care viscoelastic monitoring, which is not routinely available at most trauma centers.[7] Furthermore, a high percentage of patients at any urban center experience traumatic brain injury (TBI) superimposed on other organ systems, and there is almost no information on the safety and efficacy of TXA in that population.[6] To fill these gaps, we examined two related questions: does routine early use of TXA improve outcome in critically injured patients in an unmonitored setting, and is the efficacy of TXA influenced by TBI, OR, or transfusion? The overarching hypothesis was that early routine use of TXA reduces mortality in the highest injury acuity patients.

PATIENTS AND METHODS

After institutional review board approval, all adult patients at Ryder Trauma Center (Jackson Memorial Hospital and

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This study was presented as a poster at the 72nd annual meeting of the American Association for the Surgery of Trauma and Clinical Congress of Acute Care Surgery, September 2013, in San Francisco, California.

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TABLE 1. Comparison of Study Populations

	CRASH-2[1]	Present Study
n	20,211	300
Age	**35 ± 14**	**43 ± 20**
% male	84%	86%
Time since injury, h	**2.8–2.9**	**<1 (est)**
% penetrating	**32%**	**54%**
SBP< 75 mm Hg	**16%**	**35%**
SBP, 76–89 mm Hg	16%	16%
SBP > 90 mm Hg	**68%**	**48%**
Heart rate (HR) < 77 beats/min	**9%**	**24%**
HR, 77–91 beats/min	17%	15%
HR, 92–107 beats/min	25%	19%
HR > 107 beats/min	48%	42%
GCS score, 3–8	**18%**	**32%**
GCS score, 9–12	**13%**	**8%**
GCS score, 13–15	**68%**	**59%**
Mortality	**15%**	**27%**
Blood product transfusion	**50%**	**97%**
Surgical intervention	**48%**	**78%**

University of Miami Miller School of Medicine) from August 2009 to January 2013 who underwent emergency OR directly from the resuscitation area were prospectively entered into a registry. In general, emergency OR is required for hemorrhage control, repair/resection of organ injuries, and limb salvage. OR for isolated orthopedic and/or neurosurgical indications and minor trauma operations such as those for complex wound closures were excluded. A separate registry, which also excluded orthopedic and/or neurosurgical patients, was maintained during the same period for all patients who received any blood product transfusion in either the resuscitation area or OR. These two databases were combined and reviewed with waiver of informed consent.

On March 26, 2011, TXA was made available in the formulary of the trauma center. The institutional practice is to administer a 1-g bolus intravenously administered, followed by a 1-g infusion over 8 hours, starting within 3 hours of admission.

Resuscitation flow sheets, OR/anesthesia reports, and intensive care unit (ICU) records were reviewed. Vital signs, laboratory values, fluids, and pressor requirements were recorded for the first 24 hours. Demographics (age, sex, mechanism) and trauma registry data (ICU days, length of stay [LOS], and mortality) were also recorded.

Dead on arrival (DOA) was defined as a patient who arrived in extremis and who survived less than 2 hours, regardless of intervention.

TXA patients were matched to controls with propensity scores generated by nearest-neighbor matching.[8] Sampling without replacement was implemented in the model. No hypothetical populations were used to compare differences in distributions in the baseline characteristics of the matched TXA and non-TXA group. Age, sex, TBI, mechanism of injury, systolic blood pressure (SBP), blood transfusion, and Injury Severity Score (ISS) were the variables used to generate the model for matching using SAS version 9.4 (SAS Institute Inc., Cary, NC). After matching, continuous data with a normal distribution were compared using the Student's *t* test, and nonparametric data were compared with a Mann-Whitney U-test. Dichotomous variables were compared with χ^2 or Fisher's exact test using SPSS Statistics version 21.0 (IBM Corporation, Armonk, NY). Significance was assessed at $p < 0.05$. Data are presented as mean ± SD if normally distributed or median (interquartile range [IQR]) if not.

RESULTS

The database was comprised of 1,217 consecutive patients who required OR or blood product transfusions after admission to this Level 1 trauma center. Figure 1 shows that the propensity-matched study population was comprised of 300 patients who were 43 years old, 86% male, 54% penetrating, 25% TBI, 28 ISS, with 27% mortality, (22% mortality excluding DOA). Half received TXA, and half did not.

This is by no means typical of the average trauma patient population and represents only a tiny fraction of those admitted. Every patient was in severe traumatic shock; 80% presented with an initial SBP of less than 120 mm Hg, and 29% had an SBP of less than 70 mm Hg. Base deficit was −8 ± 7 mEq/L. OR was required in 78% at a median (IQR) of 27 (75) minutes (mean ± SD, 87 ± 152 minutes), transfusion was required in 97% at 3 (9) minutes (38 ± 172 minutes), and 75% required both emergency surgery and a transfusion.

Table 2 shows that the two groups were almost perfectly matched in terms of demographics, vital signs, and laboratory values in the resuscitation area. TXA was administered 97 (97) minutes after arrival (range, 0–886 minutes).

Table 3 shows fluid requirements and other outcomes. The TXA group required more total fluid in the emergency department, more packed red blood cells (pRBCs) and fresh frozen plasma (FFP) in the OR, and more pRBCs in the first 24 hours (all $p < 0.05$), but LOS was similar, and the apparent difference in mortality (31 vs. 23%) was not statistically significant ($p = 0.091$). However, of the 81 deaths, 20 patients arrived in extremis and survived less than 2 hours, despite lifesaving interventions. Those patients were defined as DOA and excluded from both groups. Then, the mortality rate changes and achieves statistical significance with TXA versus no TXA (27% vs. 17%, $p = 0.024$).

Table 4 demonstrates the effects of TXA administration with and without TBI. When TBI is excluded, TXA was still associated with increased mortality (30% vs. 13%, $p = 0.050$) and an increased total fluid requirement at 24 hours (12,125 (11,664) mL vs. 11,125 (7,575) mL, $p = 0.032$). In only those patients with TBI, no differences were found in mortality or fluid requirements between those TBI patients who did and did not receive TXA. However, the sample size of TBI patients in our study is much smaller, and we are likely not sufficiently powered to detect these differences.

Figure 2 shows that the effect of TXA versus no TXA varies with transfusion, SBP, need for OR, and the timing of TXA administration.

Figure 2*A* shows that the effect of TXA was determined, in part, by the amount of transfused pRBCs. For those who required 0-mL to 1,000-mL or 1,000-mL to 2,000-mL pRBCs, TXA tended to reduce mortality, but those apparent differences

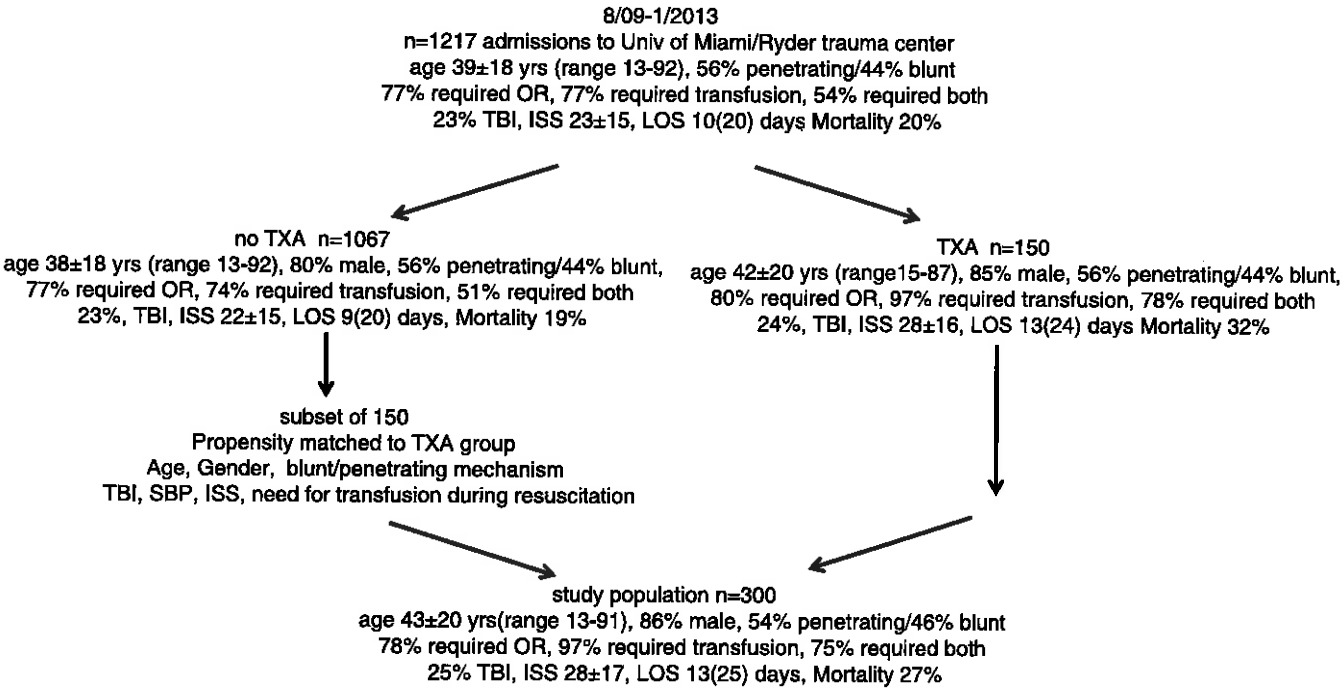

Figure 1. During a 3.5-year period, 150 of the sickest 1,217 patients at a Level 1 trauma center received TXA. These were propensity matched to 150 patients with similar demographics and injuries who did not receive TXA.

were not statistically significant. Even if the two groups were combined, the difference was still not significant (mortality, 5.7% with TXA vs. 12.7% with no TXA, $p = 0.0959$). However, in those who received greater than 2,000-mL pRBCs, mortality was 49% with TXA versus 24% without, and this difference was significant ($p = 0.0065$).

Figure 2*B* suggests that the effect of TXA was determined, in part, by admission SBP. If the two groups with an admission SBP of less than 120 mm Hg were combined, the mortality with TXA was 30.3% versus 17.4% without, and this difference was significant ($p = 0.0178$).

TABLE 2. Demographics, Admission Vital Signs and Laboratory Values, and Other Characteristics

	No TXA (n = 150)	TXA (n = 150)	*p*
Age	43 ± 20	42 ± 20	0.896
Male sex	86%	85%	0.869
Penetrating mechanism	54%	54%	1.000
TBI	26%	24%	0.689
ISS	28 ± 17	28 ± 16	0.881
Revised Trauma Score (RTS)	7.108 (1.519)	7.108 (1.721)	0.416
SBP, mm Hg	101 ± 32	98 ± 30	0.308
HR, beats/min	103 ± 29	105 ± 26	0.533
GCS score	11 ± 5	11 ± 5	0.539
Base excess, mEq/L	−7.7 ± 6.9	−7.4 ± 7.0	0.665
Hematocrit	34 ± 7	34 ± 5	0.992
pH	7.30 (0.21)	7.32 (0.19)	0.547
OR requirement	75.3%	80.0%	0.332
Time to OR, min	**35 (90)**	**24 (64)**	**0.018**
Transfusion requirement	96.7%	96.7%	1.000
Time to transfusion, min	3 (5)	3 (19)	0.885

Data are expressed as mean ± SD or median (IQR).

TABLE 3. Fluid Requirements and Other Outcomes

	No TXA (n = 150)	TXA (n = 150)	*p*
Emergency resuscitation area			
pRBC, mL	1,000 (1,000)	1,000 (750)	0.284
FFP, mL	920 ± 463	824 (593)	0.340
Crystalloid, mL	1,600 (1,950)	1,125 (1,531)	0.083
Total Fluid, mL	**2,675 (3,505)**	**2,250 (2,275)**	**0.025**
Operating room			
pRBC, mL	**1,500 (1,750)**	**2,250 (3,450)**	**0.002**
FFP, mL	**1,125 (1,250)**	**1,750 (2,500)**	**0.005**
Crystalloid, mL	4,500 (3,025)	4,000 (3,600)	0.605
Total fluid , mL	6,450 (5,100)	7,050 (8,859)	0.092
Estimated blood loss, mL	1,500 (2,413)	1,500 (3,350)	0.582
24-h totals			
pRBC, mL	**1,999 (2,000)**	**2,250 (4,188)**	**0.009**
FFP, mL	1,218 (1,060)	1,684 (2,996)	0.197
Crystalloid, mL	7,663 (5,701)	7,600 (6,137)	0.985
Total fluid, mL	10,675 (8,108)	12,102 (11,663)	0.890
Estimated blood loss, mL	1,450 (3,300)	1,528 (3,883)	0.173
Outcomes			
ICU, d	4 (14)	5 (18)	0.968
LOS, d	13 (28)	13 (24)	0.745
Mortality	23%	31%	0.091
Mortality (excluding DOA)	**17%**	**27%**	**0.024**

Crystalloid, lactated Ringer's or saline.

TABLE 4. Effect of TBI

	No TBI			TBI		
	TXA	No TXA	Effect of TXA	TXA	No TXA	Effect of TXA
	n = 109	n = 105	*p*	n = 32	n = 34	*P*
Mortality	**22.9%**	**13.3%**	**0.050**	40.6%	26.5%	0.169
ISS	21 (20)	20 (24)	0.457	36 (27)	32 (17)	0.325
Emergency resuscitation area						
pRBCs	57%	67%	0.527	78%	74%	0.348
FFP	17%	14%	0.318	38%	24%	0.333
Total fluid	**2,000 (2,220)**	**2,600 (3,250)**	**0.048**	3,575 (2,277)	4,075 (4,454)	0.808
Operating room						
pRBCs	81%	62%	0.560	72%	47%	0.550
FFP	62%	40%	0.419	63%	32%	0.687
Total fluid	7,000 (10,134)	6,250 (4,850)	0.076	9,625 (8,176)	8,250 (6,974)	0.508
24-h total						
pRBCs	97%	97%	0.286	97%	97%	0.278
FFP	61%	46%	0.430	75%	50%	0.382
Total fluid	**12,125 (11,664)**	**11,125 (7,575)**	**0.032**	15,170 (13,100)	11,123 (10,017)	0.235

Data are expressed as median (IQR).

Figure 2*C* shows that the difference in mortality between TXA and propensity-matched controls was least in the group that received TXA at 71 minutes to 132 minutes. With either rapid administration (<70 minutes) or delayed administration (>132 minutes), mortality was significantly higher with TXA versus control.

Figure 2*D* shows that in those patients who required no OR, mortality was almost 40% lower in the patients treated with TXA, but this apparent difference was not statistically significant. However, mortality was more than two times higher in those who received surgery within 30 minutes ($p = 0.0469$) or after 30 minutes ($p = 0.0124$).

DISCUSSION

The major new findings of this study are that in an extremely sick subset of trauma patients, TXA increased pRBC requirements, total fluid requirements, and mortality relative to propensity-matched controls, who did not receive the drug.

There are few studies that have had as big an impact on trauma surgery and surgical critical care as CRASH-2.[1] This was a prospective, multicentered, randomized, blinded, placebo-controlled trial that showed that an inexpensive, generic compound (TXA) safely reduced the risk of death in

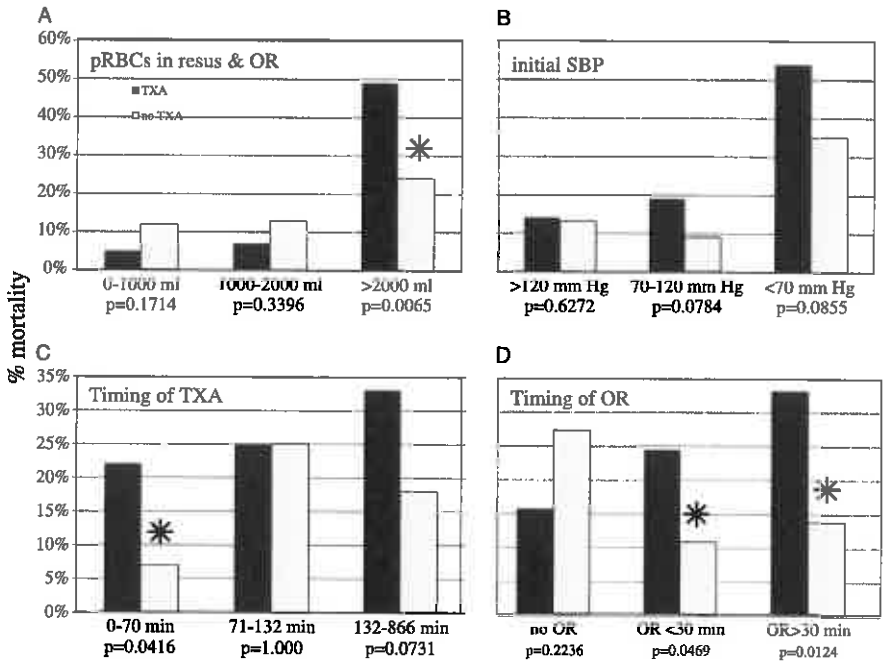

Figure 2. Mortality with and without TXA in various subgroups.

20,000 bleeding trauma patients. Nonetheless, both civilian and military thought leaders have recognized some knowledge gaps with the use of TXA.[5,6] We initially set out to review our own institution's experience with this compound and were absolutely surprised by the results.

It should be emphasized that this subset is by no means typical of the average trauma patient population. Every patient was in severe traumatic shock: 80% presented with an initial SBP of less than 120 mm Hg and 29% had an SBP of less than 70 mm Hg. Base deficit was −8 ± 7 mEq/L. OR was required in 78% at a median (IQR) of 27 (75) minutes (mean ± SD, 87 ± 152 minutes), transfusion was required in 97% at a median (IQR) of 3 (9) minutes (mean ± SD, 38 ± 172 minutes), and 75% required both emergency surgery and a transfusion.

In a retrospective analysis, the CRASH-2 authors emphasized that TXA should be given as early as possible to bleeding trauma patients.[3] With TXA versus placebo, treatment within 3 hours or less from injury, or between 1 hour and 3 hours from injury significantly reduced the risk of death caused by bleeding (relative risk, 0.68–0.79). Treatment given after 3 hours increased the risk of death caused by bleeding (relative risk, 1.44), which led to their conclusion that late administration of TXA could be harmful in some conditions.[3] However, that cannot explain these present results because most of our patients received TXA well within the recommended time frame.

Table 1 shows that our patients tended to be older, with more penetrating trauma, and were more hypotensive than the patients in CRASH-2.[1] Only approximately half of the bleeding trauma patients in CRASH-2 required an operation or transfusion; in contrast, 78% of our patients required surgery, and 97% received a transfusion. In CRASH-2, the average time from injury was 2.8 hours to 2.9 hours, whereas virtually all our patients are in the resuscitation bay in less than 1 hour. In our trauma system, the median transport time is 9 minutes, and patients with suspected bleeding receive either a transfusion or operation, often within 30 minutes, as a standard of care. Furthermore, at our institution and other Level 1 trauma centers like it, massive transfusion protocols and damage-control surgery are activated within minutes for those in extremis. When resources such as these are available, these present data suggest that TXA does not have a positive effect on trauma outcomes.

Figure 2 shows two situations where TXA was likely to have a benefit versus no TXA. In the 166 of the 300 patients who required less than 8 U of pRBCs, mortality was 5.7% with TXA compared with 12.7% without ($p = 0.0959$). A simple power calculation shows that if that trend had continued, it is likely to become significant with fewer than 50 more TXA patients and 50 more matched controls. Similarly, there were 61 of the 300 patients who did not receive surgery; if the same trend had continued, it is likely to become significant with fewer than 60 more TXA patients and 60 more matched controls.

