



Defense Health Board

Filling in the Gaps: Proposed Updates to the Tactical Combat Casualty Care Guidelines

Donald Jenkins, MD
Chair, Trauma and Injury Subcommittee

Defense Health Board Meeting
August 8, 2011



Overview

- Scope of the Problem: Preventable Deaths in Theater
- Proposed Solutions
 - Junctional Hemorrhage Pressure Control/Combat Ready Clamp™
 - Tranexamic Acid
 - Needle Decompression?
- Discussion and Voting



Preventable Deaths

Study data has historically shown that **15 to 25 percent** of combat deaths in Iraq and Afghanistan resulted from potentially survivable injuries

Over 80 percent are due to hemorrhage.

Of those, 70 percent had nontourniquetable or noncompressible wounds.

Sources: Holcomb et al, *Annals of Surgery* 2007; Kelly et al, *J Trauma* 2008; Eastridge et al, *J Trauma* 2011

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Preventable Deaths (cont'd.)

Table 4 Causes of Death Among Potentially Survivable Casualties

Cause of Death*	Group 1 (n = 93) (% Total of PS)	Group 2 (n = 139) (% Total of PS)
CNS	12 (13)	8 (6)
Head	11 (12)	6 (4) ($p < 0.04$)
Neck	1 (1)	0 (0)
Spinal cord	1 (1)	3 (2)
Hemorrhage	81 (87)	116 (83)
Tourniquetable (ext)	31 (33)	46 (33)
Noncompressible (torso)	47 (51)	68 (49)
Nontourniquetable (ax/neck/groin)	19 (20)	29 (21)
Airway	14 (15)	14 (10)
Sepsis/MSOF	2 (2)	9 (6)
Total causes of death identified	219	299

* Casualties could have 1 or more cause of death.
MSOF indicates multisystem organ failure.

Source: Kelly et al, *J Trauma*, 2008

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Recent Findings

Preliminary findings of an ongoing analysis of the causes of death in U.S. fatalities from Iraq and Afghanistan indicate that among those Killed in Action (KIA), the most common cause of death is junctional hemorrhage.

-COL Brian Eastridge, M.D., Trauma Consultant, U.S. Army Surgeon General, August 3, 2011

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Junctional (truncal) Hemorrhage

Junctional/truncal=

- Groin proximal to inguinal ligament
- Buttocks
- Gluteal and pelvic areas
- Perineum
- Axilla and shoulder girdle
- Base of the neck

terminology as established by Kraugh/Walters/Baer. Et al, *J Trauma 2008 / Ann Surg 2009*

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Recent Injury Patterns

- Recently, the incidence of dismounted complex blast injury (DCBI) has increased significantly
 - Dr. John Holcomb's presentation to the DHB, March 2011
 - U.S. Army Surgeon General appointed Task Force on DCBI

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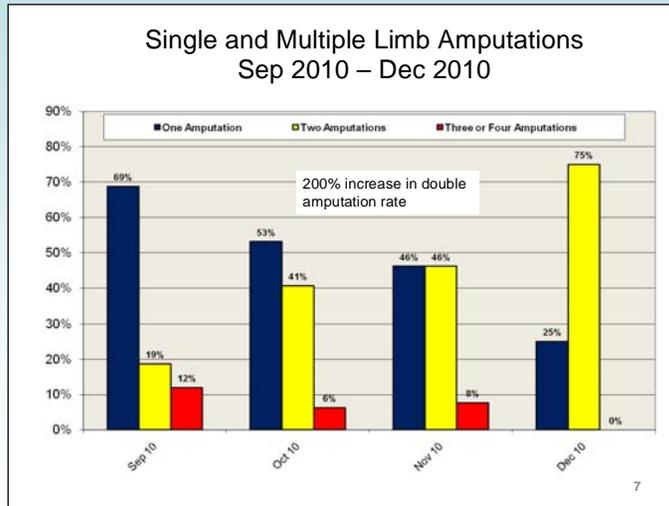
Recent Injury Patterns (Cont'd.)

