Tranexamic Acid in Trauma

Trauma Association of Canada 2014

Montreal QC

Suzanne Beno, MD, FRCPC
Trauma Co-Director
The Hospital for Sick Children
Toronto, Ontario

Disclosures

- Nothing to disclose

Mitigating Potential Bias

- N/A

Objectives

- Review the evidence base for tranexamic acid (TXA) in trauma
- Identify current knowledge gaps for TXA in trauma
- Discuss the use of TXA in pediatric trauma

Scenario 1

- A young male presents to a trauma center extremely short of breath with stab wounds to his left flank. A chest tube is placed with return of a large volume of blood. He is stabilized but remains tachycardic, pale and agitated.

Scenario 2

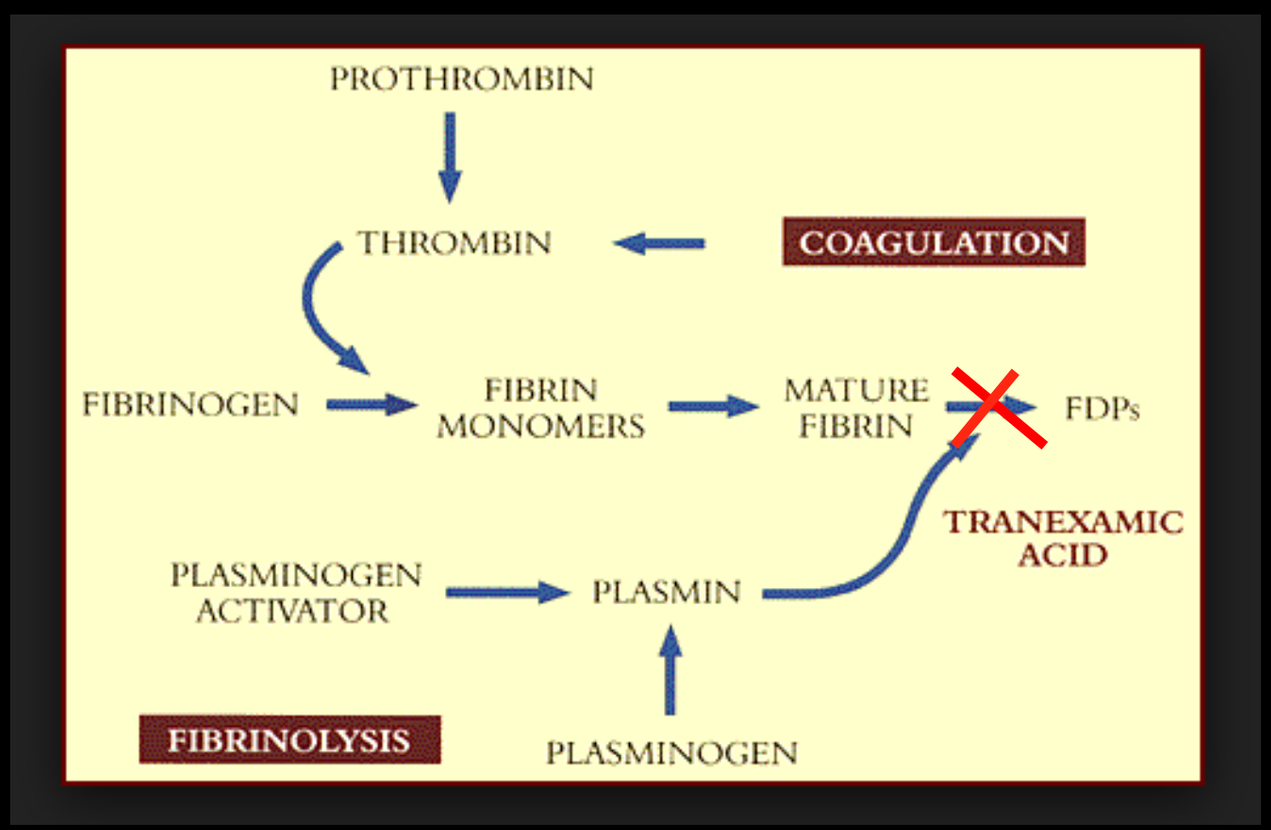
- A 5 year old girl on her bicycle is hit by a car. She presents with mild tenderness in her upper abdomen and tachycardia. Her FAST is grossly positive and an abdominal CT scan reveals a Grade 5 liver laceration. She is admitted to the ICU for observation.