The concept of acute trauma–induced coagulopathy is gaining traction. The complex pathophysiologic mechanisms implicated in this process lead to malignant thrombin generation, plasmin generation, and inflammation. This will impair the balance between clot formation and clot lysis, with an increased tendency of hyperfibrinolysis. This is present in 2% to 8% of the sickest trauma patients and associated with shock and increased mortality.[9,10]

There is accumulating evidence that viscoelastic monitoring can effectively diagnose hyperfibrinolysis and should be an important adjunct in establishing this diagnosis.[6,7,9–12] An LY30 greater than 3% defines clinically relevant hyperfibrinolysis and strongly predicts the requirement for massive transfusion and an increased risk of mortality in trauma patients presenting with uncontrolled hemorrhage. This threshold value for LY30 may represent a critical indication for treatment with TXA or other antifibrinolytics.[7,13]

However, viscoelastic monitoring is not routinely available at most trauma centers.[7] In the absence of viscoelastic monitoring, the proper time to treat this dysfunctional pathologic response could be in the immediate period following trauma,[14–16] before lifesaving interventions such as transfusion of blood products or emergency surgery. Accordingly, some trauma systems have recently begun incorporating TXA in the prehospital setting.[17] We believe there is merit in further investigating the use of TXA in the prehospital setting.

The most likely reason why our data showed no benefit of early TXA, in contrast to CRASH-2, was relatively simple. The subset who received TXA in 0 minute to 70 minutes also had 74% who required OR (in a median [IQR] of 19 [22] minutes), and 96% also received a transfusion (in a median [IQR] of 3 [7] minutes). The fact is that, in our hands, most of the time, TXA was administered in the OR after the patient had already received a transfusion.

There is no definitive explanation for the increased fluid requirements in the patients who received TXA, but we speculate that it may be related to a well-described adverse property of TXA. The initial bolus is ideally given at a rate of 100 mg/min, which is the upper limit of the recommended rate in nontrauma patients.[18] Hypotension has been observed as an adverse reaction when TXA is administered too rapidly. There are no data in trauma patients, but it is conceivable that when TXA is infused at this rate into an already hypotensive and hemorrhaging trauma patient, their hypotension could be exacerbated, leading to increased fluid requirements.

There are several limitations that must be considered. This was a retrospective, observational, single-center study, so there may have been a selection and/or surveillance bias. We tried to account for these issues by using consecutive cases and by matching by propensity scores. However, propensity score matching is limited to the variables included in the model. For nonincluded variables, the patients may not necessarily match, and since the TXA was given at the attending surgeon's discretion, other variables may have determined the need for the TXA. Nevertheless, no statistical method can truly substitute for a randomized control trial. The sample size was also composed of 150 TXA patients and 150 propensity-matched controls. In CRASH-2, 20,000 patients were needed to demonstrate a 0.8% absolute reduction in death cause by hemorrhage. A sample size this great will be difficult to replicate at any one center. Lastly, TXA did not become available at our trauma center until March 2011. There were patients from before and after this date included in the matching procedure to obtain propensity scores.

In conclusion, for our highest injury acuity patients, TXA was associated with increased, rather than reduced, mortality, no matter what time it was administered. This lack of benefit

can probably be attributed to the rapid availability of fluids and emergency OR. Prospective studies are needed to further identify conditions that may override benefits from TXA.

AUTHORSHIP

E.J.V. is directly responsible for all aspects of this study. He participated in the collection, analysis, and interpretation of data as well as drafting and revision of the manuscript, figures, and tables. C.J.A., R.M.V.H., J.M.J. participated in the collection of data as well as revision of the manuscript, figures, and tables. H.L. performed the propensity analysis and reviewed the statistical procedures A.S.L., N.N., C.I.S. were medically responsible for the patients in this study; treatments were administered at their discretion. In addition, they participated in the conception and experimental design as well as revision of the manuscript, figures, and tables. K.G.P. had overall responsibility for the study, including conception and experimental design; analysis and interpretation of data; drafting and revision of the manuscript, figures, and tables; statistical expertise and evaluation; obtaining funding for this project; and supervision.

DISCLOSURE

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PERSPECTIVE

Tranexamic acid for trauma: Filling the 'GAP' in evidence

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Abstract

Following findings of the Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage (CRASH-2) trial, tranexamic acid (TxA) use post trauma is becoming widespread. However, issues of generalisability, applicability and predictability beyond the context of study sites remain unresolved. Internal and external validity of the CRASH-2 trial are currently lacking and therefore incorporation of TxA into routine trauma resuscitation guidelines appears premature. The Pre-hospital Antifibrinolytics for Traumatic Coagulopathy and Haemorrhage (PATCH)-Trauma study is a National Health and Medical Research Council-funded randomised controlled trial of early administration of TxA in severely injured patients likely to have acute traumatic coagulopathy. The study population chosen has high mortality and morbidity and is potentially most likely to benefit from TxA's known mechanisms of action. This and further trials involving appropriate sample populations are required before evidence based guidelines on TxA use during trauma resuscitation can be developed.

Key words: *evidence-based practice, haemorrhage, resuscitation, tranexamic acid, wounds and injuries.*

Emergency and pre-hospital clinicians play an important role in the management of trauma patients. Any single intervention that purports to improve outcome is remarkable and particularly so when the intervention appears to only show benefit if administered within the first 3 h of the traumatic event. Importantly, this is a time frame directly within our sphere of influence.

Tranexamic acid (TxA) is a relatively simple compound – a synthetic derivative of the amino acid lysine. It prevents binding to the lysine residues on fibrin by plasminogen, thereby preventing the subsequent cleavage of plasmin and its degradation of fibrin. TxA has been used extensively in cardiac surgery,[1] orthopaedic surgery,[2] and in its oral form for the management of menstrual bleeding[3] and in oral surgery.[4] More recently, TxA was shown to significantly improve mortality when given to potentially bleeding trauma patients (the Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage [CRASH-2] study).[5] The present study has provoked international debate, about its generalisability, applicability and predictability beyond the context of the study sites.

We support appropriate implementation of evidence into practice, when the evidence relates to the population at risk. For 90% of the world's adult trauma patients at risk of significant bleeding, CRASH-2 provided important evidence to guide

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management. On this basis TxA has appropriately been included on the World Health Organization's list of essential medications. The current evidence supports considering TxA at any centre that has an injury epidemiology similar to the CRASH-2 trial, provided it is given within 3 h of injury.

There is substantially less certainty when interpreting and applying the CRASH-2 trial results to trauma systems and populations that are different from most of those studied in CRASH-2. There are several reasons why inferences about study results might or might not hold over variations in individuals, settings, interventions and outcomes: different populations from the study population, variation in interventions, variation in outcomes and contextual interactions. External validation of CRASH-2 is currently lacking and must be considered according to the three pillars of external validation: generalisability, applicability and predictability – the 'GAP'.[6,7]

Generalisability is the extent to which a study sample represents the study population accurately. The CRASH-2 study sample somewhat reflects it' study population – trauma patients at risk of significant bleeding, presenting to hospitals mostly in low to middle income countries, many of which had rudimentary pre-hospital care and emergency medicine capability, minimal blood supply, limited access to advanced radiological investigations and interventions, and basic operative and postoperative care facilities.

However, patients enrolled in CRASH-2 were a subgroup of such trauma patients not expected to benefit from TxA administration. Patients who were expected to benefit or to be harmed were excluded, and it is unknown how many of these there were. This might explain why there was no difference in the amounts of blood transfused between the study group and the control group.

Several limits to generalisability might therefore be postulated – (i) the population studied might not represent 'significant haemorrhaging' trauma patients. There is no reporting of the total population injured or the total number with hypotension and haemorrhage and only the numbers 'post-randomisation' are included; (ii) massively haemorrhaging patients might have been excluded from the study if the treating doctors felt TxA was indicated; and (iii) massively haemorrhaging patients might have been excluded because of a large proportion of pre-hospital deaths. It is difficult to then advocate the use of a drug across a total population when its proven benefits apply only to a subpopulation defined as those not expected to benefit.

Applicability describes the extent to which an intervention, with demonstrated outcomes, can be judged effectively for relevance to a different setting and/or to a different population group. Less than 2% of the CRASH-2 study cohort were treated in countries with advanced trauma systems similar to those available in Australasia (i.e. advanced pre-hospital and hospital-based critical care systems that routinely treat bleeding and coagulopathy with rapid access to blood products, surgery and angiography). Of those patients presenting to hospital 'at risk of significant haemorrhage', only 50% of patients were administered blood products, and a median of only 3 units to each transfused patient.

Most included hospitals are unlikely to have had facilities or practiced resuscitation supported by complex massive transfusion guidelines. The question of whether the addition of TxA to the complex management regime currently practiced in advanced trauma systems is effective and efficient remains unanswered to date. Further unanswered questions surround the interaction of TxA with components of massive transfusion guidelines and whether it predisposes to thromboembolic AEs – would such AEs be additive or multiplicative?

Predictability refers to the extent to which study outcome measures relate to meaningful health or social outcomes; for example, injury, morbidity, mortality, quality of life, and educational and economic achievements. TxA in the CRASH-2 study resulted in reduction in in-hospital mortality from 16.0% to 14.5%, an impressive 10% relative reduction in mortality. However, baseline mortality among trauma patients in Australasian trauma centres with the same characteristics as included into the CRASH-2 trial, that is hypotensive or tachycardic or both, is much lower. Significant reductions in absolute risk of death are more difficult to achieve when preventable death rates are low – in most advanced systems modern trauma care has reduced the preventable death rate from around one in three to around one in 50. It is unknown whether the risk reduction seen in this trial would apply to lower mortality settings such as ours.

It is for good reason that the incorporation of TxA into trauma resuscitation guidelines has been slow in many places. In advanced military trauma systems (systems that arguably receive the greatest number of patients with major haemorrhage), there are as yet unanswered questions regarding benefits versus harm in the use of TxA, including risks of thromboembolism and perioperative seizures, and a largely unproven mechanism of action. These concerns are reflected in a recent systematic review with persistent uncertainty on both the effectiveness in preventing mortality and the safety profile of TxA when given to patients undergoing surgery.[8]

We need to be mindful that observational studies of a similar agent, aprotinin, revealed increased thrombotic events after early trials had reported no difference.[9,10] Although no additional vascular occlusive events were detected with TxA in CRASH-2, diagnostic modalities such as CT and US were unlikely to have been extensively used. In the Military Application of Tranexamic Acid in Trauma Emergency Resuscitation (MATTER) observational study in the USA and UK Military, rates of pulmonary embolism and deep venous thrombosis were significantly higher among those who received TxA (2.7% and 2.4%) than those who did not get TxA (0.3% and 0.2%). Whether TxA is responsible for this difference, or whether it is the result of differences in injury pattern or severity, as some have advocated, cannot be answered in this non-randomised study.[11]

The degree of promotion of TxA by CRASH-2 researchers based on their trial is of concern, especially when applying the results across vastly differ-

ent trauma systems. Their conclusions relate to the total trauma population of patients with significant bleeding – a population that was likely not studied. Cartoon animations, manga comics, a choir featuring 'Stop my bleeding by giving tranexamic acid', advocacy to high profile institutions to promote use and the 'trauma promise' website all appear to 'sell' the benefits rather than present the actual evidence. Claims such that TxA could have saved a substantial proportion of soldiers buried in Arlington cemetery seem to be conjecture and unduly emotive rather than a proper application of evidence based medicine.[12]

We should be scientifically rigorous about the applicability and predictability of the evidence for TxA to trauma patients being treated in our centres. TxA is most likely to benefit patients with acute traumatic coagulopathy (ATC), in whom fibrinolysis is associated with poor outcomes. The population of patients with ATC and massive haemorrhage (measured by massive transfusions) are not the same.[13] Only about one-quarter of trauma patients who receive massive transfusions also have ATC, and many patients who have ATC do not need any blood transfusion. Patients with ATC have higher mortality rates, whether or not they have significant bleeding.[14] We should not ignore this important subgroup of patients by focusing management on massive haemorrhage only.

If the survival benefits of TxA are applicable to our setting, we will need to postulate the causal pathway in order to select the correct target population for research and subsequent management. The effect of TxA on ATC has been previously considered.[15] Possible additional mechanisms of action include effects on inflammation,[16] effects on endothelial cells that lead to strengthening and development of blood vessels,[17] or neural protection by reduction in intracranial haemorrhage or preservation of the blood–brain barrier.

Authoritative military and civilian experts have agreed on the need for a randomised controlled trial of TxA in developed trauma systems before it is incorporated into practice guidelines.[8,18] The Australasian Pre-hospital Antifibrinolytics for Traumatic Coagulopathy and Haemorrhage (PATCH)-Trauma study is the only such study planned or underway. It is a National Health and Medical Research Council (NHMRC)-funded randomised controlled trial of early administration of TxA in severely injured patients likely to have ATC. It will test the effectiveness of early (pre-hospital) administration of TxA in developed trauma systems to improve 6-month outcomes and assess adverse effects when used with current management regimes. The study population chosen has high mortality and morbidity and potentially the most likely to benefit from TxA's known mechanisms of action. The initial pathophysiology of ATC and the effect of TxA on haemostatic mechanisms will also be explored.

In populations represented in the CRASH-2 study, and patients in remote areas of developed countries where access to definitive care might be delayed, TxA should be considered. Advocating routine use across all trauma systems appears premature when the effectiveness and risks are not known. The PATCH-Trauma study is designed to fill this 'GAP' in evidence.

The PATCH-Trauma study will determine the effect of early administration of TxA, compared with placebo, on mortality and favourable outcomes (moderate disability or good recovery) at 6 months in severely injured adults at high risk of acute traumatic coagulopathy.[19] Adult (age ≥18 years) patients with a Coagulopathy of Severe Trauma score ≥3 (patients at risk of ATC)[20] where the first dose of study drug can be given within 3 h of injury will be enrolled as soon as possible after injury, with the majority of enrolments expected to be before arrival at an ED. The primary measure of outcome will be proportion of patients with a favourable outcome at 6 months (moderate disability to good recovery, Glasgow Outcome Score Extended [GOSE] scores 5–8) compared with those who have died (GOSE 1) or have severe disability (GOSE 2–4).

The PATCH-Trauma study is expected to commence across multiple sites in Australia and New Zealand enrolling a total sample size of 1184 (579 per group), which will allow for a 90% power to detect a 9% absolute difference in favourable GOSE outcome at 6 months after injury, using a two-sided 95% confidence interval.

Competing interests

All authors are investigators in the PATCH-Trauma trial. PAC is a section editor for *Emergency Medicine Australasia*.

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Design of the Study of Tranexamic Acid during Air Medical Prehospital Transport (STAAMP) Trial: Addressing the Knowledge Gaps

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ABSTRACT

Hemorrhage and coagulopathy remain major drivers of early preventable mortality in military and civilian trauma. The development of trauma-induced coagulopathy and hyperfibrinolysis is associated with poor outcomes. Interest in the use of tranexamic acid (TXA) in hemorrhaging patients as an antifibrinolytic agent has grown recently. Additionally, several reports describe immunomodulatory effects of TXA that may confer benefit independent of its antifibrinolytic actions. A large trial demonstrated a mortality benefit for early TXA administration in patients at risk for hemorrhage; however, questions remain about the applicability in developed trauma systems and the mechanism by which TXA reduces mortality. We describe here the rationale, design, and challenges of the Study of Tranexamic Acid during Air Medical Prehospital transport (STAAMP) trial. The primary objective is to determine the effect of prehospital TXA infusion during air medical transport on 30-day mortality in patients at risk of traumatic hemorrhage. This study is a multicenter, placebo-controlled, double-blind, randomized clinical trial. The trial will enroll trauma patients with hypotension and tachycardia from 4 level I trauma center air medical transport programs. It includes a 2-phase intervention, with a prehospital and in-hospital phase to investigate multiple dosing regimens. The trial will also explore the effects of TXA on the coagulation and inflammatory response following injury. The trial will be conducted under exception for informed consent for emergency research and thus required an investigational new drug approval from the U.S. Food and Drug Administration as well as a community consultation process. It was designed to address several existing knowledge gaps and research priorities regarding TXA use in trauma. **Key words** trauma; prehospital; tranexamic acid; clinical trial; hemorrhage; coagulopathy

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Introduction and Rational for Tranexamic Acid in Trauma

Hemorrhage and coagulopathy remain major drivers of preventable early death following injury.[1–4] Up to 80% of deaths in the first hour and more than 50% of deaths in the prehospital setting are due to hemorrhage.[1] It has become increasingly recognized that trauma-induced coagulopathy (TIC) occurs early and carries significant sequela. Once thought to be an iatrogenic phenomenon, several studies have now shown that coagulation abnormalities are evident at the scene of injury and upon admission to the trauma center.[2,5–7] Patients who develop TIC have been consistently shown to have worse outcomes.[2,5,8,9] TIC involves a cascade of events related to tissue injury and hemorrhage that results in systemic activation of protein C, hyperfibrinolysis, endothelial and platelet dysfunction, complement activation, and release of inflammatory mediators.[10–15] Hyperfibrinolysis has been shown to be a primary component in the development of TIC.[16]

Patients with hyperfibrinolysis are at risk for significantly worse outcomes. Authors have reported mortality rates between 52 and 88% for patients with hyperfibrinolysis on measures of viscoelastic coagulation such as thromboelastography (TEG) at admission.[16–20] Additionally, these patients are at higher risk for massive transfusion, multiple organ failure, longer intensive care unit stay, and overall length of stay.[16,18,20–22] More recently, it has been recognized that lower levels of fibrinolytic activation are associated with poor outcomes.[21] Raza et al. found only 5% of patients had hyperfibrinolysis defined on TEG; however, 57% had evidence of moderate fibrinolytic activity defined as plasmin–antiplasmin complex levels twice normal.[22]

TXA is a synthetic derivative of lysine that binds competitively to plasminogen to prevent conversion to active plasmin, which degrades fibrin. Investigators have hypothesized that the antifibrinolytic properties

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of TXA would reduce bleeding and need for blood transfusion with resultant reductions in mortality and morbidity. There is evidence that TXA may have effects outside of antifibrinolysis. Plasmin has proinflammatory effects though activation of inflammatory cells, platelets, and endothelial cells, and plays a role in innate immune signaling.[23,24] Plasmin induces chemotaxis of monocytes and dendritic cells and promotes the release of proinflammatory cytokines.[24,25] Thus, TXA may exert a beneficial action through inhibition of plasmin and attenuation of proinflammatory, ischemia–reperfusion, and complement activation responses.[11,26–28]

CIVILIAN AND MILITARY STUDIES OF TRANEXAMIC ACID IN TRAUMA

The CRASH-2 trial randomized over 20,000 patients in 40 countries to receive TXA or placebo. Tranexamic was given as a 1-g bolus over 10 minutes followed by 1 g over 8 hours, a dose known to inhibit fibrinolysis. The authors reported a significant absolute risk reduction in 28-day mortality of 1.5%, and 0.8% in death from hemorrhage among those receiving TXA.[29] There was no difference in vascular occlusive events reported. An exploratory analysis demonstrated that the greatest reduction in death from hemorrhage occurred if TXA was given within 1 hour of injury and this benefit persisted until 3 hours, after which it appear mortality increased in the TXA group.[30] These encouraging results spurred interest in TXA as a therapy for the hemorrhaging trauma patient.