- Urogenital injuries
- Multiple amputations
- High, extremely proximal amputations that are **not amenable to traditional tourniquet application**

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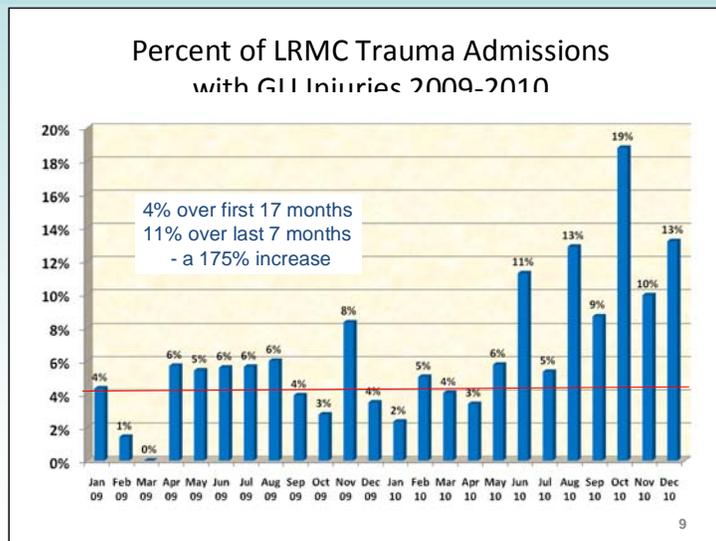
Recent Injury Patterns (Cont'd.)



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Recent Injury Patterns (Cont'd.)



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DHB RDT&E Recommendation Memorandum, June 14, 2011

- The DHB called for **further study of hemorrhage control mechanisms, particularly non-compressible hemorrhage**
- Specifically, the memo stated:
 - Follow-up studies should be conducted to determine the benefits and risks of using tranexamic acid for trauma patients with non-compressible hemorrhage.
 - Studies documenting the efficacy of truncal tourniquets as well as the ability of users to apply it effectively are needed. Case series describing outcomes from using this device in pre-hospital trauma management would also be useful.

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In the Interim...

There is a substantial gap in Tactical Combat Casualty Care that will result in further fatalities due to exsanguination on the battlefield.

We now have options to address this gap.

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Treatment Options for Non-Compressible & Junctional Hemorrhage

- Combat Gauze™ is the only TCCC-endorsed tool for treating non-compressible hemorrhage
- Studies suggest that it is safe and efficacious
- However, fatality data suggest that it is unable to stop all significant hemorrhages

Particularly given recent DCBI patterns, medics need an alternative/additional option

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Proposed Solutions

1. Mechanical pressure devices to control hemorrhage (i.e. Combat Ready Clamp™)
2. Use of an Antifibrinolytic, Tranexamic Acid, to reduce bleeding by preventing activation of anti-clotting factor

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Junctional Hemorrhage Control

MSG Harold Montgomery

Regimental Senior Medic
U.S. Army 75th Ranger Regiment

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Discussion/Vote

Mechanical Pressure Devices for
Junctional Hemorrhage Control
(i.e. Combat Ready Clamp™)

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Proposed Addition to TCCC Guidelines:

Tranexamic Acid

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Review of Evidence

- **CRASH-2 Study:**
 - Large prospective RCT of TXA use in trauma patients
 - Concluded: TXA reduces mortality in trauma patients
 - CoTCCC and JTTS Directors reviewed thoroughly and were not convinced that this was enough evidence to field TXA.
 - Cochrane Review, 2011, concluded that TXA is inexpensive and easy to administer; should be added to normal management of hemorrhaging trauma patients worldwide.
- **MATTERS Study:**
 - Retrospective study analyzing U.K. experience with TXA in Afghanistan
 - Patients admitted to Bastion (busiest MTF in theater)
 - 28-Day mortality was significantly lower in group administered TXA, overall, and in a subset of patients that were massively transfused

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CRASH-2 Study *Lancet*, Online Article, 2010

Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial



CRASH-2 trial collaborators*

- Prospective, randomized controlled trial
- 20,211 patients
- TXA significantly reduced all cause mortality from 16.0% to 14.5%
- TXA significantly reduced death due to bleeding from 5.7% to 4.9%

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CRASH-2: Timing of TXA Dosing – *Lancet*, 2011

 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*

- Subgroup analysis of 20,211 trauma patients based on time of administration of TXA
- Timing; only deaths due to bleeding
- 3076 overall deaths; 1063 due to bleeding
- **Risk of death due to bleeding was significantly reduced (5.3% vs 7.7%) if TXA given within 1 hour of injury.** At 1-3 hrs after injury, also significant (4.8 vs 6.1%)

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The MATTERS Study



Retrospective Study Analysing UK Experience of TXA in CCC

MATTERS Inclusion Criteria

- Combat Injury
- Admitted to Bastion
- Jan 09 to Dec 10 inclusive
- Received ≥ 1 unit PRBC

Received TXA

Did Not Received TXA

•End Points

- Mortality (<24hr and 28-day)
- Blood product use within 24hrs of wounding
- (Coagulation, arterial and venous thrombosis)

Team Aerospace Begins Here!



