Hemostatic Products CDER

Nicole Verdun, MD
Medical Officer
CDER/ OHOP/DHP

CDER Approved Drugs- *Antifibrinolytics*

- Off label- No specific indication for use with trauma
- Aminocaproic Acid
  - **Indication**: "*Is useful in enhancing hemostasis when fibrinolysis contributes to bleeding*."
- Tranexamic Acid
  - **Indication**: *For the reduction of peri- and post-operative blood loss and the need for blood transfusion in patients undergoing cardiac surgery or total knee arthroplasty or total hip arthroplasty*
  - Competitive inhibitor of plasminogen activation
  - Noncompetitive inhibitor of plasmin at higher concentrations
  - 10x more potent than Aminocaproic Acid *in vitro*

CRASH-2 Trial

CRASH-2 Trial Collaborators. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomized, placebo-controlled trial Lancet, 2010: 376: 23-32

- Randomized controlled trial, 274 hospitals, 40 countries
- 20,211 adult trauma patients with or at risk of bleeding within 8 h of injury received tranexamic acid or placebo
- *Primary outcome*:
  - In-hospital death within 4 weeks of injury

Results, CRASH-2

- All cause mortality reduced with TXA (14.5% vs. 16%, RR 0.91, p=0.0035)
- Risk of death due to bleeding reduced with TXA (4.9% vs. 5.7%, RR 0.85, p=0.0077)
- *Survival benefit occurred if TXA was given within 3 h of injury.*
  - Increase in mortality due to bleeding in TXA group if treatment initiated >3h after injury (3.1% to 4.4%, p=0.0049)

Criticisms, CRASH-2

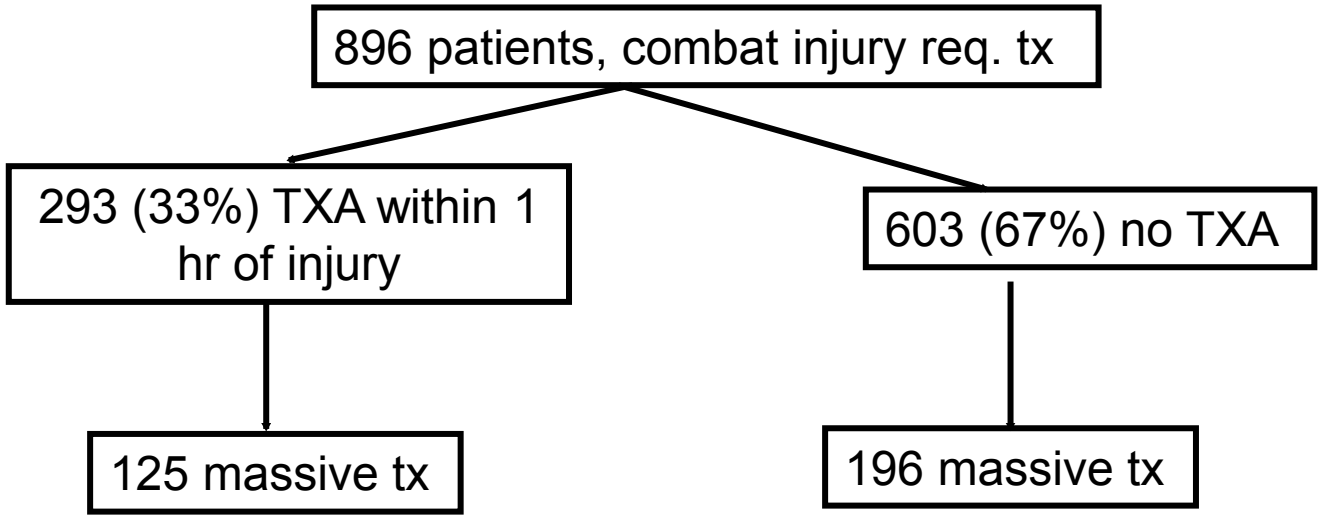
- Variability in countries with regard to trauma resuscitation and care standards, including blood product use
- Only 5% of patients had bleeding as a cause of death
- No data regarding fibrinolysis status on admission
- No data on injury severity
- No data on blood loss
- Only 50% of study cohort received blood transfusion
- Small number of patients with hypotension or tachycardia
- Small effect size (0.8% absolute reduction in death caused by bleeding)
- Lack of systematic AE reporting

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

Morrison et. al. Military Application of Tranexamic Acid in Trauma Emergency Resuscitation (MATTERs) Study. Arch Surg. 2012: 147:113-119

- Retrospective observational study, 896 admissions with combat injury
- Comparison of TXA administration with no TXA in patients receiving ≥1 u PRBCs
  - Subgroup analysis (≥10 u PRBCs)
- *Primary outcome*:
  - Mortality at 24 hrs, 48 hrs, and 30 days
  - Influence of TXA on postop coagulopathy
  - Rate of thromboembolic complications

MATTERs Study



Results, MATTERs

- TXA group lower mortality than no TXA group (17.4% vs. 23.9%, p=0.03) despite a higher baseline injury severity score (25.2 vs. 22.5, p=0.01)
- Benefit greatest in those receiving massive transfusion (14.4% vs. 28.1%, p=0.004)
- TXA independently associated with survival (odds ratio 7.228), less coagulopathy (p=0.003)
- Higher rates of VTE events in TXA group
  - *Several factors make this assoc. difficult (small numbers of events, higher injury burden in TXA group)*

CDER Hemostatic Agents

- Antifibrinolytics seem to have some benefit in trauma settings, but the exact dosing, timing, and mechanism need further prospective evaluation
- Off label use, while not ideal, allows for use for trauma indications
- FDA and CDER are committed to the development of such agents, and encourage further study and new exploration