Despite this, several concerns have been raised surrounding the CRASH-2 trial.[31,32] Only half of patients received red cell transfusions and no data were collected on injury or shock severity, coagulopathy or fibrinolysis, or other blood products administered. There was no evaluation of the mechanism of these improved outcomes. Importantly, there was no difference in transfusion requirements between groups, suggesting the benefits seen may be due to effects outside the antifibrinolytic properties of TXA. Adverse events were not systematically collected. Finally, the trial took place almost exclusively in the developing world, with only 1.4% of patients treated in hospitals with developed trauma systems. Although this trial has resulted in implementation of TXA in many trauma centers around the world, there remain concerns about the applicability to modern developed trauma systems in the United States and Europe.

Military application of TXA has been promising as well. The MATTERs study of nearly 900 combat casualties was a retrospective cohort that demonstrated a 6.5% lower unadjusted mortality despite higher injury severity, and independent association with lower adjusted mortality and coagulopathy in those receiving TXA.[33] These findings were confirmed in the MATTERs II study in over 1,000 combat casualties.[34] These studies also demonstrated the greatest benefit of TXA in massive transfusion patients. The retrospective nature of these studies made it impossible to investigate underlying mechanisms driving these benefits. Transfusion requirements were higher in the TXA group; however, the higher injury severity confounds the finding. A higher rate of venous thromboembolic events was also found in the TXA group, raising safety concerns.

Although the reduction in mortality persists in both civilian and military studies, the discrepancies between MATTERs and CRASH-2 demand further analysis regarding safety, mechanism, dosage, and timing of TXA. There is little evidence supporting the use of TXA in the civilian prehospital setting.[35] The benefits of TXA given within the first hour from injury have stimulated interest in potential prehospital administration, bolstered by success of prehospital administration in military studies.[30,36] Vu and colleagues report the first administration of civilian prehospital TXA; however, there was no follow-up for patient outcomes or adverse events.[37]

Care must be taken prior to widespread adoption of TXA in the civilian prehospital setting. The safety profile remains uncertain. In light of concerns over increased venous thromboembolism events in the MATTERs trial and the limitations of the adverse event reporting in the CRASH-2 trial, optimal safety has not been established.[29,32,33] There are further concerns related to aeromedical evacuation times that have not been adequately studied to justify widespread integration.[38] Development of rigorous protocols for patients at risk of hemorrhage with robust performance improvement are necessary, as one study reported that 30% of patients receiving prehospital TXA did not meet indications.[36]

DESIGN OF THE STAAMP TRIAL

Given the evidence supporting early TXA use in trauma, as well as the unanswered questions regarding safety, applicability in modern trauma systems, and prehospital administration, the United States Department of Defense (DoD) issued a program announcement requesting proposals for prospective clinical trials examining the effects of TXA in the treatment of patients with traumatic hemorrhage.[39] In response, we designed the Study of Tranexamic Acid during Air Medical Prehospital transport (STAAMP) trial.[40] The objective of this trial is to determine the effect of prehospital TXA infusion as compared to placebo during air medical transport in patients at risk of traumatic hemorrhage on 30-day mortality. We hypothesize that TXA will result in improved outcomes when administered by air medical providers during the prehospital

TABLE 1. Specific aims of the STAAMP trial

Primary aim	Determine whether prehospital tranexamic acid compared to placebo reduces 30-day mortality in patients at risk for traumatic hemorrhage
Secondary aim 1	Determine whether prehospital tranexamic acid compared to placebo reduces the incidence of hyperfibrinolysis and coagulopathy[a]
Secondary aim 2	Determine whether prehospital tranexamic acid compared to placebo results in a lower incidence of 24-hour mortality, acute lung injury, multiple organ failure, nosocomial infection, pulmonary embolism, shock parameters, and early resuscitation requirements[b]
Secondary aim 3	Investigate potential novel mechanisms by which tranexamic acid alters the inflammatory response to injury independent of effects on hyperfibrinolysis[c]
Secondary aim 4	Determine whether different dosing regimens of tranexamic acid are associated with improvements in hyperfibrinolysis, markers of coagulopathy, clinical outcomes, and the early inflammatory response[d]

[a]Hyperfibrinolysis defined as estimated percent lysis (EPL) > 7.5% on rapid-TEG; coagulopathy defined as INR >1.4.
[b]ALI defined as 1992 American–European Consensus Conference definition[48]; MOF defined as Denver MOF score > 3[49]; NI defined by quantitative culture data for pneumonia (>10^4 CFU/mL BAL), catheter-associated bloodstream infections (>15 CFU/segment), and urinary tract infections (>10^5 organisms/mL urine); PE defined as radiographically confirmed PE by CT, echocardiogram, or ventilation/perfusion scan; Shock parameters defined as base deficit and lactate; early resuscitation requirements at 6 and 24 hours.
[c]To include investigation of TXA effects on platelet and leukocyte activation, plasmin-mediated complement activation, and circulating cytokine levels.
[d]Early inflammatory response defined as platelet and leukocyte activation, plasmin levels, complement activation, HMGB1 levels, circulating pro-inflammatory cytokine levels.

phase in developed trauma systems. The specific aims for the STAAMP trial are found in Table 1.

This study is designed as a multicenter, double-blind, placebo-controlled, randomized clinical trial. The intervention includes both a prehospital phase and in-hospital phase. Participating sites include the University of Pittsburgh (coordinating site), University of Rochester, University of Texas San Antonio, and University of Utah. All sites are large academic level I trauma centers with active air medical programs. Eligible subjects include trauma patients undergoing air medical transport to one of the participating centers within 2 hours of injury, with systolic blood pressure (SBP) < 90 mmHg and heart rate (HR) >110 bpm (SBP and HR criteria need not be simultaneous). We selected these inclusion criteria to mimic the physiologic inclusion criteria from CRASH-2, while narrowing the population to those within 2 hours of injury to maximize benefit and exclude those who may be harmed. Exclusion criteria include age <18 or >90 years old, inability to obtain intravenous access, cervical spinal cord injury with motor deficit, prisoner, pregnancy, cardiac arrest > 5 minutes without return of vital signs, penetrating cranial injury, traumatic brain injury with brain matter exposed, isolated drowning or hanging victims, or wearing an opt-out bracelet (see below).

Patients meeting inclusion criteria will be randomized for the prehospital phase by the treating air medical provider. A single prehospital treatment box containing numerically labeled allocation treatment packs in blocks of 8 generated by a computer random number generator will be available on each helicopter. These packs contain identical unlabeled TXA or placebo that will be administered sequentially to enrolled subjects. TXA is stable in a wide variety of field conditions for up to 12 weeks.[41] The prehospital phase includes the intervention arm in which subjects receive 1 g of TXA or the control arm in which subjects receive 1 g of identical placebo. Both TXA and the placebo will be diluted in 100 mL of normal saline (prepared on the helicopter) and infused intravenously over 10 minutes.

The treatment pack number will be provided to research staff upon arrival. This will be entered into a web-based secure program that will provide the in-hospital random allocation to the pharmacy for the in-hospital phase. All subsequent study drug administration will be prepared by the pharmacy to be identical and blinded to subjects and providers. For subjects receiving placebo in the prehospital phase, they will receive an additional 1-g placebo bolus diluted in 100 mL of normal saline over 10 minutes followed by 1 g of placebo infused over 8 hours in-hospital. Thus, placebo patients will receive no TXA throughout the study duration. Subjects receiving TXA in the prehospital phase will be randomized to one of three treatment arms for the in-hospital phase.

Since variable dosing regimens have been used in prior clinical studies,[29,33] the optimal dosing strategy remains unclear. To address this, we have designed 3 dosing regimens that subjects assigned to prehospital TXA may receive (Figure 1). The first is the standard regimen, designed to deliver a similar total TXA dose and administration structure as the CRASH-2 trial. In-hospital subjects will receive a placebo bolus followed by TXA infusion over 8 hours. Subjects will thus receive a total 2-g dose including the prehospital TXA bolus and in-hospital TXA infusion. The second is the repeat regimen, designed to deliver a higher TXA dose. In-hospital, subjects will receive a TXA bolus followed by TXA infusion. Subjects will thus receive a total 3-g dose including the prehospital and in-hospital TXA doses. The third is the abbreviated regimen, designed to deliver only the prehospital TXA dose. In-hospital subjects will receive a placebo bolus followed by placebo infusion. Subjects will thus receive a total 1-g dose from the prehospital bolus, with no further TXA in-hospital. All patients will receive a bolus and infusion in-hospital regardless of in-hospital treatment

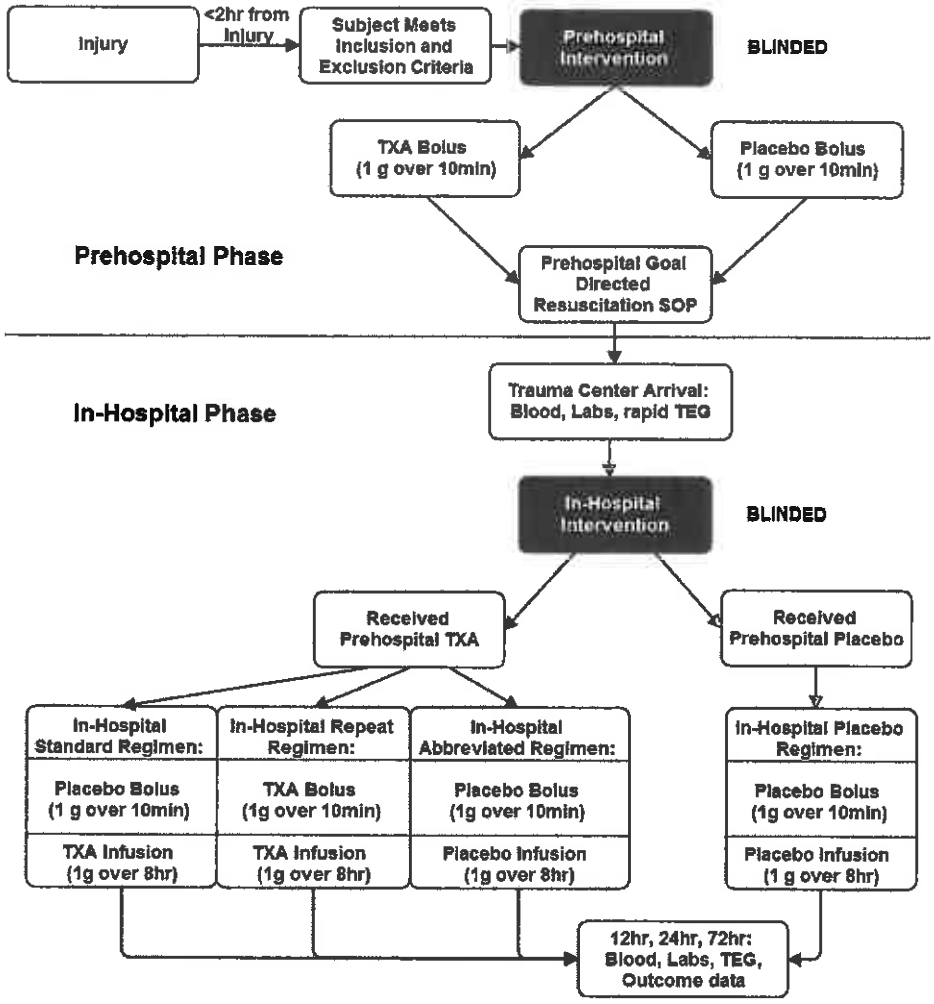

FIGURE 1. 2-phase STAAMP trial intervention schematic.

assignment to maintain blinding during the in-hospital phase of the intervention.

These alternate dosing regimens were designed to provide total doses above and below the current standard regimen used in CRASH-2 and at our institution (1 g TXA bolus followed by 1 g TXA infusion over 8 hours) to examine the possibility of dose–response effects for TXA on clinical or laboratory outcomes. If higher doses prove more effective, investigation of higher TXA dosing will be warranted. However, if the abbreviated regimen produces similar benefits as higher doses, additional doses of TXA may be foregone.

To address the aims of the study, research staff will collect blood for laboratory analysis and outcome data at several time points. Upon arrival, blood will be drawn for laboratory and rapid TEG analysis. Blood will also be collected at 12, 24, and 72 hours. Laboratory analysis includes rapid TEG, conventional coagulation parameters (prothrombin time, partial thromboplastin time, international normalized ratio), base deficit, and D-dimer levels. As part of the investigation into the mechanisms of action, the analysis will also include measurement of activated protein C levels, plasmin–antiplasmin complex levels, serum plasmin levels, plasmin-mediated complement activation (C3a and factor B), high mobility group box 1 (HMGB-1) levels, and a panel of 10 cytokine levels. Additionally, flow cytometry and RT-PCR will be used to determine leukocyte activation and inflammatory gene expression, and the collection at serial time points will allow for an ongoing assessment of TXA effect on these parameters following repeat dosing. Mortality outcomes will be collected at 24 hours, 30 days, and in-hospital. Resuscitation requirements of packed red blood cells, plasma, platelets, and crystalloid will be collected at 6 and 24 hours. Specific adverse events to be collected in-hospital include acute lung injury (ALI), nosocomial infection (NI), multiple organ failure (MOF), seizures, and pulmonary embolism (PE).

Sample size was determined using the primary outcome of 30-day mortality and the primary comparison

for the two prehospital intervention groups. We estimated a 16% baseline mortality based on CRASH-2 as well as the Inflammation and the Host Response to Injury study conducted at eight large academic level I trauma centers in the United States, which included two participating sites for this trial.[42] We sought to detect an effect size of 6.4% difference in 30-day mortality. Using a two-sided alpha of 0.05 and power of 85%, 497 subjects are required per arm in the prehospital phase with a total study sample size of 994 subjects. Based on the expected volume of eligible patients across the participating sites, recruitment will occur over a 3-year period to achieve our sample size. All analyses will be conducted as intention to treat and site stratification will be accounted for in statistical tests. All outcomes will be compared between both the prehospital phase TXA and placebo groups. Outcomes will also be compared between the different TXA dosing regimens from the in-hospital phase; however, these will be primarily exploratory as the study was not powered to compare all four possible dosing regimens. Predefined subgroups selected for additional exploratory analysis include subjects defined by 1) blood transfusion status; 2) traumatic brain injury; 3) transfer status; 4) requirement for operative intervention within 24 hours of admission; 5) therapeutic anticoagulation status; and 6) massive transfusion status. Two interim analyses are planned and will be overseen by the data safety monitoring board.

This study will be performed under exception from inform consent for emergency research as outlined under U.S. Federal regulation 21 CFR 50.24.[43] This represents one of the major challenges to conducting prehospital emergency research, as significant scrutiny and safeguards are in place to ensure appropriate provision of this standard. Under this regulation for emergency research, the study must meet the conditions outlined in Table 2.[44]

Although it may seem intuitive that prehospital emergency research is ideally suited to be conducted under this waiver, substantial justification and support is required by regulatory bodies to ensure all conditions are satisfactorily fulfilled prior to approving an exception from informed consent. For studies pursuing an exception from informed consent for emergency research, the institutional review board (IRB) must determine whether the proposed intervention and study fall under the regulation of the U.S. Food and Drug Administration (FDA). If a study does fall under the regulations of the FDA, the study must be conducted under an investigational new drug application (IND) or investigational device exemption (IDE). This study has completed the FDA IND approval process (IND# 121102). In cases where the IRB determines FDA regulations do not apply, the IRB must also determine whether the study meets the Department of Health and Human Services (HHS) requirements for Emergency Research Consent Waiver under 45 CFR Part 46 and report this to the HHS Office for Human Research Protections.[45]

The exception from informed consent for emergency research also requires a community consultation process at each participating site. This process consists of two parts: 1) public notification of the study, and 2) community consultation. For this study, a multipronged approach was planned. The notification process includes distribution of information regarding the trial in several mediums. A website was created within the existing acute care research website for the University of Pittsburgh (acutecareresearch.org). Bumper ads on Pittsburgh Port Authority buses were designed to direct people to the website. Fliers will be distributed throughout area hospital waiting rooms and local community center boards. In-person presentations are planned for several local-area EMS, fire, and police agencies regarding the study. Additionally, an informational video will be posted on YouTube.

The consultation process involves monitoring traffic and hits on the above website. Additionally, the website allows email communication with the study coordinators either anonymously or with return contact information. Phone numbers to the coordinators are also listed and welcome direct feedback. Periodic sampling of view and attitudes of enrolled subjects and family will be recorded. The study will also be presented to the Pennsylvania Department of Health for feedback. A telephone survey will be conducted by an independent company with random digit dialing for 500 households in the study region over 4 weeks. The survey provides information regarding willingness to be enrolled and potential reservations or concerns regarding the study. It also collects demographics, social economic status, and attitudes toward emergency research in general from respondents.

Finally, opt-out bracelets will be made available to any community member by phone or by email. The bracelet is to be worn at all times by the individual who

TABLE 2. Requirements for exception from informed consent for emergency research

1. Presence of a life-threatening medical condition requiring urgent intervention
2. Available treatments are unproven or unsatisfactory for treating the condition
3. Need for scientific study of the intervention to determine safety and/or effectiveness
4. Subjects cannot consent because of their medical condition
5. Therapeutic window is narrow enough to justify intervention before consent can be obtained from patient or representative
6. Potential for direct benefit to subjects
7. Absence of a method to prospectively identify subjects who may become eligible for enrollment
8. Investigation cannot be practicably carried out without the waiver

prospectively does not wish to be enrolled in the case of severe injury, and air medical providers have been trained to look for these prior to enrolling the patient. For patients who are enrolled, informed consent will be obtained to use the patient's data from the patient or legally authorized representative as soon as feasible after in the intervention, as required for exception from informed consent. Although this process is demanding, it is necessary to assure ethically responsible and high-quality emergency research trials, while maintaining public trust and confidence. Our prior experience with the regulatory requirements and community consultation process[46] have streamlined these procedures in the STAAMP trial, and allowed us to help our participating sites navigate these elements as well.

ADDRESSING KNOWLEDGE GAPS

Pusateri et al. developed a consensus list of current knowledge gaps and research priorities regarding the use of TXA in trauma.[32] This trial has the prospect of providing evidence for many of the priority areas identified. This trial is primarily designed to address prehospital use of TXA. This study will also rigorously collect in-hospital complications and morbidity related to the safety profile of TXA, including thromboembolic events, which have not been captured before and can address concerns related to venous thromboembolism and seizures raised in prior studies.[31,33] Further, this study will address the need for additional evidence of efficacy in the civilian trauma population treated within developed trauma systems. Subjects in this trial will have the most advanced trauma care available to them, and will be able to assess the added benefit, if any, of TXA in this setting. Our secondary aims utilize sophisticated laboratory and analysis techniques to investigate the multiple potential mechanisms of action underlying any benefits seen in trauma patients due to TXA administration, including not only the impact on hyperfibrinolysis and coagulopathy, but also the off-target effects on proinflammatory mediators, the complement pathway, and inflammatory cell activation. We have planned an a priori subgroup analysis in traumatic brain injury patients to assess all efficacy and safety outcomes. Further, we will investigate the moderating effect of TXA and blood product resuscitation, and will also explore subgroup analysis outcomes among subjects who did and did not receive blood transfusion. Finally, we will evaluate potential differences in all outcomes among 3 different dosing options in subjects receiving TXA. As a result, this trial directly addresses many of the current knowledge gaps in the field of TXA for trauma.