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Patients



MERT Retrieval
n = 411
(PHB = 182)

FOB Dwyer
n = 8

Other
n = 477

Bastion
n = 896

TXA
n = 293
MT n = 125
Mean dose: 2.3g ± 1.3

No-TXA
n = 603
MT n = 196

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Mortality Analysis



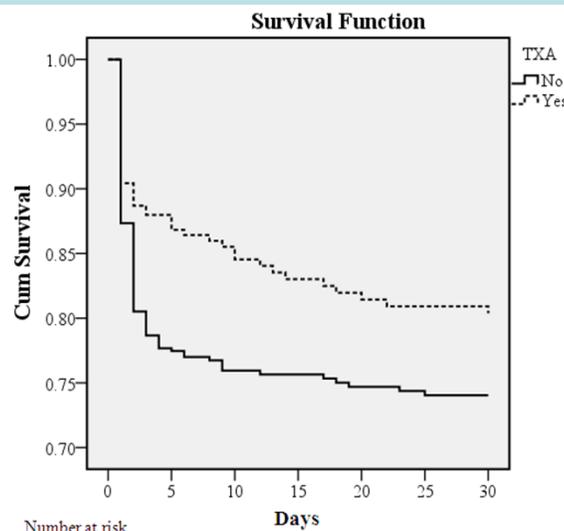
Overall	TXA	No-TXA	p Value
< 24 Hr	8.2%	8.5%	0.892
28 Day	16.4%	23.2%	0.018

MT	TXA	No-TXA	p Value
<24 Hr	8.8%	9.2%	0.907
28 Day	13.6%	27.6%	0.003

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MATTERS: Kaplan-Meier survival curve of the overall cohort



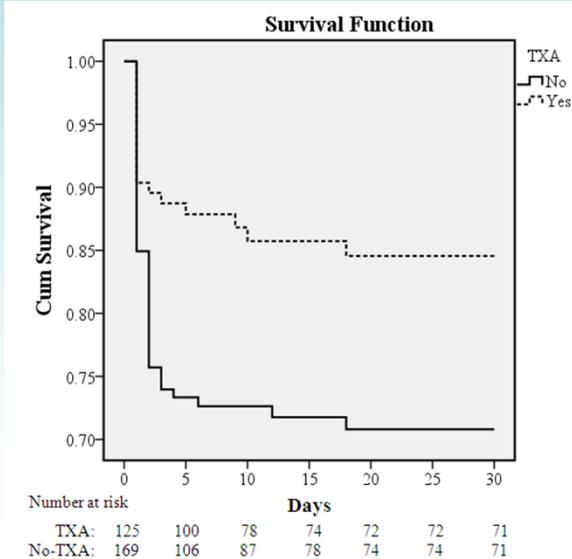
p = 0.006
(Wilcoxon
Statistic)

Number at risk		Days						
		0	5	10	15	20	25	30
TXA:	603	351	269	246	231	226	218	
No-TXA:	293	220	172	159	155	152	148	

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MATTERS: Kaplan-Meier survival curve of the massive transfusion group receiving TXA



p = 0.004
(Wilcoxon
Statistic)

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Conclusions

- Tranexamic acid is the only drug to have a demonstrated benefit in treating significant trauma induced hemorrhage.
- Timing of administration appears to be critical in trauma
- Use only within 3 hours of injury; earlier is better.
- Overall safety profile is very reassuring.
- Only available dosing guidance provided by CRASH-2 (1gm load over 10 minutes, then 1gm over 8 hours).
- Bastion experience includes 1 gm dose intravenous push followed by 1 to 2 additional grams within the next few hours.

