Article Title/Citation:
Effects of tranexamic acid (TXA) on death, vascular occlusive events, and blood transfusion in trauma patients with significant hemorrhage (CRASH-2): a randomized, placebo-controlled trial


Study objectives/purpose: (and research hypothesis if applicable)
To evaluate the efficacy and safety of short course tranexamic acid administration to trauma patients with suspicion of significant hemorrhage. The authors believed (based on surgical literature) that the use of tranexamic acid would reduce the receipt of blood transfusions and potentially operative interventions.

Brief Background: (why issue is important, summary of previous literature)
One third of all deaths from trauma are related to bleeding. Significant hemorrhage increases the risk of MSOF and therefore mortality. Trauma related bleeding is a complex process which “hyper-fibrinolysis” is thought to be a main contributor. Anti-fibrinolytic medications have been used in a number of surgical situations (Cardiac and Gyne) with proven safety and efficacy. A number of systematic reviews published in the Cochrane database has concluded that the administration of TXA reduces the amount of blood transfusions required without a significant increase in vascular occlusive events but has no effect on mortality.

Methods

Study design and Methodology: (type of trial, Randomization, blinding, Controls, study groups, Length of study, etc.)

Large (20,211) Multi-centre, placebo-controlled trial. Randomization was balanced by centre with allocation sequences in blocks of 8. The randomization service used a minimization algorithm balancing for sex, age time since injury, type of injury (blunt or penetrating), GCS, systolic BP, RR, central cap filling time, and country. Study groups were well balanced with regards to baseline characteristics. Study enrollment began May 2005 and ended in early 2010
Patient selection and Enrollment: (inclusion/Exclusion criteria, sample Size etc.)

Sample size: 20211
Inclusion: All adult (>16 yo) trauma victims with or at risk of significant bleeding defined as systolic BP < 90 or HR >110 bpm or both, or who were considered to be at risk of significant hemorrhage and were within 8 hours of injury and whom the treating physician was not sure to treat with TXA or not.
Exclusion: Patients with a clear indication for TXA administration, patients with a clear contra-indication to TXA as decided by the treating physician.

Interventions: (if applicable)

Loading dose of TXA 1g over 10 mins, followed by an infusion of 1g over 8 hours (125mg/hr)

Outcome measures/Endpoints:
Primary: In-hospital death within 4 weeks
Secondary: Vascular occlusive events (MI, PE, CVA, DVT)
Need for surgical intervention
Receipt of blood transfusions
Number of units of blood received
Dependency (modified oxford handicap scale)

Statistical analysis:

Intention-to-treat
Relative Risk was calculated for each binary outcome
Heterogeneity in treatment effects across subgroups was assessed by X² tests
No imputation for missing data

Results
Enrollment & Baseline Characteristics: TXA vs. Placebo
Sex Male: 83.6-84%
Age: 34.6-34.5
Time since injury: 2.8-2.9hrs
Type of injury: 67.5-67.7% Blunt
Systolic BP <75: 15.5-15.9%
RR 10-29: 82.8-83.4%
Cap refill time >4s: 16.8%-16.5%
HR>107: 48.3-48%
GCS 3-8: 17.8-18.2%
Summary of primary & secondary outcomes: (including subgroup analysis etc. include both efficacy and safety parameters)

Any Cause of death TXA vs Placebo: 14.5% vs 16% RR 0.91  p=0.0035
Bleeding Death TXA vs. Placebo: 4.9% vs. 5.7% RR 0.85 p=0.0077
Vascular Occlusive Events TXA vs. Placebo: 1.7% vs. 2% RR0.84 p=0.084
Need for Blood TXA vs. Placebo: 50.4% vs. 51.3% ns
Need for Surgery TXA vs. Placebo: 47.9% vs. 51.3% ns
Dependency (no symptoms) TXA vs. Placebo: 14.7% vs. 13.3% RR 1.11 p=0.0023

Pertinent figures/diagrams:

<table>
<thead>
<tr>
<th>Table 2: Death by cause</th>
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<tbody>
<tr>
<td>Any cause of death</td>
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<tr>
<td>TXA (n=10 060)</td>
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<tr>
<td>Any cause of death</td>
</tr>
<tr>
<td>Bleeding</td>
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<tr>
<td>Vascular occlusion*</td>
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<td>Multiorgan failure</td>
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<td>Head injury</td>
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<td>Other causes</td>
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Data are number (%), unless otherwise indicated. RR-relative risk. *Includes myocardial infarction, stroke, and pulmonary embolism.

Figure 3: All-cause mortality by subgroups
GCS=Glasgow Coma Score. *95% CI.
**Author’s Discussion and Conclusions**

**Brief summary of Authors’ main discussion points:**

Inclusion criteria completely clinical (no labs) therefore easy to apply and is appropriate to generalize. Baseline prognostic factors well balanced with almost no loss of follow-up. Based on the clinical criteria alone (of traumatic hemorrhage) the power of the trial to show an effect of TXA might have been diminished given that some of the patients may not have been bleeding. There were no differences in non-fatal vascular occlusive events but they only investigated events with clear clinical evidence thereof maybe underestimating the frequency of these events. The mechanism of TXA reduction in mortality is unclear. Early administration of TXA justified because of the high frequency of early deaths due to bleeding in trauma. Fixed dosing of TXA justified based on equality of high/low dose in literature previously published.

**Author’s conclusions:**

The administration of fixed doses of TXA given to patients experiencing or at high risk of developing significant traumatic hemorrhage reduces the chance of death. In this clinical situation there is not a significant increase in vascular occlusive events.

**Your Discussion and Conclusions**

**Study strengths:**

Large sample size (20211), randomized, placebo-controlled, double-blinded, intention-to-treat, simple inclusion criteria.

**Study limits, weaknesses, Potentials for bias:**

Definition of “traumatic hemorrhage” insensitive (only based on BP/HR)

Not clear how many patients screened.

No Prehospital/hospital account/quantification of resuscitation

Reduced deaths due to bleeding but no effect on number of units transfused??

Mechanism of action unclear.

Fibrinolysis not measured.

No data on when blood was transfused.

Goal Hgb?

No data on blood/blood product ratio

Defn’ of “Bleeding death” not stated. Unclear if it was death from “medical” vs. “surgical” bleeding.

Unclear surgical capabilities of enrollment centres.

**Applicability & impact:**

Benefit limited to first hour post-trauma which largely eliminates its utility in ICU more applicable to EMS+/-ER
Conclusions and Recommendations:

Interesting results although lots of issue with inclusion criteria and limited goal directed resuscitation. The limited time window for administration makes the applicability of use problematic. More hypothesis generating than anything. Little application in Canadian Critical Care settings. Certainly not game-changing and would caution against early adoption.