SUMMARY AND FUTURE DIRECTIONS

Successful completion of the aims of this study will have implications for the care of both civilian and military trauma patients, and allow evidence-based decisions regarding TXA efficacy in developed trauma systems, safety profile, and optimal dosing regimens. Furthermore, the basic science component will lend insight into the mechanism of action of TXA, including both the role in anti-fibrinolysis as well as inflammatory and immunomodulatory effects. This trial received one of three awards funded by the DoD to investigate TXA in trauma. The Resuscitation Outcomes Consortium (PI: Martin Schreiber, MD; Susanne May, PhD) and Washington University St. Louis (PI: Philip Spinella, MD) will also evaluate the use of TXA in trauma, specifically exploring issues related to dosing and traumatic brain injury. These studies, combined with the Pre-hospital Anti-fibrinolytics for Traumatic Coagulopathy and Haemorrhage (PATCH) trial underway in Australia and New Zealand,[35,47] and coupled with the efforts of the Transagency Collaboration for Trauma Induced Coagulopathy (TACTIC) consortium, will contribute tremendously to our understanding of the mechanism and optimal therapeutic approaches to coagulopathy in the hemorrhaging trauma patient.

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Tranexamic Acid (TXA) Administration – Trial Study

(Only for designated agencies participating in the trial study)

I. PURPOSE

To determine the role of Pre-Hospital Tranexamic Acid (TXA) to improve hemorrhagic shock outcomes. And prevent massive internal bleeding by helping to help stabilize clot formation and decrease extravascular bleeding in trauma patients.

II. INCLUSION CRITERIA

Patients must meet trauma triage criteria related to anatomic, physiologic, and mechanism of injury as established by ICEMA. Refer to ICEMA Reference #15030 - Trauma Triage Criteria And Destination Policy.

- Additionally, patient must be: at least 18 years or older, less than three hours post injury, and meet any of the criteria listed below:
  - Blunt or penetrating trauma to the torso with signs and symptoms of hemorrhagic shock including a systolic blood pressure (SBP) of less than 90 mmHg.
  - Major amputation of any extremity, proximal to the wrist and ankle.
  - Bleeding uncontrolled by direct pressure or tourniquet.
  - Estimated external blood loss (EBL) of 500 ml or more in the field.

IV. CONTRAINDICATIONS

- Patients under 18 years old.
- Injury occurred greater than 3 hours ago.
- Isolated head injury.
- Amputation distal to the wrist and ankle.
- Allergy (hypersensitivity or anaphylactic reaction) to TXA.
- Patients with active thromboembolic event such as a stroke, ST Elevation MI (STEMI), Deep Vein Thrombosis (DVT) or pulmonary embolism (PE) occurring within the last 24 hours.

Special Consideration: TXA may be administered, if patients arrive in a non-trauma hospital and is transferred using Continuation of Care and meets the inclusion criteria listed above either prior to or after arrival at the transferring hospital. Refer to ICEMA Reference #8120 – Continuation of Care.

V. PROCEDURE

If patient meets inclusion criteria listed above:

- Administer TXA 1 gm in 100 ml of NS via IV/IO over 10 minutes.
  (Do NOT administer IVP. This will cause hypotension.)

- Place the approved red wristband on patient prior to transporting patient to Trauma Center (TC)

- Trauma base hospital contact is mandatory. Advise trauma base hospital of:

  - Patient assessment, vital signs, EBL and condition
  - TXA administration.

VI. DOCUMENTATION REQUIREMENTS

Must use the ICEMA approved ePCR system:

- Documentation must include:

  - Meets Trauma Triage Criteria
  - Age
  - Weight
  - Date / Time of Injury Onset of Symptoms
  - Mechanism of Injury
  - Initial SBP and vital signs
  - EBL: pre and post TXA administration
  - Blunt or penetrating Trauma location and description of injuries
  - Vital signs including Glasgow Coma Scale (GCS): pre and post TXA administration
  - Date/Time TXA was started.
  - Past medical history
  - Allergies
  - Race/Ethnicity
  - Gender
  - Any service defined questions related to TXA on the ICEMA approved ePCR system.

TRAUMA TRIAGE CRITERIA AND DESTINATION POLICY

I. PURPOSE

To establish Trauma Triage Criteria that is consistent with the American College of Surgeons standards that will help identify trauma patients in the field, and based upon their injuries, direct their transport to an appropriate Trauma Center.

II. DEFINITIONS

Adult Patients: A person appearing to be > 15 years of age.

Pediatric Patients: A person appearing to be < 15 years of age.

Critical Trauma Patients (CTP): Patients meeting ICEMA's Critical Trauma Patient Criteria.

Trauma Center: A licensed general acute care hospital designated by ICEMA's Governing Board as a trauma hospital in accordance with State laws and regulations.

Pediatric Trauma Center: A licensed acute care hospital which usually treats (but is not limited to) persons <15 years of age, designated by ICEMA's Governing Board, meets all relevant criteria, and has been designated as a pediatric trauma hospital, according to California Code of Regulations, Title 22, Division 9, Chapter 7, Section 100261.

Inadequate Tissue Perfusion: Evidenced by the presence of cold, pale, clammy, mottled skin, and/or capillary refill time > 2 seconds. Pulse rate will increase in an attempt to pump more blood. As the pulse gradually increases (tachycardia), it becomes weak and thready. Blood pressure is one of the last signs to change (hypotension). Altered level of consciousness may also be an indicator to inadequate tissue perfusion, especially in the very young.

III. POLICY

A. Transportation For Patients Identified as a CTP

- Adult patients will be transported to the closest Trauma Center.
- Pediatric patients will be transported to a Pediatric Trauma Center when there is less than a 20 minute difference in transport time to the Pediatric Trauma Center versus the closest Trauma Center.

- Helicopter transport shall not be used unless ground transport is expected to be greater than 30 minutes and EMS aircraft transport is expected to be significantly more expeditious than ground transport. If an EMS aircraft is dispatched, adherence to ICEMA Reference #8070 - Aircraft Rotation Policy (in San Bernardino County) is mandatory.

- Patients with an unmanageable airway shall be transported to the closest receiving hospital for airway stabilization. Trauma base hospital contact shall be made.

- Hospital Trauma Diversion Status: Refer to ICEMA Reference #8060 - San Bernardino County Hospital Diversion Policy.

- Multi-Casualty Incident: Refer to ICEMA Reference #5050 - Medical Response to a Multi-Casualty Incident Policy.

- CTP meeting physiologic or anatomic criteria with associated burns will be transported to the closest Trauma Center.

B. Trauma Triage Criteria of the CTP

A patient shall be transported to the closest Trauma Center when any one of the following physiologic and/or anatomic criteria is present following a traumatic event (Trauma base hospital contact shall be made):

1. Physiologic Indicators:

- **Glasgow Coma Scale (GCS)/Level of Consciousness (LOC)**

  - **Adult**
    - GCS $\leq$ 13
    - LOC > 3 minutes
    - nausea/vomiting in the setting of significant head trauma

  - **Pediatric**
    - GCS $\leq$ 13
    - any LOC
    - nausea/vomiting in the setting of significant head trauma

- **Respiratory**

  - **Adult**
    - requiring assistance with ventilation **or**

- hypoxic = O_2 saturation that is consistently < 90% **and a**
- RR < 10 or > 29

➢ **Pediatric**
- requiring assistance with ventilation **or**
- hypoxic = O_2 saturation that is consistently < 90% **and a**
- < 10 years: RR < 12 or > 40
- < 1 year: RR < 20 or > 60

- **Hypotension**

➢ **Adult**
- exhibits inadequate tissue perfusion
- BP < 90 mmHG
- tachycardia

➢ **Pediatric**
- exhibits inadequate tissue perfusion
- abnormal vital signs (according to age)

2. **Anatomic Indicators**:

- **Penetrating injuries to:**

➢ head
➢ neck
➢ chest
➢ abdomen/pelvis extremity proximal to the knee or elbow

- **Blunt chest trauma resulting in**:

➢ ecchymosis
➢ unstable chest wall
➢ flail chest

- **Severe tenderness to**:

➢ head
➢ neck
➢ torso
➢ abdomen
➢ pelvis

- **Paralysis**:
  - traumatic
  - loss of sensation
  - suspected spinal cord injury
- **Abdomen**:
  - tenderness with firm and rigid abdomen on examination
- **Amputations**:
  - above the wrist
  - above the ankle
- **Fractures**:
  - evidence of two or more proximal long bone fractures (femur, humerus)
  - open fractures
  - two or more long bone fractures
- **Skull Deformity**
- **Major Tissue Disruption**
- **Suspected Pelvic Fracture**

3. **Mechanism of Injury**:

If a patient has one or more of the following mechanisms of injury **with** any of the above physiologic or anatomic criteria transport to the closest Trauma Center.

If there are no associated physiologic or anatomic criteria and the potential CTP meets one or more of the following mechanisms of injury, contact a Trauma base hospital for physician consultation to determine the patient destination. In some cases, a Trauma base hospital may direct a patient a non-trauma receiving hospital.

- **High Speed Crash**:
  - initial speed > 40 mph
  - major auto deformity > 18 inches
  - intrusion into passenger space compartment > 12 inches

- unrestrained passenger
- front axle rearward displaced
- bent steering wheel/column
- starred windshield

- **Vehicle Rollover**:
  - complete rollover
  - rollover multiple times
  - unrestrained
  - restrained with significant injuries or high rate of speed

- **Motorcycle Crash**:
  - 20 mph **and/or**
  - separation of rider from the bike with significant injury

- **Non-Motorized Transportation (e.g., bicycles, skate boards, skis, etc.)**:
  - with significant impact > 20 mph and/or
  - pedestrian thrown > 15 feet or run over

- **Pedestrian**:
  - auto-pedestrian with significant impact > 10 mph
  - pedestrian thrown > 15 feet or run over

- **Blunt Trauma to**:
  - head
  - neck
  - torso

- **Extrication**:
  - 20 minutes with associated injuries

- **Death of Occupant**:
  - in same passenger space

- **Ejection**:
  - partial or complete ejection of patient from vehicle

- **Falls**:
  - **Adult**
    - ≥ 15 feet
  - **Pediatric**
    - 3 times the child's height or > 10 feet
- **Submersion with Trauma**

4. **Age and Co-Morbid Factors**

   If the patient does not meet any of the above criteria, make Trauma base hospital contact to determine if a Trauma Center should be the destination for the following patients:

   - pediatric < 9 years of age
   - adult > 65 years of age
   - history of respiratory, cardiac, liver disease, or diabetes
   - history of hematologic or immunosuppressive conditions
   - isolated extremity injury with neurovascular compromise (time sensitive injury)
   - pregnant (> 20 weeks in gestation)
   - inability to communicate, e.g., language, psychological and/or substance impairment

C. Exceptions

The patient is identified as a CTP or a potential CTP, but presents with the following:

- **Unmanageable Airway**:
  - Transport to the closest receiving hospital when the patient **requires intubation**:
    - an adequate airway cannot be maintained with a BVM device; **and**
    - the paramedic is unable to intubate or if indicated, perform a successful needle cricothyrotomy.
- **Severe Blunt Force Trauma Arrest**:
  - Refer to ICEMA Reference #12010 - Determination of Death on Scene.
    - Severe blunt force trauma, pulseless, without signs of life and cardiac electrical activity less than 40 bpm).

- If indicated, pronounce on scene.

➢ If patient does not meet determination of death criteria, transport to closest receiving hospital.

- **Penetrating Trauma Arrest:**

➢ Refer to ICEMA Reference #12010 - Determination of Death on Scene.
- If the patient does not meet the *"Obvious Death Criteria"* in the ICEMA Reference #12010 - Determination of Death on Scene, contact the Trauma base hospital for determination of death on scene for those patients who suffer a traumatic cardiac arrest in the setting of penetrating trauma with documented asystole in at least two (2) leads, and no reported vital signs (palpable pulse and/or spontaneous respirations) during the EMS encounter with the patient.

➢ Resuscitation efforts on a penetrating traumatic arrest victim are not to be terminated without Trauma base hospital contact.

➢ If indicated, transport to the closest receiving hospital.

- **Burn Patients**:

➢ Refer to ICEMA Reference #8030 - Burn Criteria and Destination Policy.

➢ Burn patients meeting CTP, **transport to the closest Trauma Center.**

➢ Burn patients not meeting CTP, **transport to the closest receiving hospital or a Burn Center.**

- **EMS Aircraft Indications**:

➢ An EMS aircraft may be dispatched for the following events:
- MCI
- Prolonged extrication time (> 20 minutes)
- **Do Not Delay Patient Transport** waiting for an en route EMS aircraft.

- **EMS Aircraft Transport Contraindications:**

  - The following are contraindications for EMS aircraft patient transportation:
    - Patients contaminated with Hazardous Material who cannot be decontaminated and who pose a risk to the safe operations of the EMS aircraft and crew.
    - Violent patients with psychiatric behavioral problems and uncooperative patients under the influence of alcohol and/or mind altering substances who may interfere with the safe operations of an EMS aircraft during flight.
    - Stable patients.
    - Ground transport is < 30 minutes.
    - Traumatic cardiac arrest.
    - Other safety conditions as determined by pilot and/or crew.

- **Remote Locations:**

  - Remote locations may be exempted from specific criteria upon written permission from the ICEMA Medical Director.

D. Considerations

- Scene time should be limited to 10 minutes under normal circumstances.

- Burn patients with associated trauma, should transported to the closest Trauma Center. Trauma base hospital contact shall be made.

E. Radio Contact

- If not contacted at scene, the receiving Trauma Center must be notified as soon as possible in order to activate the trauma team.

- CTP meeting all Trauma Triage Criteria (physiologic, anatomic, mechanism of injury, and/or age and co-morbid factors), a Trauma base hospital shall be contacted in the event of patient refusal of assessment, care and/or transportation.

- In Inyo and Mono Counties, the assigned base hospital should be contacted for CTP consultation and destination.

IV. REFERENCES

Number	Name
5050	Medical Response to a Multi-Casualty Incident Policy
8030	Burn Criteria and Destination Policy
8060	San Bernardino County Hospital Diversion Policy
8070	Aircraft Rotation Policy (San Bernardino County Only)
12010	Determination of Death on Scene

CONTINUATION OF CARE
(San Bernardino County Only)

I. PURPOSE

To develop a system that ensures the rapid transport of patients at the time of symptom onset or injury, to receiving the most appropriate definitive care. This system of care consists of public safety answering point (PSAP) providers, EMS providers, referral hospitals (RH), Specialty Care Centers (Trauma, STEMI or Stroke), ICEMA and EMS leaders combining their efforts to achieve this goal.

This policy shall only be used for:

- Rapid transport of Trauma, STEMI and Stroke patients from RH to Specialty Care Center.
- Specialty Care Center to Specialty Care Center when higher level of care is required.
- EMS providers transporting unstable patients requiring transport to a Specialty Care Center to stop at any closest paramedic receiving hospital for airway stabilization, and continue on to a Specialty Care Center.

It is <u>not</u> to be used for any other form of interfacility transfer of patients.

II. AUTHORITY

California Health and Safety Code, Division 2.5, 1797.204
California Code of Regulations, Title 22

III. DEFINITIONS

Neurovascular Stroke Receiving Centers (NSRC): A licensed general acute care hospital designated by ICEMA's Governing Board as a NSRC.

Referral Hospital (RH): Any licensed general acute care hospital that is not an ICEMA designated TC, SRC or NSRC.

Specialty Care Center: ICEMA designated Trauma, STEMI or Stroke Center.

STEMI Receiving Centers (SRC): A licensed general acute care hospital designated by ICEMA's Governing Board as STEMI Receiving Center with emergency interventional cardiac catherization capabilities.

Trauma Center (TC): A licensed general acute care hospital designated by ICEMA's Governing Board as a trauma hospital in accordance with State laws, regulations and ICEMA policies.

IV. INCLUSION CRITERIA

- Any patient meeting ICEMA Trauma Triage Criteria, (refer to ICEMA Reference #15030 - Trauma Triage Criteria and Destination Policy) arriving at a non-trauma hospital by EMS or non-EMS transport.
- Any patient with a positive ST-elevation MI requiring EMS to a SRC (refer to ICEMA Reference #6070 - Cardiovascular "STEMI" Receiving Centers).
- Any patient with a positive mLAPSS or stroke scale requiring EMS transport to the NSRC.

V. INITIAL TREATMENT GOALS AT RH

- Initiate resuscitative measures within the capabilities of the facility.
- Ensure patient stabilization is adequate for subsequent transport.
- Do not delay transport by initiating any diagnostic procedures that do not have direct impact on immediate resuscitative measures.
  - TIMELINES

    < 30 minutes at RH (door-in/door-out).
    < 30 minutes to complete paramedic continuation of care transport.
    < 30 minutes door to intervention at RC.
- RH shall contact the appropriate Specialty Care Center ED physician directly without calling for an inpatient bed assignment. Refer to attachment SRH-SRC Buddy System Table.
- EMS providers shall make Specialty Care Center Base Station contact.
- The Specialty Care Centers shall accept all referred trauma, stroke and STEMI patients unless they are on Internal Disaster as defined in ICEMA Reference #8060 - Requests for Hospital Diversion Policy (San Bernardino County).
- The Specialty Care Center ED physician is the accepting physician at the Specialty Care Center and will activate the internal Trauma, STEMI, or Stroke Team according to internal TC, SRC or NSRC protocols.

- RH ED physician will determine the appropriate mode of transportation for the patient. If ground transportation is > 30 minutes consider the use of an air ambulance. Requests for air ambulance shall be made to 9-1-1 and normal dispatching procedures will be followed; however, the air ambulance Continuation of Care patient will be transported to the Specialty Care Center identified by the RH.

- Simultaneously call 9-1-1 and utilize the following script to dispatch:

  "This is a Continuation of Care run from ____hospital to ____Trauma, STEMI or Stroke Center"

  Dispatchers will only dispatch transporting paramedic units without any fire apparatus.

- RH must send all medical records, test results, radiologic evaluations to the Specialty Care Center. DO NOT DELAY TRANSPORT - these documents may be FAXED to the Specialty Care Center.

VI. SPECIAL CONSIDERATIONS

- If the patient has arrived at the RH via EMS, the RH ED physician may request that transporting team remain with patient and immediately transport them once the minimal stabilization is done at the RH.

- EMT-Ps may only transport patients on Dopamine, Lidocaine and Procainamide drips. Heparin and Integrillin drips are not within the paramedic scope of practice and require a critical care transport nurse to be in attendance. Unless medically necessary avoid using medication drips that are outside of the paramedic scope of practice to avoid any delays in transferring of patients.

- The RH may consider sending one of its nurses with the transporting paramedic unit if deemed necessary due to the patient's condition or scope of practice.

- Nurse staffed critical care (ground or air) transport units maybe used; but may create a delay due to availability. Requests of nurse staffed critical care transport units must be made directly to the transporter agency by landline.