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Proposed Changes

Tactical Field Care and Tactical Evacuation Care sections: (Add in both sections before Intravenous Fluids section)

- If a casualty is anticipated to need significant blood transfusion (for example: presents with hemorrhagic shock, one or more major amputations, penetrating torso trauma, or evidence of severe bleeding)
 - Administer 1 gram of tranexamic acid in 100 cc in Normal Saline or Lactated Ringer's as soon as possible but not later than 3 hours after injury.
 - Begin second infusion of 1 gm TXA after Hextend or other fluid treatment.

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Proposed Recommendation

- That the Board approve the proposed addition to the TCCC Guidelines
- That the Board note in its recommendation memorandum that ongoing analysis of the use of TXA in theater be a critical element in Performance Improvement Measures by the Services

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Discussion/Vote

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Back-Up Slides

**Proposed Change to the TCCC
Guidelines:**

Needle Decompression

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Traumatic Cardiac Arrest Guidelines: Current Wording

Tactical Field Care:

17. Cardiopulmonary resuscitation (CPR):

Resuscitation on the battlefield for victims of blast or penetrating trauma who have no pulse, no ventilations, and no other signs of life will not be successful and should not be attempted.

Tactical Evacuation (TACEVAC) Care:

None.

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Proposed Change: Tactical Field Care

17. Cardiopulmonary resuscitation (CPR):

Resuscitation on the battlefield for victims of blast or penetrating trauma who have no pulse, no ventilations, and no other signs of life will not be successful and should not be attempted. However, casualties with torso trauma or polytrauma who have no pulse or respirations should have bilateral needle decompression performed to ensure that they do not have a tension pneumothorax prior to discontinuation of care (the procedure is the same as described in section 3 above).

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Proposed Change: Tactical Evacuation Care

16. Casualties with torso trauma or polytrauma who have no pulse or respirations during TACEVAC should have bilateral needle decompression performed to ensure that they do not have a tension pneumothorax (the procedure is the same as described in section 2 above).
17. CPR may be attempted during this phase of care if the casualty does not have obviously fatal wounds and will be arriving at a medical treatment facility with surgical capability within a short period of time. CPR should not be done at the expense of compromising the mission or denying lifesaving care to other casualties.

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Back-Up Slides

Tranexamic Acid
(slides from COL Dorlac's
presentation, August 2-3, 2011)

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Contributors to TXA Review

- MAJ Jonathan J. Morrison
- Maj Joseph J. Dubose
- COL Todd E. Rasmussen
- CAPT Mark Midwinter
- Dr Richard B. Weiskopf
- MAJ Andrew Cap
- Chris Droege, Pharm D
- Col Lorne Blackbourne

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Changing epidemiology of trauma deaths leads to a bimodal distribution

Mark Gunst et al, *Proc (Bayl Univ Med Cent)* 2010;23(4):349–354

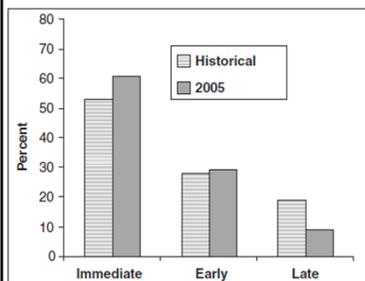


Figure 3. Timing of trauma deaths in the historical group from Trunkey's 1983 study (3) and in the group of 678 trauma deaths in Dallas County in 2005.

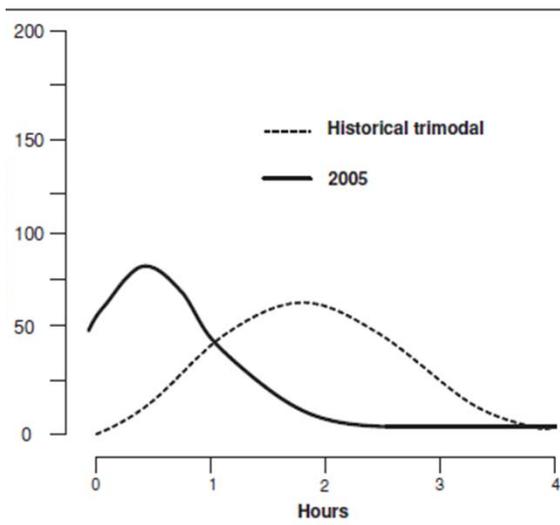
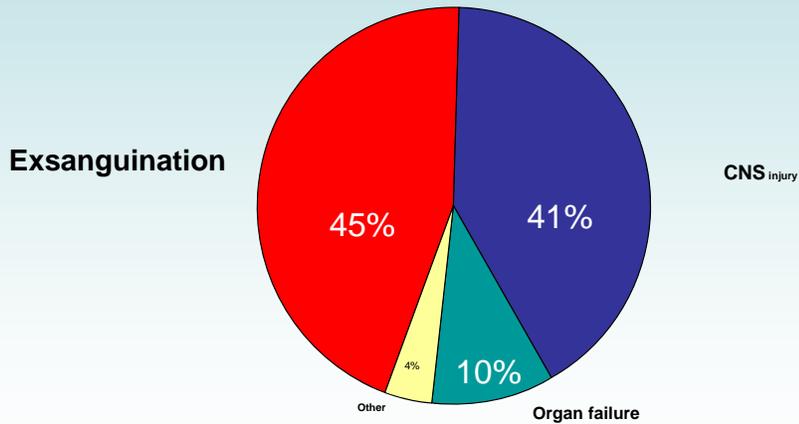