Trauma

- Leading cause of death in North Americans 1-44 years of age
- Hemorrhage most preventable cause of death after trauma in both adults and children
- Hemostatic resuscitation and recognition of *acute traumatic coagulopathy* (ATC) and specifically *hyperfibrinolysis*
- No medical therapy has proven survival benefit in children, but evidence *DOES* exist in adults

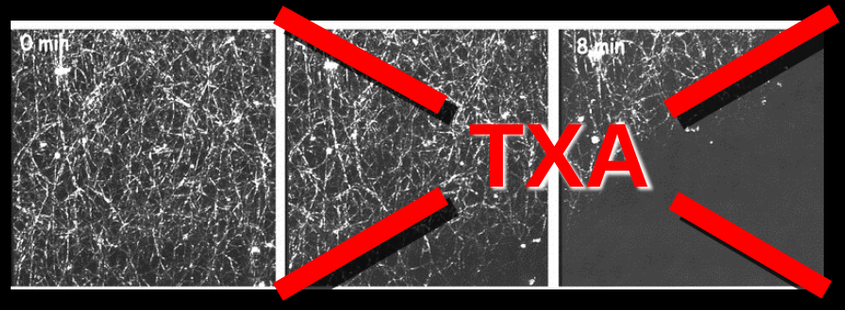
Tranexamic Acid

- antifibrinolytic: reversibly binds to plasminogen preventing the binding of plasmin to fibrin and the subsequent degradation of fibrin



Tranexamic Acid

- Prevents the breakdown of clots



Fibrin Fibrinolysis

- Mitigates the systemic anti-inflammatory response to massive hemorrhage

Tranexamic Acid

- First clinical trial using oral TXA published in 1968 - heavy menstrual bleeding - FDA 2009
- Dental extractions with hemophilia reported in 1972 - FDA approval 1986
- TXA now widely used in many conditions
- *Extensive safety and efficacy profile* in reducing the need for blood transfusions in elective surgery both adults and children

Cap AP et al. J Trauma 201

TXA in Trauma

What's the evidence?

CRASH-2

Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage

Clinical Trials Unit LSHTM

LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

A large randomised placebo controlled trial among trauma patients with, or at risk of, significant haemorrhage, of the effects of antifibrinolytic treatment on death and transfusion requirement

ISRCTN86750102

- prospective randomized placebo-controlled trial of 20,211 patients, 274 hospitals, 40 countries

- Inclusion criteria: adults (16 years and up) with unstable vital signs or high clinical suspicion for hemorrhage within 8 hours of injury
- Randomized to TXA versus placebo
- One gram over 10 minutes followed by a second one gram infusion over 8 hours

CRASH 2 Analyses
Summary Results

- Decreased all-cause mortality 16.0% to 14.5%, NNT 67
- Decreased risk due to bleeding 5.7% to 4.9%, NNT 121
- Greatest reduction in deaths due to bleeding:
  - Severe shock (≤ 75 mmHg) 14.9% vs 18.4%
  - Within first hour - benefit seen within 3h of injury
  - *Increased* risk of death if administered after 3 hours
- TXA not associated with ↑ vascular occlusive events
- TXA safe and effective across all mortality groups

ORIGINAL ARTICLE

ONLINE FIRST

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

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

- Retrospective, observational
- Military environment
- Overall: AR 7.6%, 6.5%
- MT: AR 13.7%, RR 49% OR for survival 7.228 [95% CI 3.0 to 17.3]

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, %)		*P* Value[a]
	TXA	No TXA	
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.