VII. SPECIALTY CARE CENTER - REFERRAL HOSPITAL BUDDY SYSTEM TABLE

NEUROVASCULAR STROKE RECEIVING CENTERS (NSRC)	NEUROVASCULAR STROKE REFERRAL HOSPITALS (NSRH)
Arrowhead Regional Medical Center	• Barstow Community Hospital • Community Hospital of San Bernardino • Desert Valley Hospital • Kaiser Fontana Medical Center • St. Bernardine Medical Center • St. Mary Medical Center
Desert Regional Medical Center	• Colorado River Medical Center • Hi-Desert Medical Center
Loma Linda University Medical Center	• Bear Valley Community Hospital • J.L. Pettis VA Hospital (Loma Linda VA) • Mountains Community Hospital • St. Mary Medical Center • Victor Valley Global Medical Center • Weed Army Community Hospital at Fort Irwin
Pomona Valley Hospital Medical Center	• Chino Valley Medical Center • Montclair Hospital Medical Center
Redlands Community Hospital	• Bear Valley Community Hospital • Community Hospital of San Bernardino • St. Bernardine Medical Center
San Antonio Community Hospital	• Chino Valley Medical Center • Kaiser Ontario Medical Center • Montclair Hospital Medical Center
STEMI RECEIVING CENTER (SRC)	STEMI REFERRAL HOSPITAL (SRH)
Desert Valley Hospital	• Barstow Community Hospital • Victor Valley Global Medical Center • Weed Army Community Hospital at Fort Irwin
Loma Linda University Medical Center	• Arrowhead Regional Medical Center • Bear Valley Community Hospital • J. L. Pettis VA Hospital (Loma Linda VA) • Redlands Community Hospital
Pomona Valley Hospital Medical Center	• Chino Valley Medical Center • Montclair Hospital Medical Center
San Antonio Community Hospital	• Chino Valley Medical Center • Kaiser Ontario Medical Center • Montclair Hospital Medical Center
St. Bernardine Medical Center	• Colorado River Medical Center • Community Hospital of San Bernardino • Kaiser Fontana Medical Center • Mountains Community Hospital
St. Mary Medical Center	• Barstow Community Hospital • Bear Valley Community Hospital • Hi-Desert Medical Center • Robert E. Bush Naval Hospital-29 Palms • Victor Valley Global Medical Center

VIII. REFERENCES

Number	Name
6070	Cardiovascular "STEMI" Receiving Centers
8060	Requests for Hospital Diversion Policy (San Bernardino County)
15030	Trauma Triage Criteria and Destination Policy

TXA Trial Study Proposal: Attachment D
EMS System CQI Plan

STUDY PARTICIPANTS AND QUALITY ASSURANCE LEADERS:

Inland Counties EMS Agency (ICEMA)

- Reza Vaezazizi, MD, Medical Director
- Chris Yoshida-McMath, RN, Trauma Systems Manager

Arrowhead Regional Medical Center (ARMC) - IRB Approval received on June 2, 2014.

- Michael Neeki, DO, Emergency Department Physician and Principal Investigator
- David Wong, MD, Trauma Medical Director
- Richard Vara, RN, Trauma Program Manager (TPM)
- Joy Peters, RN, Prehospital Liaison Nurse
- Other designees.

Loma Linda University Medical Center (LLUMC) - Currently in the process of obtaining IRB approval.

- Richard Catalano, MD Trauma Medical Director
- Xian Luo-Owen, MD Trauma Research Coordinator
- Michael May, RN, Trauma Program Manager
- Other designees

Rialto Fire Department (RFD)

- Michael Neeki, MD, Medical Director
- Joe Powell, EMS Coordinator

American Medical Response (AMR)

- Sam Chua, MD, Medical Director
- Lisa Higuchi, EMS Coordinator

San Bernardino County Fire Department (SBCFD)

- Leslie Parham, RN, EMS Coordinator

Rancho Cucamonga Fire District (RCFD)

- Sandy Carnes, RN, EMS Coordinator

Big Bear Fire Department (BBFD)

- Randy Harold, Battalion Chief
- Brian Parham, EMS Coordinator

TXA Trial Study Proposal: Attachment D
EMS System CQI Plan

ARMC will be the central data collection point that will unify the prehospital data and the trauma center data. Richard Vara, TPM and designated trauma registrars will be will be maintaining the data and correlating the EMS data and trauma registry data received.

The data elements collected is as follows:
EMS ePCR data:

- Date and time of incident
- PCR Incident number
- Type of Injury
- Primary Impression
- Mechanism of Injury (Blunt/Penetrating)
- Patient age:
- Weight (kg)
- Gender
- Race/Ethnicity
- Pre-and Post-TXA: Vital signs and Assessment
    - HR
    - RR
    - Temp
    - BP
    - Cap Refill
    - Skin signs
    - GCS
    - Estimated Blood Loss
- Time of Injury (Onset Time)
- Time of TXA administration
- TXA dose
- Reassessment findings (e.g. repeated vital signs etc.)
- Narrative with details including attempts to control bleeding, patient assessment and reassessment findings.
- Additional required data elements

Trauma Registry Data Elements:

- Date and time of incident
- Referral hospital arrival and discharge date and time
- Trauma center arrival date and time
- ICD9/ICD10 Codes
- Mechanism of Injury

TXA Trial Study Proposal: Attachment D
EMS System CQI Plan

- Procedures List
- Date and time of Procedures
- Area of Injury
- Abbreviated Injury Scale (AIS)
- Date and time to OR
- Date and time of blood products
- Number of transfused blood products
- Ventilator date and time.
- Disposition (Date and time and discharge status)
- Complications

Analysis Measures:

- Survival at 24 hours, 48 hours, and 28 days
- Cause of death (hemorrhage, other causes)
- Mechanism of injury (blunt, penetrating, combination of blunt and penetration, amputation)
- Area of injury
- Head, chest, abdomen, extremity, multiple areas
- Blood product Used: Packed red blood cells, fresh frozen plasma, platelets, cryoprecipitate
- Estimated blood loss
- Pre-hospital and hospital estimate, operating room estimate, and chest tube output
- Number of transfused unit(s) of blood products (< 2 units, 2-4 units, >4 units i.e. massive transfusion
- Time to emergency care: Time from EMS encounter to emergency department (ED), time spent in emergency department, time from ED arrival to operating room
- Hospital length of stay, Intensive care unit length of stay, discharge disposition
- Ventilator days
- Adverse side effects; thromboembolic, seizures
- Deep venous thrombosis prophylaxis timing
- Matching of historical control group to the treatment group based on AIS

Primary Outcome

- Mortality at 24 hrs, 48 hrs, and 28 days

Secondary Outcomes

- Total amount and types of blood products transfused in 24 and 48 hours
- Total amount of estimated blood loss
- Occurrence of thromboembolic events

TXA Trial Study Proposal: Attachment D
EMS System CQI Plan

EMS CQI PLAN

System CQI will be completed using ePCR system reports as well as through QA of incidents.

1. 100% of all patients meeting inclusion criteria and transported by study participants will receive TXA by transport provider during the 18 month study
   - Monitor all patients transported by study participants that met inclusion criteria (denominator)
   - Determine number that met inclusion criteria and received TXA (numerator)

2. 100% of all patients will have pre-and post-TXA VS documented during the 18 month study.
   - Monitor the ePCR for the presence of pre- and post- TXA vital signs reassessment findings.(numerator)
   - Monitor the total number of patients receiving TXA. (denominator)

3. 100% of all patients will have pre- and post- TXA estimated blood loss documented on the ePCR.
   - Monitor the ePCR for the presence of pre- and post- TXA estimated blood loss findings. (numerator)
   - Monitor the total number of patients receiving TXA. (denominator)

4. 100% of TXA study patients with any adverse effects will be identified and reported immediately to the EMS Coordinator, ICEMA. (So that ICEMA may report to the Principal Investigator and EMSA.)
   - Monitor reassessment findings and narrative on the ePCR (numerator)
   - Monitor the total number of patients receiving TXA (denominator)

EMS System CQI Indicators:

Any study patient (less than 100%):

1. Meeting inclusion criteria that did not receive TXA by paramedic provider
2. Who received TXA that did not have pre- and post- TXA vital signs documented
3. Who received TXA that did not have pre-and post- TXA estimated blood loss documented.
4. Who received TXA and experienced an adverse effect that was not identified and reported.

TXA Trial Study

Education

October 1, 2014

Goals & Objectives

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

- Describe the three mechanisms involved in hemostasis
- Explain how the extrinsic and intrinsic coagulation pathways lead to the common pathway, and the coagulation factors involved in each
- Discuss Products involved in treating Hemorrhagic shock
- Tranexamic Acid (TXA), Evidence-based medicine
- State the inclusion criteria for the TXA study.
- State the EMS ePCR documentation requirements

Hemostasis In Traumatic Hemorrhagic Shock

The Use Of TXA

Michael Neeki, DO, MS, FACEP

Arrowhead Regional Medical Center

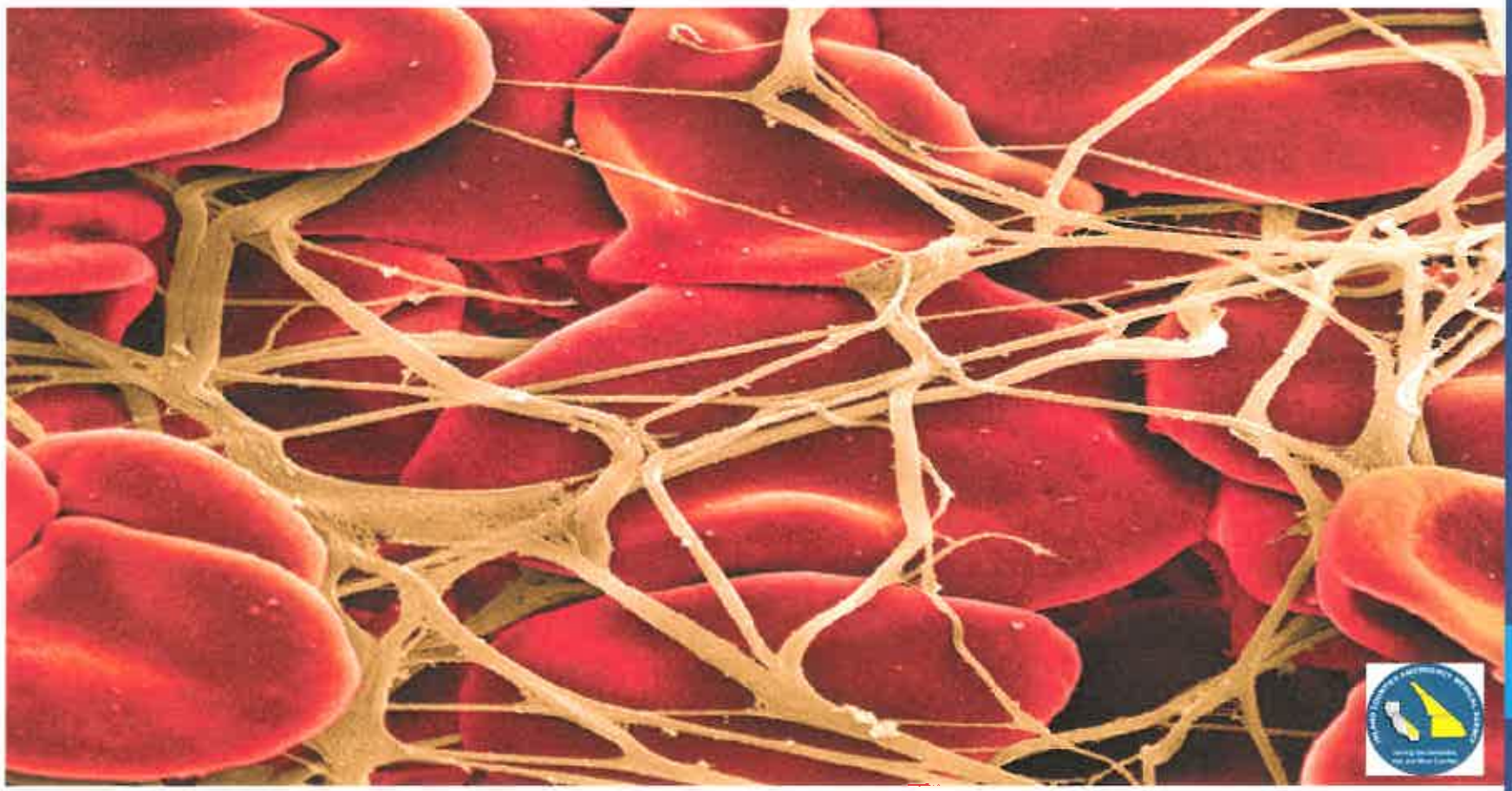
"What's that?" I said

- The other day at an interdisciplinary rounds meeting at the hospital, one of our nurses who is also an emergency medical technician mentioned that in Britain injured patients receive tranexamic acid before arriving at the hospital because it reduces death from bleeding.
- "What's that?" I said

- Coagulopathy that is frequently encountered in hemorrhagic shock has been shown to be an independent risk factor for death after trauma.

McLeod JBA et.al.,*Early coagulopathy predicts mortality in trauma. J Trauma 2003;55:39-44.*

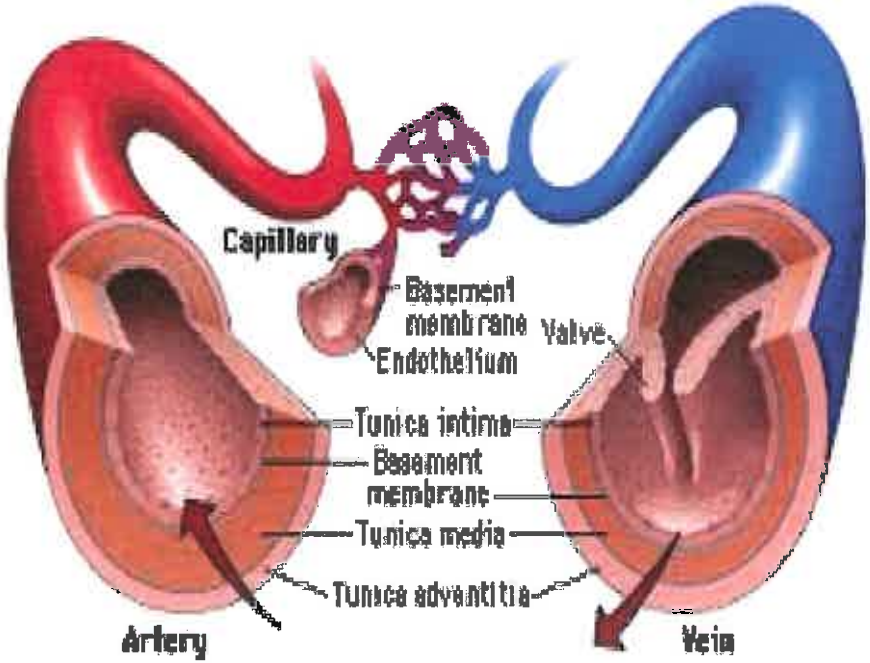
Platelets In Fibrin Mesh

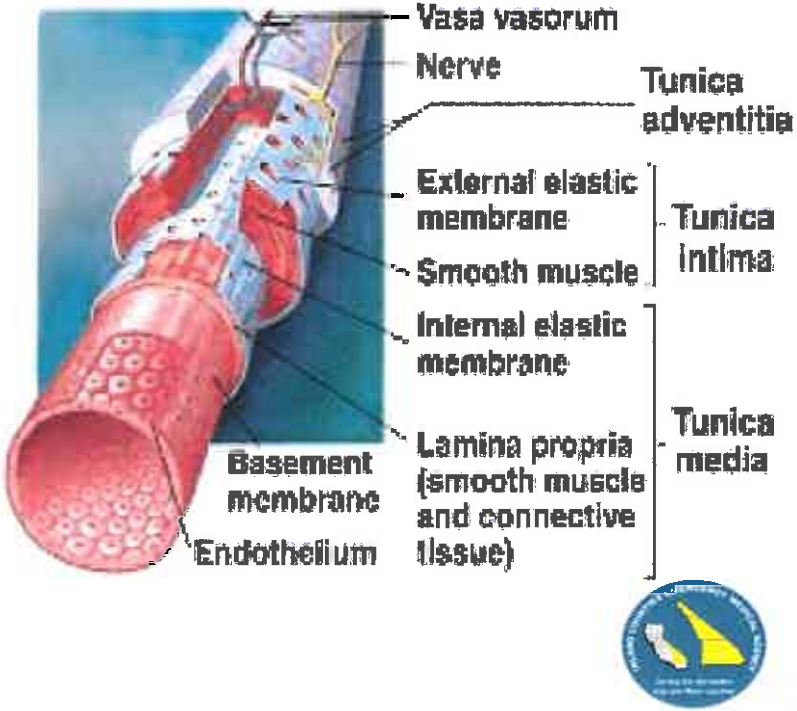


Three steps to achieve Hemostasis

- Vascular Spasm
- Formation of the Platelet Plug
- Coagulation

Anatomy Of Blood Vessels





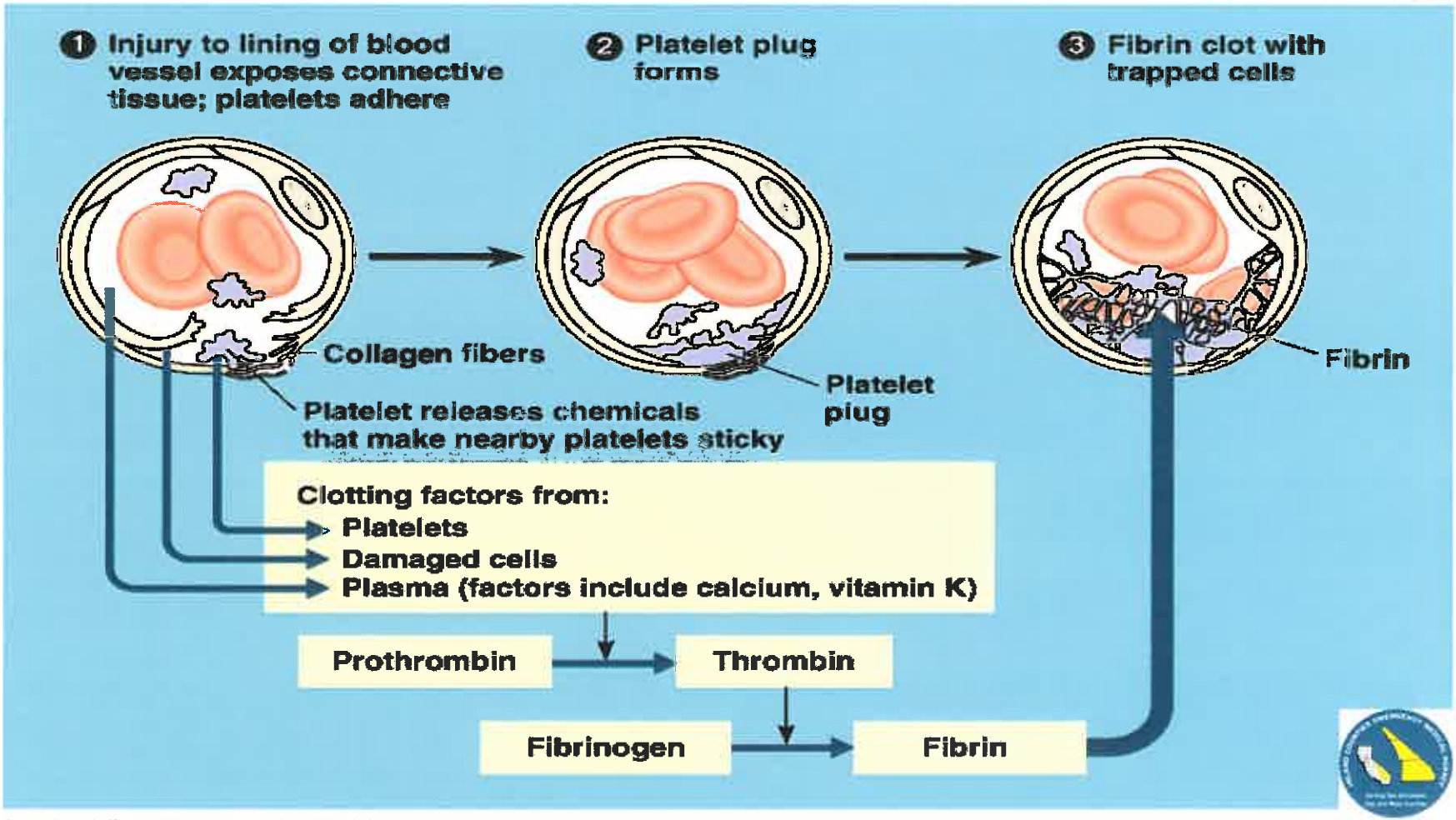
Vascular Spasm

- The smooth muscle in the walls of the vessel contracts dramatically. Has both circular layers; larger vessels also have longitudinal layers.