Figure 5. Time shift in early deaths in the group of 678 trauma deaths in Dallas County in 2005 compared with the historical group from Trunkey's 1983 study (3).

In-hospital trauma deaths



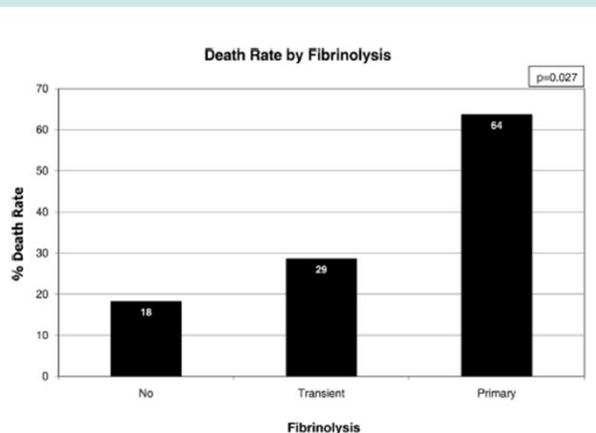
Sauaia A et al. Epidemiology of trauma deaths: a reassessment. J Trauma 1995;38:185-193



Primary Fibrinolysis Is Integral in the Pathogenesis of the Acute Coagulopathy of Trauma

Jeffry L. Kashuk, MD,*† Ernest E. Moore, MD,*† Michael Sawyer, MD,*† Max Wohlauer, MD,*†
 Michael Pezold, BA,*† Carlton Barnett, MD,*† Walter L. Biffi, MD,*† Clay C. Burlew, MD,*†
 Jeffrey L. Johnson, MD,*† and Angela Sauaia, MD, PhD*†

(Ann Surg 2010;252: 434-444)

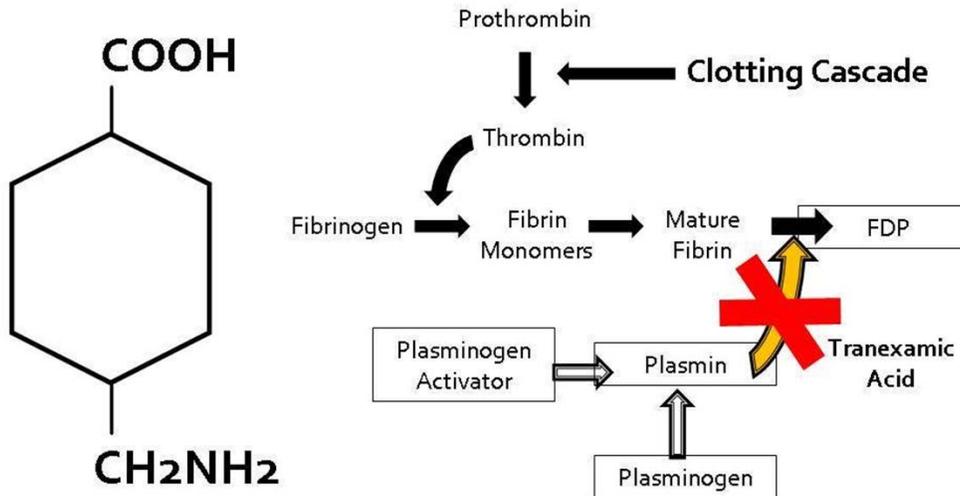


Primary Fibrinolysis was present in 34% of those requiring a Massive Transfusion within 6 hours