TXA Is Cost Effective

OPEN ACCESS Freely available online

PLoS one

Cost-Effectiveness Analysis of Administering Tranexamic Acid to Bleeding Trauma Patients Using Evidence from the CRASH-2 Trial

Carla Guerriero[1]*, John Cairns[1], Pablo Perel[2], Haleema Shakur[2], Ian Roberts[2], on behalf of CRASH 2 trial collaborators

1 Department of Health Services Research and Policy, London School of Hygiene and Tropical Medicine, London, United Kingdom, **2** Clinical Trials Unit, London School of Hygiene and Tropical Medicine, London, United Kingdom

Findings: Administering TXA to bleeding trauma patients within three hours of injury saved an estimated 372, 315 and 755 LYs per 1,000 trauma patients in Tanzania, India and the UK respectively. The cost of giving TXA to 1,000 patients was $17,483 in Tanzania, $19,550 in India and $30,830 in the UK. The incremental cost of giving TXA versus not giving TXA was $18,025 in Tanzania, $20,670 in India and $48,002 in the UK. The estimated incremental cost per LY gained of administering TXA is $48, $66 and $64 in Tanzania, India and the UK respectively.

Conclusion: Early administration of TXA to bleeding trauma patients is likely to be highly cost effective in low, middle and high income settings.

- One dose TXA costs ~ $5.40 - $65
- One dose Factor VIIa costs ~ $8500

Adverse Effects

- Seizures (perioperative - high dose)
- Rapid infusion hypotension
- Thromboembolism
  - no difference between groups in CRASH 2
  - not seen in pediatric surgery (high doses)
  - systematic reviews *have not found* a concern

Henry et al Cochrane Review 2011
Ker et al BMJ 2012,
Faraoni D, Goobie SM Anesth Analg 20

Ideal hemostatic Agent

- Easy to store and use
- Stops inappropriate hemorrhage
- Does not clot working vessels
- No side effects *(minimal)*
- Free (*cheap*)

Richard Dutton EMCrit Conference 2011

CRASH-2 goes viral!

Hospitals shun cheap drug used to stop bleeding

LISA PRIEST
The Globe and Mail
Published Friday, May. 11 2012, 10:23 PM EDT
Last updated Monday, Jun. 18 2012, 10:30 AM EDT

or does it?

Knowledge Translation

- Audit of UK hospitals in 2011: of 412 patients requiring transfusion and were eligible for TXA, only 12(3%) received it.

The Lancet 2011;**378**: 1758

- Survey - Trauma Center Association of America
  - 24 member institutions
  - 2 were using TXA as institutional protocol and 7 were considering its use.

www.traumafoundation.org

Knowledge Translation

- RoadPeace: survey of 291 UK hospitals 2012
- 72% response rate of 291 hospitals
- 89% include TXA in their protocol
- 8% transfused patients received TXA in 2011
- Of the 285 trauma patients transfused in major trauma centers, 13 (5%) received TXA
- It’s in the protocol, but it’s not being given!

The Lancet 2013; **382**: 208

Knowledge Gaps

- Use in significant traumatic brain injury? (CRASH 3)
- Optimal dosing?
- Mortality benefit in advanced trauma systems (PATCH)
- "*True*" risk of thromboembolism?
- Role of fibrinolysis testing prior to giving TXA?
- Indications in *pediatric trauma?*

Traumatic Coagulopathy Pediatrics

- ATC is *prevalent* in pediatric trauma (27, 38, 77%)
- ATC *strongly* associated with ↑ mortality in children (civilian and in combat support hospitals) OR 2.2
- TBI and early coagulopathy significantly ↑ mortality (fourfold)

Hendrickson et al. *J Pediatr Surg* 2012
Patregnani et al. *Pediatr Crit Care Med* 2012 Whittaker et al. *Shock* 2013

Hyperfibrinolysis
Pediatric Trauma

- not clearly described
- Fibrinogen levels low in 52% of children needing transfusion [20% < 100 mg/dL]
- rTEG in pediatric trauma
- Pediatric coagulopathic response to injury *similar* to adults

Hendrickson et al. *J Pediatr Surg* 2012 Vogel etal. *J Pediatr Surg* 2013

TXA in Pediatric Trauma

Why it makes sense

- Hemorrhage, *like in adults*, is the second leading and main preventable cause of traumatic death
- Trauma-associated coagulopathy exists in kids
- Hyperfibrinolysis - very likely
- Track record of safety and efficacy when used in HIGH doses in pediatric surgery
- Healthier vascular systems