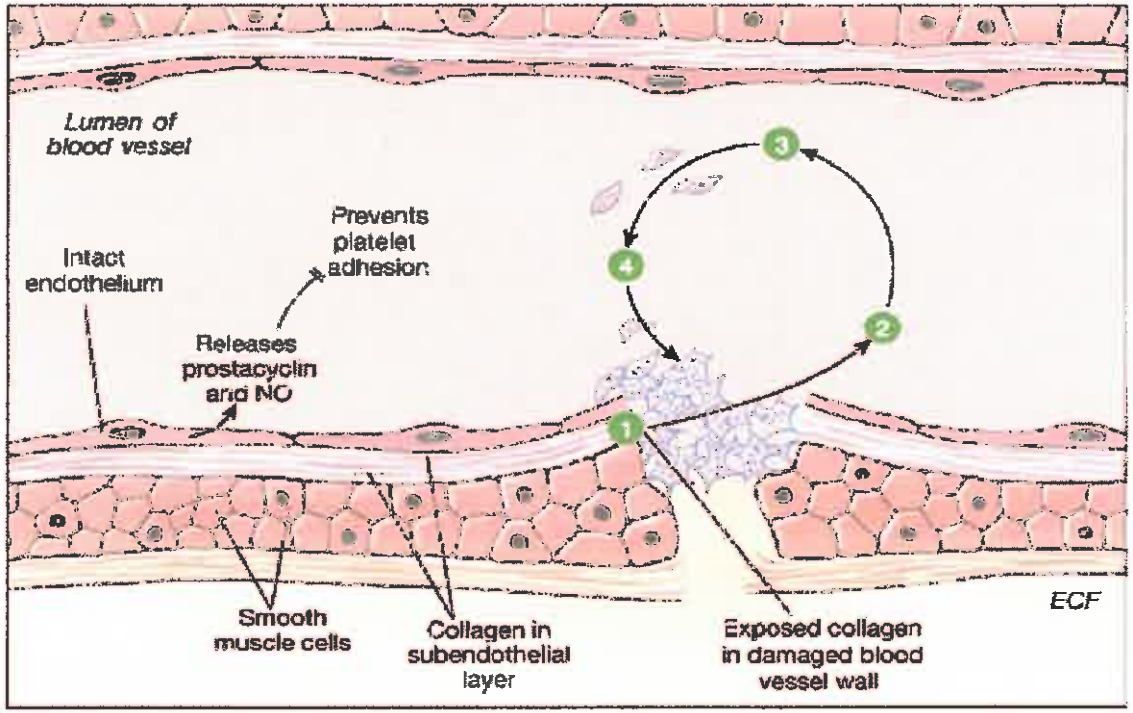
- The circular layers tend to constrict the flow of blood, whereas the longitudinal layers, when present, draw the vessel back into the surrounding tissue.

Formation of the Platelet Plug

- The platelets begin to clump together, become spiked and sticky, and bind to the exposed collagen and endothelial lining.
- This process is assisted by a glycoprotein in the blood plasma called **von Willebrand factor**, which helps stabilize the growing *platelet plug*. As platelets collect, they simultaneously release chemicals from their granules into the plasma that further contribute to hemostasis.



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

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.

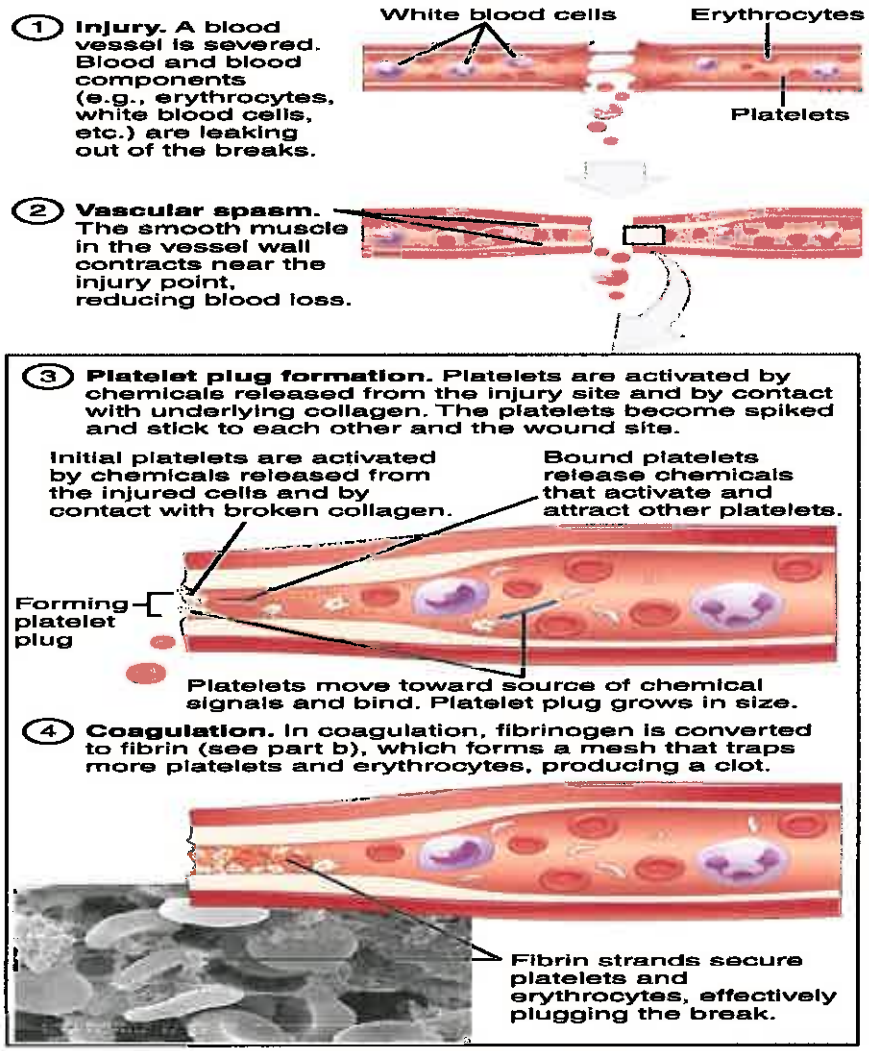
Clotting Factors Involved in Coagulation

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:

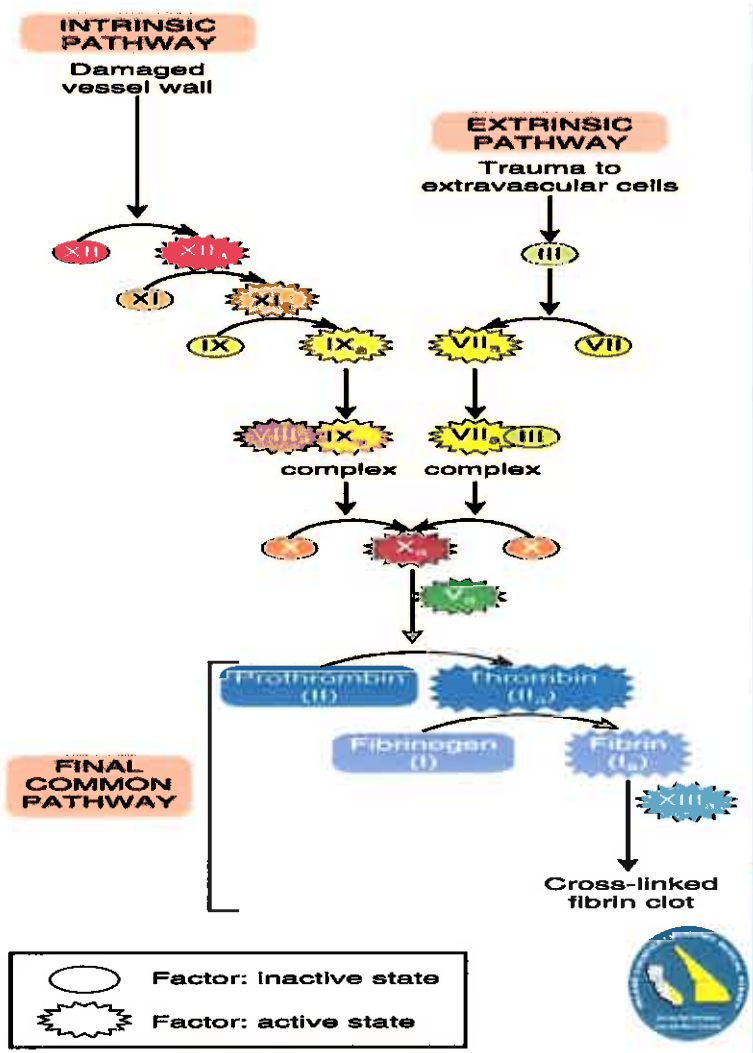
- **The extrinsic pathway**, which normally is triggered by trauma.
- **The intrinsic pathway**, which begins in the bloodstream and is triggered by internal damage to the wall of the vessel.
- Both of these merge into a third pathway, referred to as **the common pathway**

Clotting Factors Involved in Coagulation

- All three pathways are dependent upon the 12 known clotting factors, including Ca^{2+} and vitamin K .
- Clotting factors are secreted primarily by the **liver** and the platelets. The liver requires the vitamin K to produce many of them. Vitamin K (along with biotin and folate).
- The calcium ion, considered factor IV . The 12 clotting factors are numbered I through XIII according to the order of their discovery.

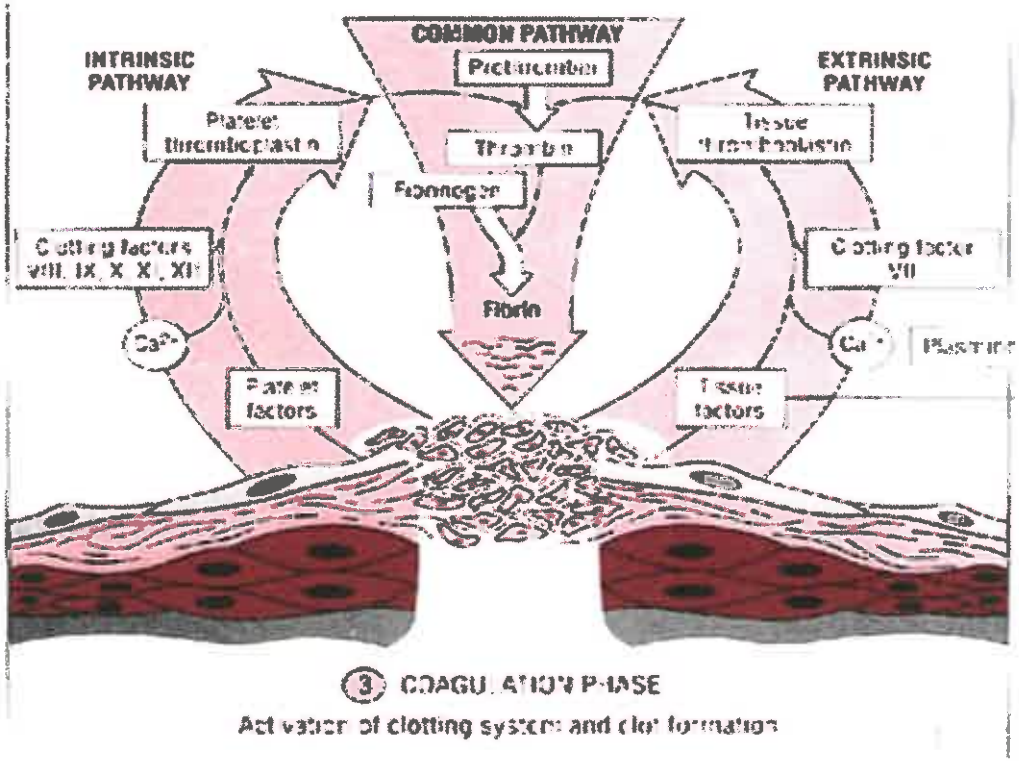


(a) The general steps of clotting



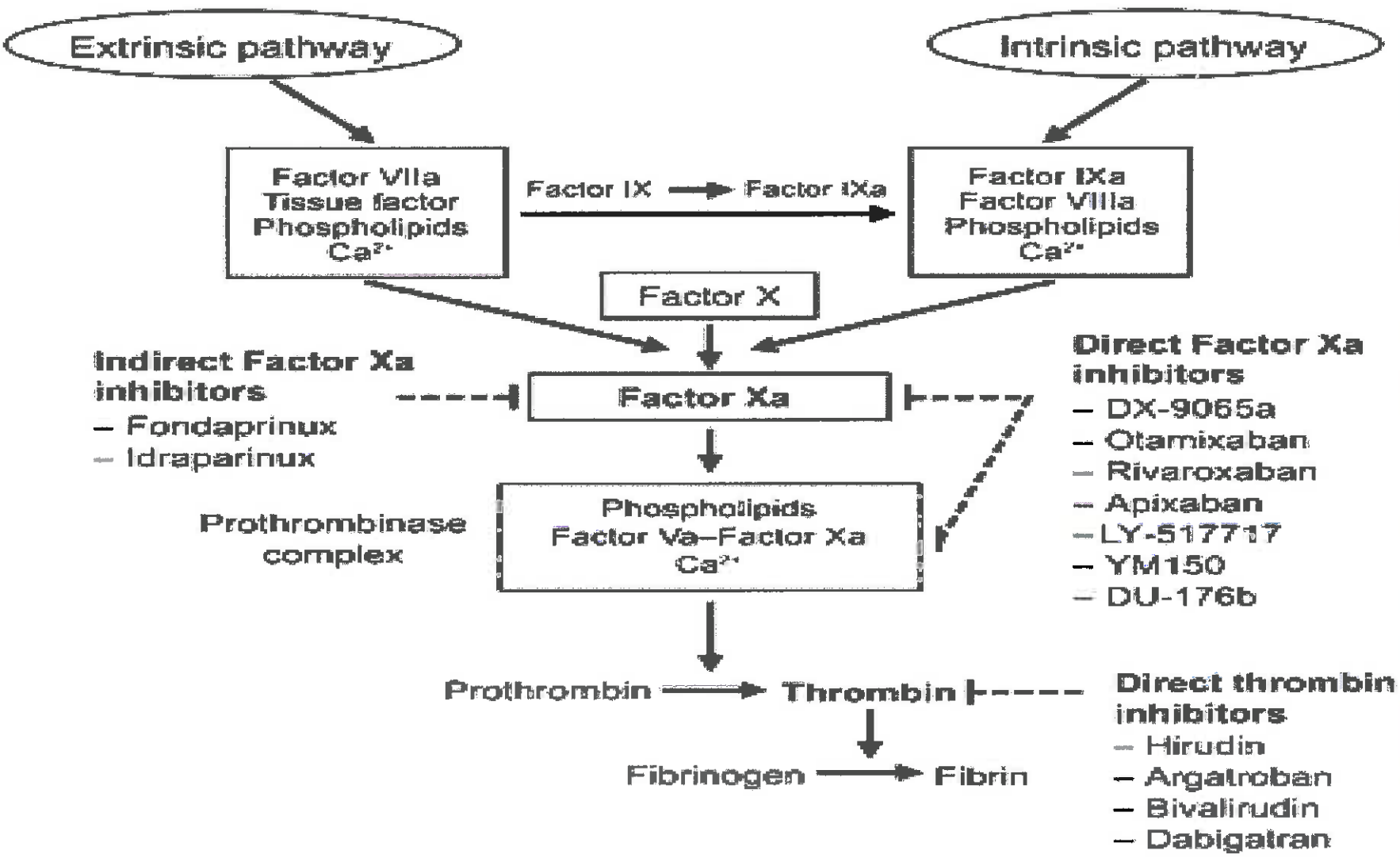
(b) Fibrin synthesis cascade

Step 3. Coagulation Phase



③ COAGULATION PHASE

Activation of clotting system and clot formation


Extrinsic pathway
Intrinsic pathway
Factor VIIa
Tissue factor
Phospholipids
Ca2+
Factor IX
Factor IXa
Factor IXa
Factor VIIIa
Phospholipids
Ca2+
Factor X
Indirect Factor Xa inhibitors
– Fondaprinux
– Idraparinux
Factor Xa
Direct Factor Xa inhibitors
– DX-9065a
– Otamixaban
– Rivaroxaban
– Apixaban
– LY-517717
– YM150
– DU-176b
Prothrombinase complex
Phospholipids
Factor Va–Factor Xa
Ca2+
Prothrombin
Thrombin
Direct thrombin inhibitors
– Hirudin
– Argatroban
– Bivalirudin
– Dabigatran
Fibrinogen
Fibrin

Transfusion Products

- Primary resuscitation approach to minimize trauma-induced coagulopathy. Plasma, red blood cell and platelet ratios of 1:1:1.

  (6 RBC: 6 FFP: 6 platelet)

- Activated prothrombin complex concentrate*

  -Use to reverse **Rivaroxaban and Dabigatran**

  - promising effect in hypothermia and acidosis

  - better in combination with TXA

- **Activated factor VII (rFVIIa; NovoSeven)**

Transfusion Products

- Vitamin K (Increases Factors II, VII, IX, X, Protein C and S)
- **Fresh-frozen plasma** (indicated when there is multi-factor deficiencies associated with severe bleeding and/or DIC)
- **Cryoprecipitate** (may be indicated if the plasma fibrinogen is less than 1 g/l)

VWF concentrate (with factor VIII)	(See Humate P, Wilate) Types 1, 2 and 3 VWD
Factor I concentrate (fibrinogen)	(See Clottagen, Fibrinogen Concentrate) Factor I Deficiency
Recombinant Factor VIIa concentrate, Factor VII concentrate	(See Niastase – NovoSeven) Factor VII Deficiency
Recombinant Factor VIII concentrate	(See Kogenate FS, Helixate FS, Advate, Xyntha) Hemophilia A carriers
Recombinant Factor IX concentrate	(See Benefix) Hemophilia B carriers
Factor X concentrate	Factor X Deficiency
Factor XI concentrate	Factor XI Deficiency
Factor XIII concentrate	Factor XIII Deficiency
Prothrombin complex concentrate	Factor II, X Deficiencies

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.

Cotton et.al. J Trauma Acute Care Surg. 2012 Aug;73(2):365-70; discussion 370. doi: 10.1097/TA.0b013e31825c1234.

Animal Study

- Acidosis PH 7.1 increased fibrinolysis by 1.8 fold with no effects on fibrinogen synthesis.
- Hypothermia of 32°C decreased fibrinogen synthesis, with no effects on fibrinogen degradation
- Acquired fibrinogen deficiency
- HF Cannot be predicted reliably in trauma patients, but appears to be linked to the severity of the trauma

Assessment of fibrinolysis

- Plasma fibrinolytic activity was evaluated by:

_Measuring D-Dimer concentrations

_ Fibrin degradation products

_ Euglobulin lysis time

(Can tell the difference between primary fibrinolysis and DIC. The test can also be used to monitor patients who are on streptokinase or urokinase therapy for acute MI)

_ Thrombelastography (elasticity during Clot formation)

Fibrinogen Levels

- Clinical data from gyn, neuro,& cardiac surgery show that perioperative and postoperative hemorrhagic tendency is increased when fibrinogen levels are below 150–200 mg dl.
- A retrospective study in 252 seriously injured soldiers who received massive transfusion correlated the amount of fibrinogen given (a combination of cryoprecipitate and fresh-frozen plasma) and survival.
- Four other small prospective studies looked at the use of fibrinogen concentrate . coagulation was optimized, perioperative bleeding was reduced by 32%, and transfusion requirement was significantly reduced.
- fibrinogen plasma levels should be maintained at a minimum of 150–200 mg dl.