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TXA Background



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Tranexamic Acid Use

INTRAVENOUS INFUSION

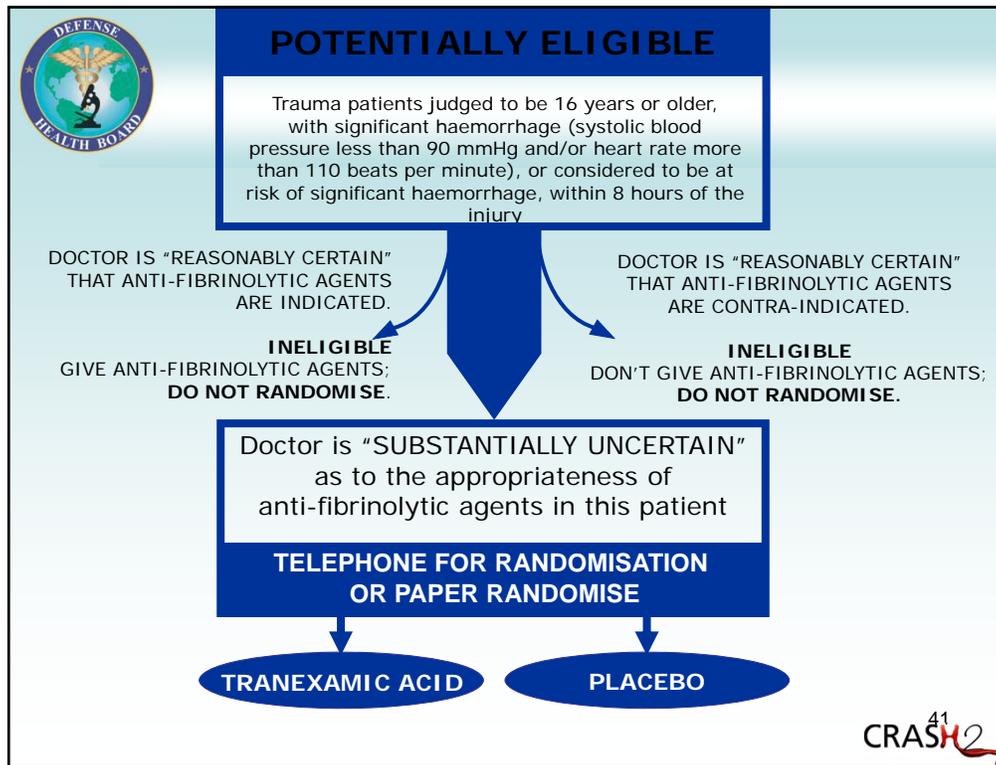
- For intravenous infusion, TXA may be mixed with most solutions
 - electrolyte solutions, carbohydrate solutions, amino acid solutions, and Dextran solutions.
- Should be prepared the same day to be used.
- Should NOT be mixed with blood.
- The drug is a synthetic amino acid, and should NOT be mixed with solutions containing penicillin.

HOW SUPPLIED

- CYKLOKAPRON Injection 100 mg/mL
- NDC 0013-1114-10 10 x 10 mL ampules

STORAGE

- Store at 25°C (77°F); excursions permitted to 15°- 30°C (59°- 86°F)



TXA – CRASH 2 Study Lancet Online Article 2010

USAISR Information Paper:

- FDA-approved for dental procedures in hemophiliacs and Oral form approved in menorrhagia
- Noted to increase cerebral ischemia in SAH
- Randomized, double-blinded, placebo-controlled trial – highest level of clinical evidence
- No subgroup analysis for patients requiring massive transfusion or those with TBI
- Cost: \$80 for 2-dose regimen used in CRASH 2
- Used for the past year by UK forces
- Might have saved 23 of 1500 preventable deaths in OIF/OEF

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TXA - CRASH 2 Study Lancet Online Article 2010

Holcomb comments:

- In a drug that was supposed to decrease bleeding:
- 50% of the patients did not get any RBCs
- The rate of transfusion was the same between groups = 6 units
- Only 48% had any surgery
- The difference in mortality due to bleeding was 0.8%
- Hours 1-3 after injury is where all the benefit was
- How do you determine if these was a significant type 1 error?