Royal College of
Paediatrics and Child Health

Leading the way in Children's Health

Evidence Statement

Major trauma and the use of tranexamic acid in children

November 2012

Key points

- Tranexamic acid reduces mortality in adult trauma
- Early administration is vital for efficacy
- Due to the lack of published data on the use of tranexamic acid in paediatric patients who have undergone major trauma there is no evidence for a specific dose in this situation
- The RCPCH and NPPG Medicines Committee recommend a pragmatic dosage schedule – 15mg/kg tranexamic acid loading dose (max 1g) over 10 minutes followed by 2mg/kg per hour

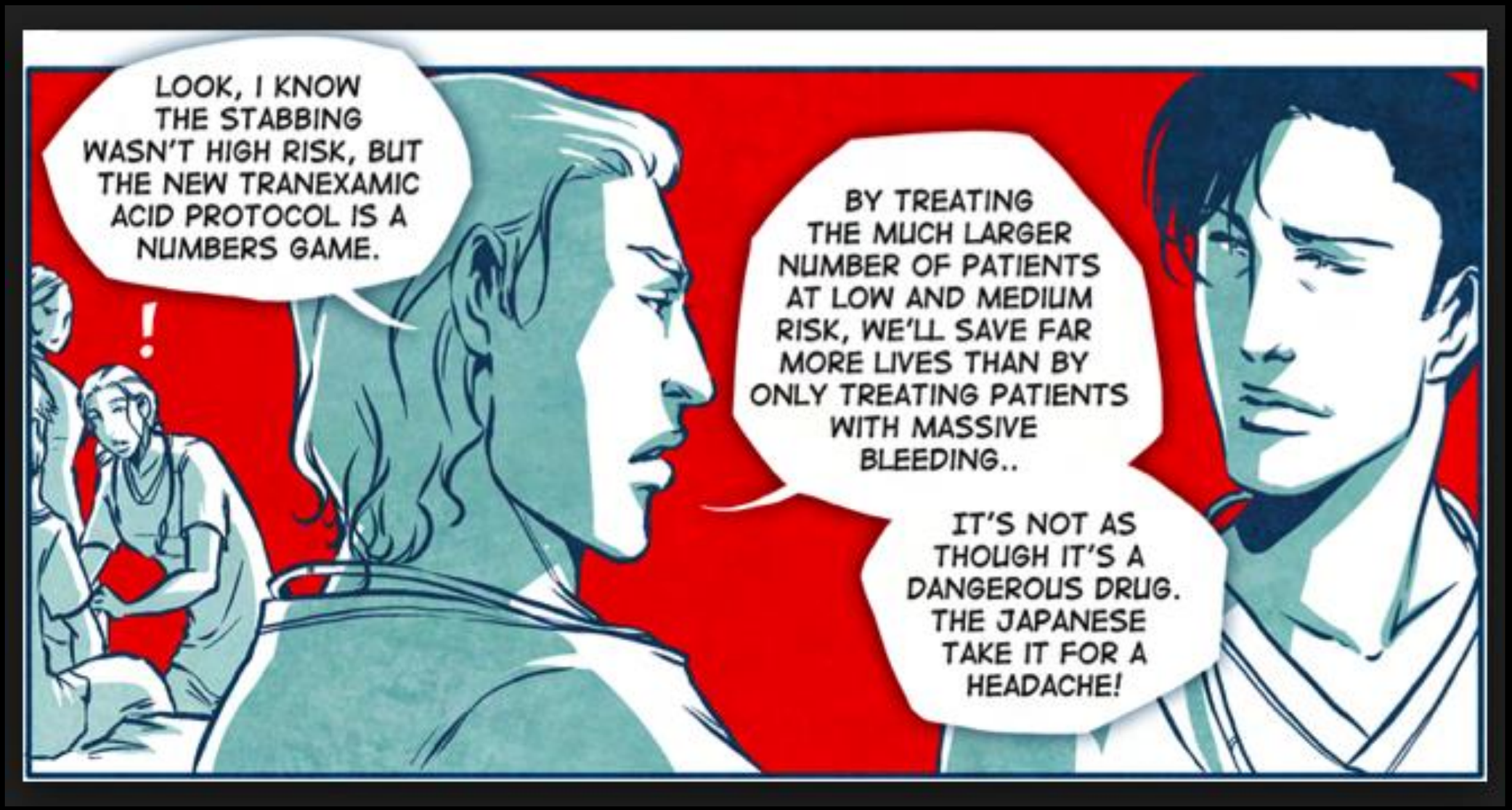
Practical Considerations
Pediatric Trauma