Tissue & Endothelial injury

T-PA (tissue plasminogen activator)

PAI-1 (plasminogen activator inhibitor)

In Initial Phase t-PA > PAI-1

Antifibrinolytics
Fibrinogen conc.
Cryoprecipitate

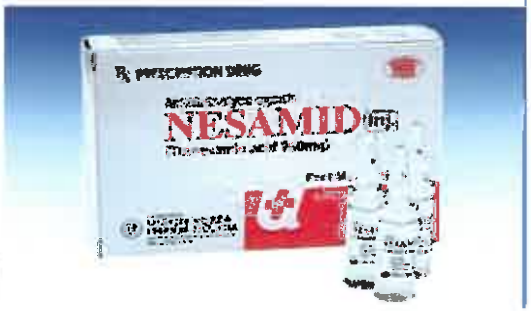
Hyperfibrinolysis and Hemorrhagic Shock


Pfizer
CYKLOKAPRON
100 mg/mL


TRANEXAMIC ACID
INJECTION
1000 mg/10 mL (100 mg/mL)
FOR INTRAVENOUS USE ONLY


MANX Pharma
Tranexamic Acid
500mg Tablets
Tranexamic Acid PhEur
60

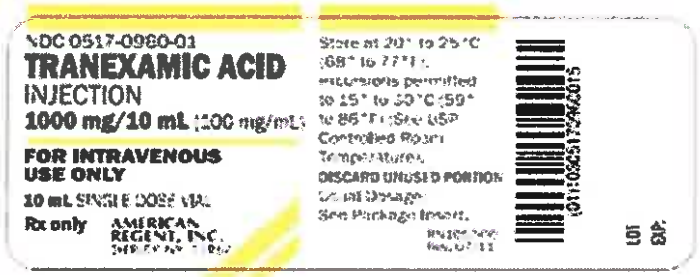

Tranexamic Acid
100 mg/mL
SANDOZ


NESAMID


트라넥사민산 주사 250mg

Antifibrinolytics

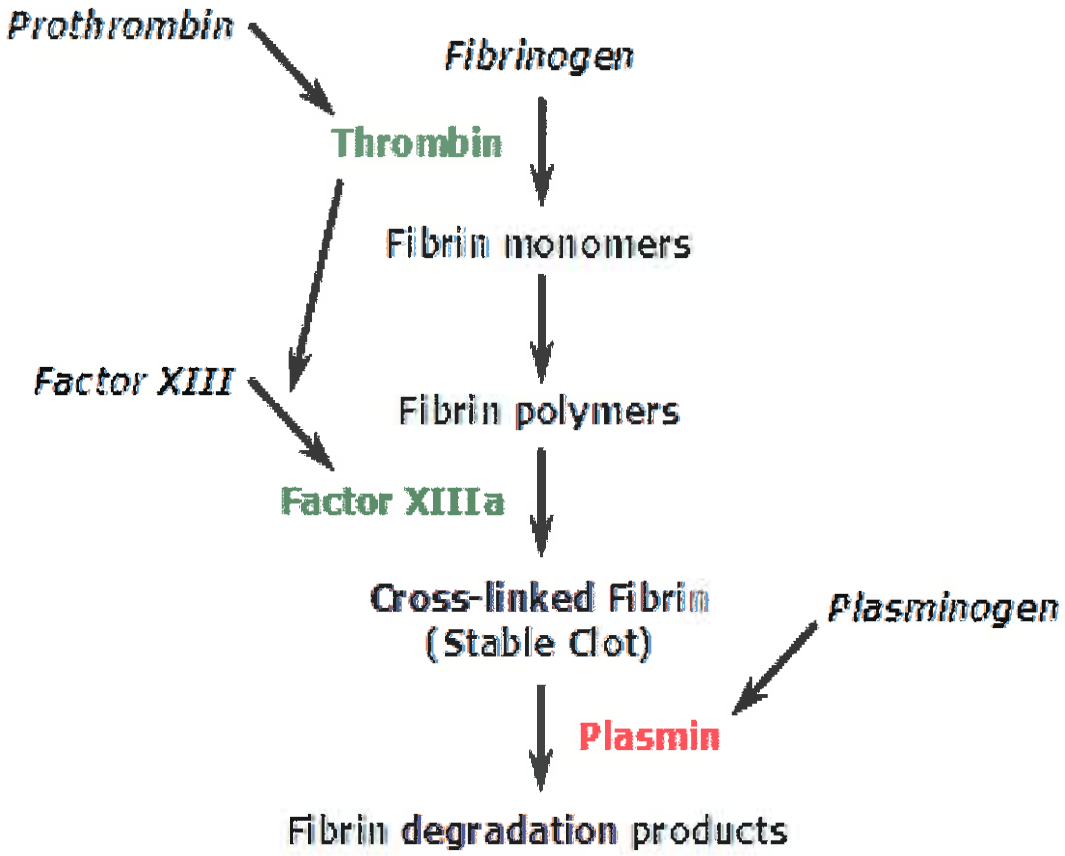
- These agents enhance hemostasis when fibrinolysis contributes to bleeding
- Lysine analogs
  * EACA (e-AminoCaproic acid
  * TXA (Tranexamic acid
  * Aprotinin (No marking since 2007)

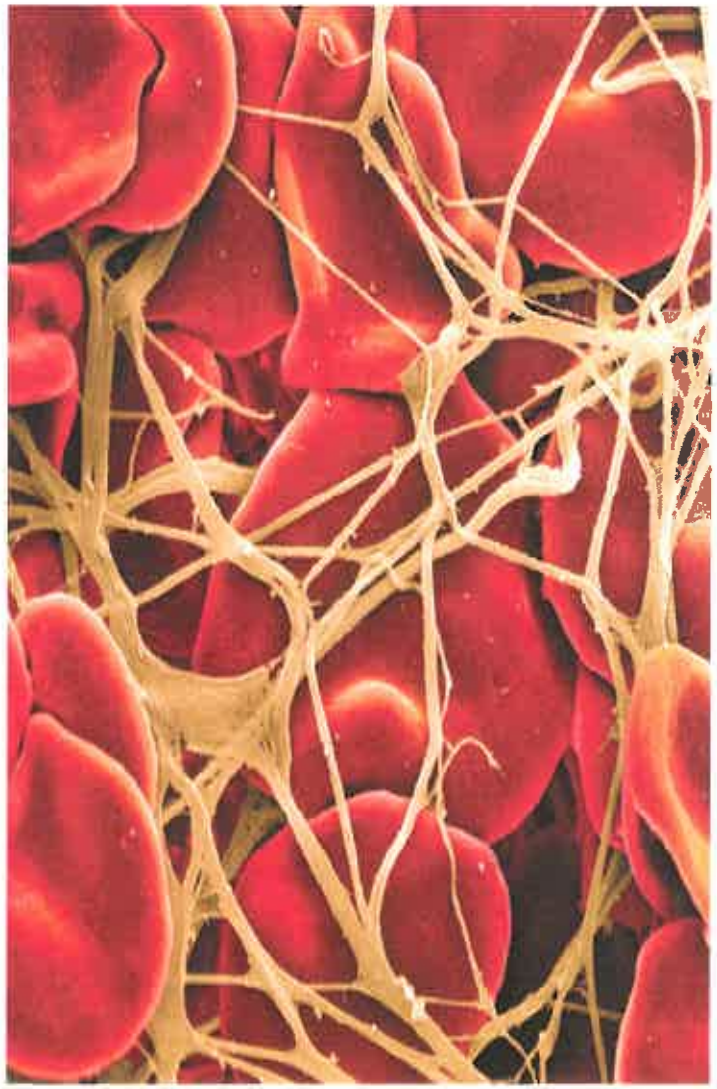


Mechanism of Action

- 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

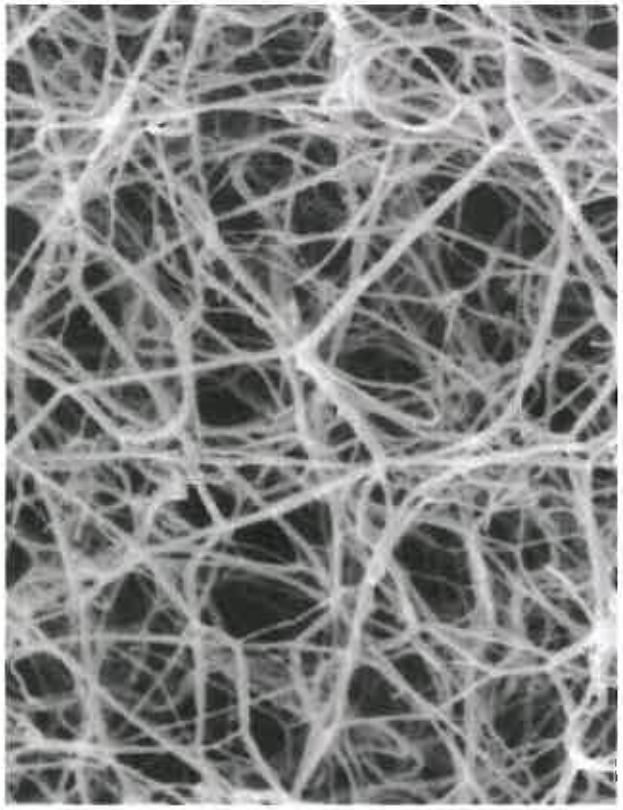

Prothrombin
Fibrinogen
Thrombin
Fibrin monomers
Factor XIII
Fibrin polymers
Factor XIIIa
Cross-linked Fibrin
(Stable Clot)
Plasminogen
Plasmin
Fibrin degradation products



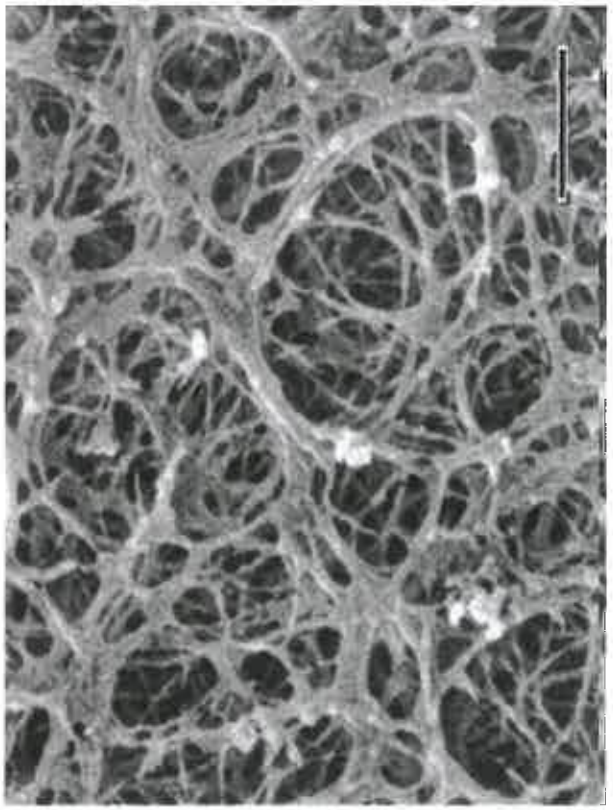
TXA

- 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

Pharmacokinetics

- Absorption

  -Onset of action: 5-15 minutes

  -Duration: 3 hours

- Distribution

  -Protein binding ~ 3%; primarily to Plasminogen

- Metabolism

  -Only a small fraction of the drug is metabolized (less than 5%).

  -T1/2: 2-11 hours

- Excretion

  -Urine (>95% as unchanged drug)

Protein binding

- The plasma protein binding of TXA is about 3% at therapeutic plasma levels and seems to be fully accounted for by its binding to plasminogen (does not bind serum albumin).
- Pass the Blood Brain Barrier and placenta
- In patients with hereditary angioedema, inhibition plasmin by TXA may prevent attacks of angioedema by decreasing plasmin-induced activation of the first complement protein (C1).

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

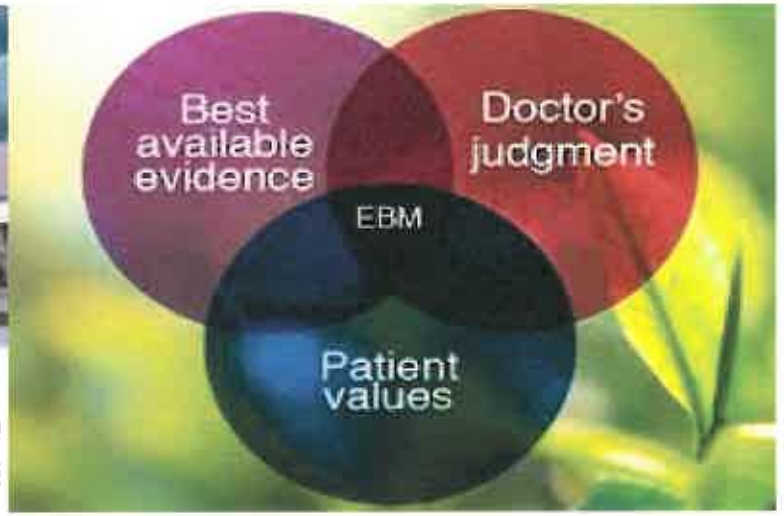
- Acquired defective color vision
- SAH
- Active intravascular clotting
- Hypersensitivity to TXA

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)

Evidence-Based Medicine

ARROWHEAD
REGIONAL MEDICAL CENTER



CRASH-2:Clinical Randomization of an Antifibrinolytic in Significant Hemorrhage

- Randomized prospective
- 274 hospitals in 40 countries
- Evaluated 20,211 trauma patients randomized and treated within 8 hours of injury with either 2 grams of tranexamic acid (1 gram load, then 1 gram over 8 hours) or placebo.
- The primary outcome was in-hospital mortality within 4 weeks of injury; vascular occlusive events,
- Transfusions or surgical interventions were secondary outcomes.

CRASH 2

	N	All causes of death	Bleeding death	Non-bleeding death
Overall	20127	0·91 (0·85–0·97); p=0·0035	0·85 (0·76–0·96); p=0·0077	0·94 (0·86–1·02); p=0·13
Time to treatment (h)				
≤1	7451	0·87 (0·76–0·97)	0·68 (0·57–0·82)	1·04 (0·89–1·21)
>1–3	6033	0·87 (0·77–0·97)	0·79 (0·64–0·97)	0·91 (0·78–1·05)
>3	6634	1·00 (0·90–1·13)	1·44 (1·12–1·84)	0·89 (0·78–1·02)
χ^2 test of homogeneity	..	4·411 (p=0·11)	23·516 (p=0·0000)	2·537 (p=0·28)

Table 1: Relative risk (95% CI) of death with tranexamic acid, overall and by time to treatment

	≤1 h (n=7451)	>1–3 h (n=6033)	>3 h (n=6634)
Age (years)			
Mean (SD)	33·4 (13·9)	35·0 (14·0)	35·5 (14·8)
<25	2283 (30·6%)	1557 (25·8%)	1773 (26·7%)
25–34	2360 (31·7%)	1832 (30·4%)	1882 (28·4%)
35–44	1356 (18·2%)	1177 (19·5%)	1262 (19·0%)
>44	1452 (19·5%)	1467 (24·3%)	1716 (25·9%)
Systolic blood pressure (mm Hg)			
≤75	1380 (18·5%)	1012 (16·8%)	768 (11·6%)
76–89	1203 (16·1%)	1064 (17·6%)	1029 (15·5%)
>89	4867 (65·2%)	3955 (65·6%)	4837 (72·9%)
Heart rate (beats per min)			
<77	681 (9·1%)	450 (7·5%)	602 (9·1%)
77–91	1169 (16·0%)	971 (16·1%)	1326 (20·0%)
92–107	1888 (25·3%)	1562 (25·9%)	1625 (24·5%)
>107	3637 (48·8%)	2990 (49·6%)	3059 (46·1%)
Respiratory rate (breaths per min)			
<10	149 (2·0%)	82 (1·4%)	77 (1·2%)
10–29	6144 (82·5%)	4992 (82·7%)	6290 (94·8%)
>29	1077 (14·5%)	901 (14·9%)	923 (13·9%)
Capillary refill time (s)			
<2	2450 (32·9%)	2140 (35·5%)	2207 (33·3%)
2–4	3472 (46·6%)	2773 (46·0%)	3110 (46·9%)
>4	1131 (15·2%)	968 (16·0%)	1257 (19·0%)
Glasgow coma score			
Severe (3–8)	1000 (13·4%)	1124 (18·6%)	1494 (22·5%)
Moderate (9–12)	868 (11·7%)	915 (15·2%)	909 (13·7%)
Mild (13–15)	5577 (74·9%)	3994 (66·2%)	4214 (63·5%)
Continents			
Asia	1213 (16·3%)	2475 (41·0%)	3666 (55·1%)
Africa	2490 (33·4%)	1437 (23·8%)	872 (13·1%)
Central and South America	2453 (32·9%)	1456 (24·1%)	1355 (20·4%)
North America, Europe, and Oceania	1295 (17·4%)	665 (11·0%)	741 (11·2%)

Data are number (%), unless otherwise stated.