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TXA - Crash 2 Study Lancet Online Article 2010

Additional comments – Bryan Cotton:

- It would be interesting to study this drug in patients who actually had "traumatic hemorrhage."
- Not surprised to see that such a drug would not have any effect on the number of units transfused in such a general population.
- Sub-group analysis on patients arriving in shock?
- Here is a trauma paper without any mention that I can find of ISS, base deficit, lactate.
- **MOST IMPORTANT:** we're talking about a 0.7% absolute reduction in "death due bleeding"
- Zero POINT seven
- This translates into number needed to treat of 132

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TXA- CRASH 2 Study Lancet Online Article 2010

Additional comments:

- TXA administered 2.8-2.9 hours after injury
- Given to those “at risk” of hemorrhage
- 68% had SBP > 90 mmHg
- What should protocol be in at MTFs?
- Prehospital protocol?
- JTTS Directors conference 23 July 10 – no decision to add TXA to theater formulary

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CRASH-2:TXA Use for Trauma: Weiskopf Conclusions (DoD Hemorrhage Steering Committee)

- Lack of rigor of standard phase III clinical trials
 - Lack of clarity of study population
 - Lack of clarity of care provided
 - Excessive impact of at least 4 countries
- Only 1.4% patients from developed world; **NONE from US**
 - Problematic methodology impacting efficacy
 - Lack of important information impacting efficacy
 - Inadequate reporting of safety data
 - Standards for efficacy and safety **NOT met**
- This trial would not likely be the basis for approval of TXA for use in trauma

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CRASH-2: Timing of TXA Dosing – Lancet 2011

Ⓜ 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*

- Cochrane Review 2011: “The review concluded that tranexamic acid safely reduces mortality in bleeding trauma patients without increasing the risk of adverse events.”
- “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.”

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BMJ

BMJ 2011;343:d3795 doi: 10.1136/bmj.d3795

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RESEARCH

Effect of tranexamic acid in traumatic brain injury: a nested randomised, placebo controlled trial (CRASH-2 Intracranial Bleeding Study)

- 270 adult trauma patients with same inclusion criteria BUT who also had Traumatic Brain Injury (GCS \leq 14 with CT evidence of TBI)
- 133 received TXA- mean hemorrhage growth was 5.9 ml
 - new focal ischemic lesions in 6 (5%)
 - 14 (11%) deaths (adjusted odds ratio 0.51 (95% confidence interval 0.18 to 1.44)
- Vs.
- 137 placebo group- mean hemorrhage growth was 8.1 ml
 - new focal ischemic lesions in 12 (9%)
 - 24 (18%) deaths (adjusted odds ratio 0.47 (0.21 to 1.04)

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MATTERS Overall Cohort

- TXA group was more severely injured (ISS: 25.2 ± 16.6 vs. 22.5 ± 18.5 ; $p < 0.001$)
- required more blood (11.8 ± 12.1 vs. 9.8 ± 13.1 pRBC units; $p < 0.001$)
- had a lower Glasgow Coma Score (7.3 ± 5.5 vs. 10.5 ± 5.5 ; $p < 0.001$)
- had an initial systolic blood pressure (112 ± 29.1 vs. 122.5 ± 30.3 mmHg)
- but also had a lower unadjusted mortality than the no-TXA group (17.4% vs. 23.9%; $p = 0.028$).

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TXA Review Article J Trauma 2011

REVIEW ARTICLE

Tranexamic Acid for Trauma Patients: A Critical Review of the Literature

Andrew P. Cap, MD, PhD, David G. Baer, PhD, Jean A. Orman, MPH, ScD, James Aden, PhD, Kathy Ryan, PhD, and Lorne H. Blackbourne, MD

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TXA Review Article J Trauma 2011

Conclusions: This inexpensive and safe drug should be incorporated into trauma clinical practice guidelines and treatment protocols. Further research on possible alternate mechanisms of action and dosing regimens for TXA should be undertaken. Concurrent to these endeavors, TXA should be adopted for use in bleeding trauma patients because it is the only drug with prospective clinical evidence to support this application.

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Potential adverse events with TXA

- GI Disturbances
- Visual Disturbances
- Thromboembolic events
- Seizure activity (3-6x proposed dose)
- Avoid in giving with:
 - Prothrombin Complex Concentrate
 - Factor IX Complex Concentrates

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CRASH 2: Thromboembolic events