- Intraosseous route (no data)
- Pre-hospital administration (by age?)
- Adolescents and children (different)
- Careful prospective monitoring

TXA in Trauma - 2014

- TXA reduces mortality in bleeding adult trauma patients if given within 3 hours of injury, and is *not* associated with increased thrombotic complications.
- TXA is inexpensive and cost-effective.
- Knowledge translation is needed.
  Knowledge gaps do exist.
- TXA safely used in pediatric surgical patients, adult trauma patients, and most likely safe/effective for pediatric trauma patients.
  Further research needed.

Questions?


LOOK, I KNOW THE STABBING WASN'T HIGH RISK, BUT THE NEW TRANEXAMIC ACID PROTOCOL IS A NUMBERS GAME.
!
BY TREATING THE MUCH LARGER NUMBER OF PATIENTS AT LOW AND MEDIUM RISK, WE'LL SAVE FAR MORE LIVES THAN BY ONLY TREATING PATIENTS WITH MASSIVE BLEEDING..
IT'S NOT AS THOUGH IT'S A DANGEROUS DRUG. THE JAPANESE TAKE IT FOR A HEADACHE!

Select Key References

- CRASH-2 trial collaborators, Shakur H, Roberts I, Bautista R et al. **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.** *Lancet* 2010; **376**: 23-32.

- Morrison JJ, Dubose JJ, Rasmussen TE, Midwinter MJ: Military Application of Tranexamic Acid in Trauma Emergency Resuscitation (MATTERS) Study. *Arch Surg* 2012; 147: 113-119.

- CRASH-2 trial collaborators, Roberts I, Shakur H, Afolabi A et al. **The importance of early treatment with tranexamic acid in bleeding trauma patients: an exploratory analysis of the CRASH-2 randomised controlled trial.** *Lancet* 2011, **377**:1096-1101.

Select Key References

- Ker K, Junko K, Perel P et al. **Avoidable mortality from giving tranexamic acid to bleeding trauma patients: an estimation based on WHO mortality data, a systematic literature review and data from the CRASH-2 trial.** *BMC Emergency Medicine* 2012, **12**:3.

- Pusateri AE, Weiskopf RB, Bebarta V et al. US DoD Hemorrhage and Resuscitation Research and Development Steering Committee. **Tranexamic Acid and Trauma: Current Status and Knowledge Gaps with Recommended Research Priorities.** *Shock* 2013; **39**(2): 121-126

- Cap AP, Baer DG, Orman JA, Aden J, Ryan K, Blackbourne LH: **Tranexamic Acid for Trauma Patients: A Critical Review of the Literature.** *J Trauma* 2011; **71**: S9-S14.

- Napolitano LM, Cohen MJ, Cotton BA, Schreiber MA, Moore EE: **Tranexamic acid in trauma: How should we use it?** *J Trauma Acute Care Surg* 2013; **74**(6): 1575-1586.

Select Key References

- Harvey V, Perrone J, Kim P: Does the Use of Tranexamic Acid Improve Trauma Mortality? *Ann Emerg Med* 2013 Oct 3. pii: S0196-0644(13)01341-3. annemergmed.2013.08.028. [Epub ahead of print]

- Royal College of Paediatrics and Child Health. Evidence Statement. **Major trauma and the use of tranexamic acid in children**. November 2012. [http://www.collemergencymed.ac.uk/ShopFloor/Clinical%20Guidelines/External%20Guidelines/default.asp]

- Faraoni D, Goobie SM. The Efficacy of Antifibrinolytic Drugs in Children Undergoing noncardiac Surgery: A Systematic Review of the Literature. Anesth Anal 2014;118:628-36