Table 2: Patient characteristics by time to treatment

What was Planned to be Reported In CRASH 2

Four Baseline Characteristics;

1. Estimated hours since injury (<1, 1-3, 3-8 h)
2. SBP (<75, 76-89, > 90 mmHg)
3. GCS (severe 3-8, moderate 9-12, mild 13-15)
4. Type of injury (penetrating only, or blunt, combination)

CRASH 2

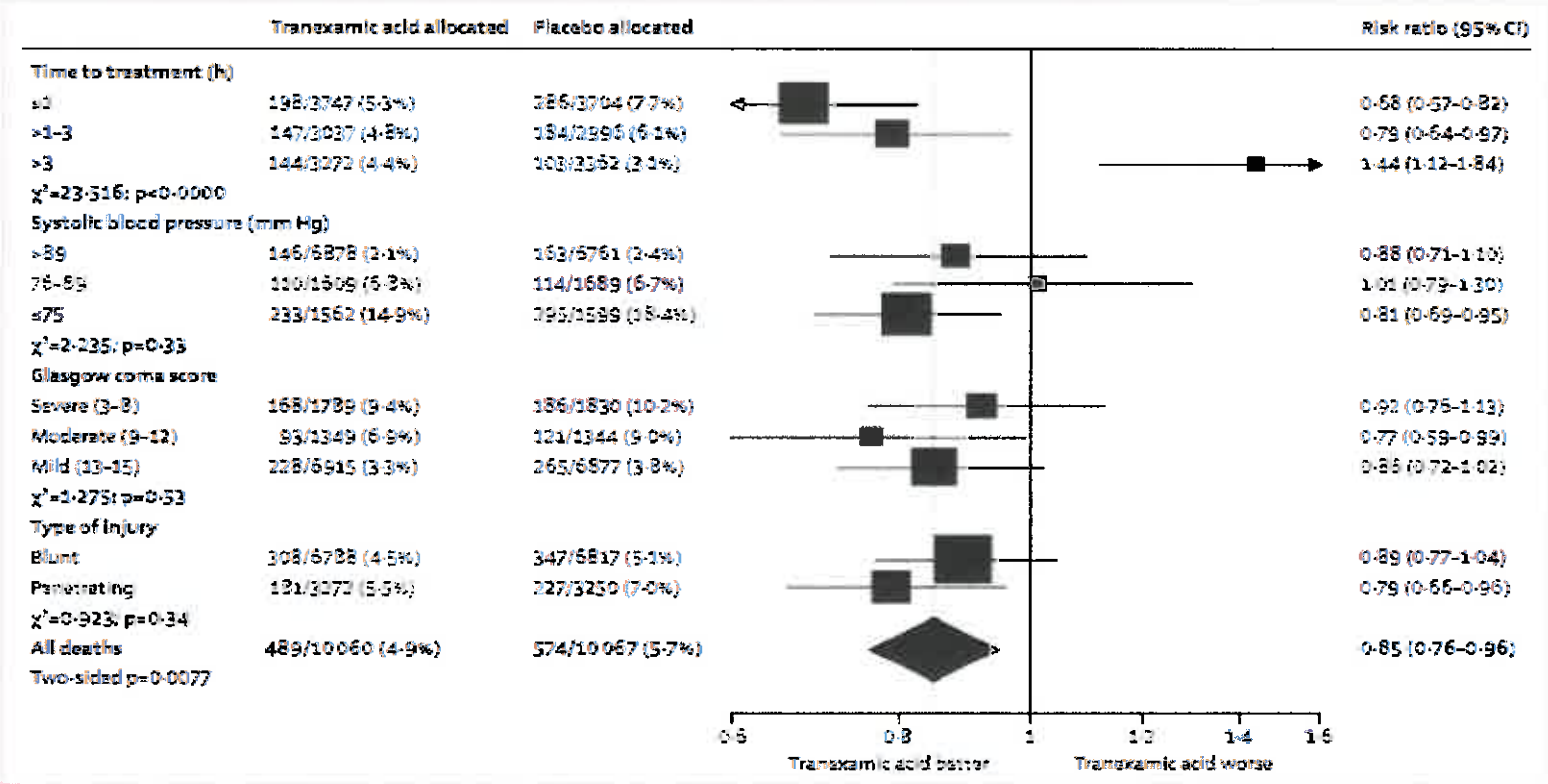


Figure 1: Mortality due to bleeding by subgroups

Crash 2 and Tranexamic Acid

- First came the Crash 2 Trial (Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant hemorrhage (CRASH-2): a randomized, placebo-controlled trial. Lancet 2010; 376: 23–32),
- Then the subgroup reanalysis (Lancet. 2011 Mar 26;377(9771):1096) showing the benefit of treatment as early as possible.

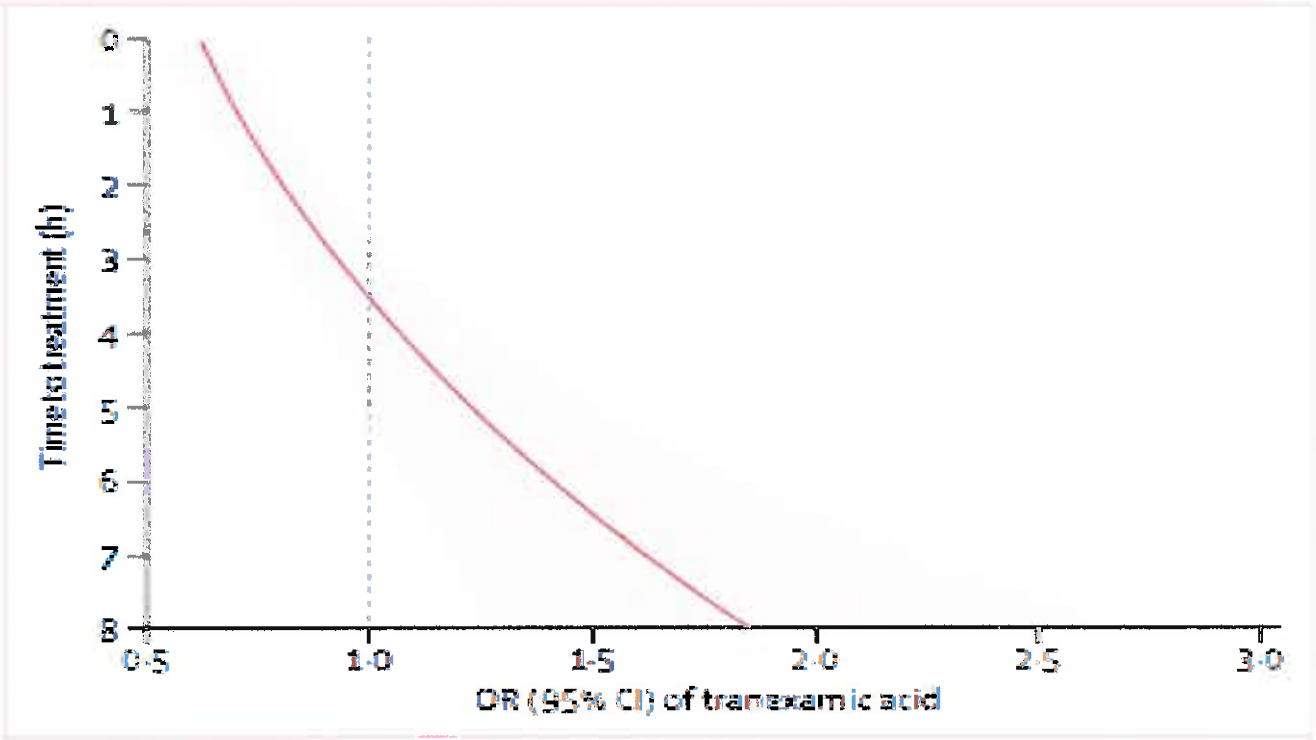


Figure 2: **Effect of tranexamic acid on death due to bleeding by time to treatment**
Shaded area shows 95% CI. OR=odds ratio.

CRASH 2

CRASH 2
Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage

- Reduction in all-cause mortality;
  - 14.5% in the TXA (1463/10,060)
  - 16% in the placebo (1613/10,067),P=0.0035
- Bleeding-related mortality reduced;
  - 4.9% in TXA vs. 5.7% in Placebo

  without an increase in fatal vascular occlusive events.
- All cause mortality decreased;
  - 10% (RR0.91,95% CI 0.85-0.97)
- Risk of death from bleeding decreased;
  - 15% (RR 0.85, 95% CI 0.76-0.96).

Military Application of TXA in Trauma Emergency Resuscitation Study

MATTERs

- Retrospective, observational trial
- Compared TXA administration with non-TXA in combat casualties receiving at least 1u PRBC.
- A subset of patients receiving a massive transfusion was also analyzed
- 896 consecutive patients with combat casualties of which 293 received TXA

Military Application of TXA in Trauma Emergency Resuscitation Study

MATTERs

- TXA group had lower unadjusted mortality;
  (17.4% vs. 23.9%; P=0.3)
- Benefit greater in patients receiving Massive Transfusion (14.4% vs. 28.1%; P=.04);
- TXA independently associated with higher survival rate (OR=7.7228; CI 3.016-17.322).

Meta Analysis of non-trauma

- BMJ May 2012 (K Ker et al.)
- 129 Trials; 10488 patients;

reduced the probability of receiving a blood in elective surgery transfusion **by a third**

(risk ratio 0.62, 95% CI 0.59 to 0.65; P<0.001)

- Fewer deaths in TXA group

(0.61, 0.38 to 0.98; P=0.04)

– Statistical concerns about this group

TXA

- Significantly reduced all-cause mortality and death due to bleeding in trauma patients with significant bleeding, particularly when administered early after injury.

(Less than 3 hours)

ARMC Study

- To determine if pre-hospital administration of TXA in trauma patients with signs of hemorrhagic shock provides for a statistically significant decrease in mortality, total blood product usage and total estimated blood loss, without a significant increase in thromboembolic complications

ARMC TXA Study

- Prospective Cohort, Retrospective comparison
- Total of 800 patient, 4 groups(200 in each group)
- Multi-agency with ICEMA and regional cooperation
- Following the CRASH-2 protocol to replicate the study in our region with
- Pre-hospital/paramedic importance in cooperation with Air-Medical Component
- Outcome (Mortality, Blood Loss, Use of blood product)

Outcome Measurements

- Survival at 24 hours, 48 hours, and 28 days
- Cause of death **(hemorrhage, other causes)**
- Mechanism of injury (blunt, penetrating, combination of blunt and penetration, amputation)
- Area of injury
  - Head, chest, abdomen, extremity, multiple areas
- Blood product Used:
  - Packed red blood cells, fresh frozen plasma, platelets, cryoprecipitate.

Outcome Measurements

- Estimated blood loss
  - Pre-hospital and hospital estimate, operating room estimate, and chest tube output
- Number **of transfused unit(s) of blood products** (< 2 units, 2-4 units, >4 units i.e. massive transfusion.
- Time to emergency care: Time from EMS encounter to emergency department (ED), time spent in emergency department, time from ED arrival to operating room.
- Hospital length of stay, Intensive care unit length of stay, discharge disposition, Ventilator days
- Adverse side effects; thromboembolic, seizures, Deep venous thrombosis prophylaxis timing

Antifibrinolytic therapy

- Causes a greater reduction in hemorrhagic shock,
- Improve mortality and morbidity
- Decrease the use blood product and clotting factors
- Cost-effective
- Safe to administer early on in the hemorrhagic shocks
- Still some basic science questions outstanding and in the process of being answered.

- BOTTOM LINE – Severe trauma - GIVE

"So the story of tranexamic acid is another excellent example of how simpler, cheaper and sometimes more effective treatments are not being widely used in the US, even though our patients may receive exorbitantly expensive medications and treatments of dubious or minimal benefit. This is because we allow powerful pharmaceutical companies to inform our practice. Sometimes this actually works, when companies produce groundbreaking innovations and encourage us to adopt them."

What Is Still Unknown about TXA?

- Whether TXA has any impact on trauma outcomes when damage-control resuscitation or MT protocols are used;
- The mechanism by which TXA reduced mortality in trauma in the CRASH-2 Trial. Fibrinolysis assessment and coagulation testing were not part of the study design, and determination of time to cessation of hemorrhage was not required in the study;
- Whether fibrinolysis testing should be performed before consideration of TXA treatment;
- What is the optimal dose and timing of TXA in trauma;
- Whether other antifibrinolytic agents could be substituted for TXA use in trauma;

What Is Still Unknown?

- Whether TXA is associated with higher seizure rates in trauma or TBI patients. Increased postoperative seizures have been reported in cardiac surgery with TXA doses that are 2-fold to 10-fold higher than those used in CRASH-2.
- 75–80 these seizures have been associated with an increased incidence of neurologic complications (delirium and stroke), prolonged recovery, and higher mortality rates. A proposed mechanism for seizures is TXA-mediated inhibition of glycine receptors as a potential cause of neurotoxicity. A recent warning has been added to the FDA drug label: "Convulsions have been reported in association with tranexamic acid treatment."

"Medicine is a science of uncertainty and an art of probability"

Sir William Osler

Bleeding in the Streets of Rialto

A Trial Study by ARMC and the Rialto Fire Department

Bleeding In the Streets of Rialto

Introduction

Arrowhead Medical Center and Rialto Fire Department have come together to form a new trial study; we will gauge the benefits of introducing Tranexamic Acid in the pre-hospital setting to hemodynamically unstable trauma patients. Our mission is to decrease the mortality rate of traumatic patients due to excessive bleeding.

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.

Trauma continued

- 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.

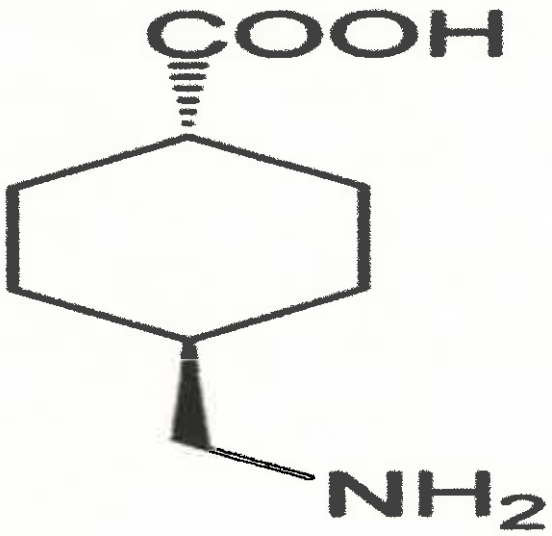
The Future of Trauma Care

- 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



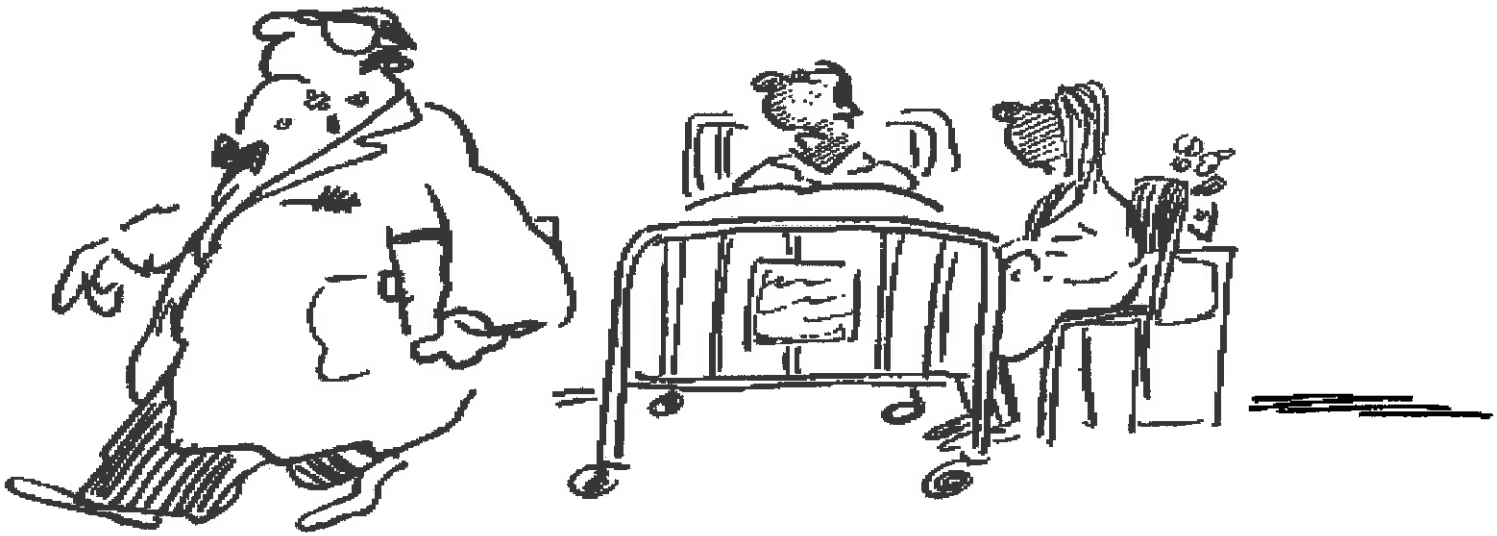
What is TXA?

- 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.

Not So Funny



"Yes - that's my surgeon - the one who cuts himself shaving ..."

New Studies
CRASH2 and MATTERS

- CRASH2: Clinical Randomization of Antifibrinolyitic 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

CRASH-2 CONTINUED

- 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

Studies cont'
CRASH2 AND MATTERS

- 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%.

MATTERS Continued

- 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!

TXA in Rialto

- ICEMA and the State are in the process of approving a trial study here in Rialto
- We will be administering TXA in the pre-hospital setting to trauma patients meeting a specific criteria
- This will be the first trial study any where introducing TXA in the pre-hospital setting, with the initial administration being done by paramedics

TXA in Rialto

- 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

TXA in Rialto

- What is the criteria for administering TXA?
  - TXA should be considered for any trauma patient exhibiting signs and symptoms of hemorrhagic shock:
    - Systolic blood pressure less than 90mmHG
    - Estimated blood loss of 500 milliliters in the field
    - Penetrating trauma to neck or torso proximal to knee
    - Bleeding not controlled by direct pressure or tourniquet
    - Major amputation to any of the four extremities

TXA in Rialto

The Black Knight could use some TXA!!!

TXA in Rialto

- 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.

TXA in Rialto

- What would exclude patients from receiving TXA?
  - Any Patient under 18 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 two hours post injury

TXA in Rialto

TXA in Rialto

- TXA administration and route
  - TXA will be given twice during patient care.
  - The first dose by the EMS crew of the Rialto Fire Department, (1gm in 100cc's of NS)
  - The first dose should be given as soon as possible but no later than two hours after injury!
  - The second by the Emergency Trauma Team at Arrowhead Regional Medical Center
  - The second dose will be an infusion of 1 gram via IV or IO over 8 hours in 0.9% Normal Saline.

TXA in Rialto

- 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.
    - 110mLx10gtts/10mins
    - Drip rate equals 110gttsmin
  - Any patient with a GCS of 15 requires verbal consent, all patients with GCS of ≤14 shall fall under implied consent

TXA in Rialto

- 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 patients who receive TXA must be clearly identified with an approved RED wristband in place prior to transport
  - All TXA patients will be transported to ARMC only, without exception

TXA in Rialto

- Data Collection:
  - Each patient who receives TXA will need to a have 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

TXA in Rialto

- Data Collection Continued:
  - Baseline characteristics continued:
    - Glasgow coma scale (pre treatment, 24 hours, 48 hours)
      - ≤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

TXA in Rialto

- 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

TXA in Rialto

- Statistical Analysis:
  - Our goal is to have a study group of two hundred people over a time period of 18 months
  - 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

TXA in Rialto

- 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.
  - Documentation will be shared and reviewed by both us and ARMC.

TXA in Rialto

- Continued education:
  - We will be required to take and pass a test based on TXA administration in the field.
  - We will have a skills demonstration of medication administration.
  - We are required to have a refresher class every 6 months during the course of this study.

EMS EPCR DOCUMENTATION REQUIREMENTS

Patient Information Tab

- Age (Date of Birth)
- Weight in kilograms
- Gender
- Race/Ethnicity

Call Conditions Tab

- Type of Injury

Incident Tab

- Date of Incident
- PCR Incident Number (auto generated)

Assess/Treatment Tab

- Time of Injury (Onset Time)

Assess/Treatment Tab Subcategory: Vital Signs

- Heart rate
- Respiratory Rate
- Temperature
- BP
- Cap Refill
- GCS
- Skin Signs

REASSESSMENT

Assess/Treatment Tab Subcategory: Procedures

- Time of TXA Administration
- Dose

Assess/Treatment Tab Subcategory: Trauma

- Estimated Blood Loss
- Mechanism of Injury

REASSESSMENT

Assess/Treatment Tab Subcategory: NARRATIVE

- The narrative must paint a complete picture.
- If the you are unable to locate the data element for documentation, place findings in the narrative section.

REASSESSMENT!

Incident Completion Requirements

- All incidents will be reported to the EMS Coordinator after **immediate** completion of the ePCR.

QA/CQI

- All incidents will be reviewed by the EMS Coordinator.
- Incident information will be joined with trauma outcome data at the trauma centers.
- CQI will be done at ICEMA.

Remember to report any adverse effects!

QUESTIONS?

Contact:

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