Tranexamic Acid (TXA) for Postpartum Hemorrhage

Mark Rollins, MD, PhD
Professor & Director Obstetric Anesthesia
University of Utah
Department of Anesthesiology
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Questions to ponder

• What is TXA?
• Why the recent focus on TXA for PPH?
• Does it work?
• What about clot risk?
• Is it available? Expensive?
• When and how should TXA be used?
• Should we just give it to prevent PPH?
What is Tranexamic Acid (TXA)?

TXA is a synthetic derivative of lysine
High affinity for lysine binding sites on plasminogen to block plasmin from binding and degrading linked fibrin

95% excreted un-metabolized in urine
Elimination half-life is 3 hours

Plasminogen → Plasmin → Fibrin Degradation

Fibrinogen → Fibrin polymers → Linked Fibrin →TXA → Fibrin Degradation
TXA Outside of Pregnancy?

• Category A1 (efficacy): Meta-analysis of 24 RCTs
  - 9 cardiac, 9 ortho, 2 neuro, 2 oncology, 1 gyn, 1 oral surgery
  Demonstrated reduced blood loss and transfusion

• Category A2 (safety): 7 RCTs
  - 6 cardiac and 1 vascular
  No Difference in Stroke, MI, or Death

## TXA Outside of Pregnancy?

Meta-analysis of effect of tranexamic acid on risk of blood transfusion

<table>
<thead>
<tr>
<th>Type of surgery</th>
<th>No of events (tranexamic acid/control)</th>
<th>Pooled risk ratio (95% CI)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac</td>
<td>622/835</td>
<td>0.65 (0.60 to 0.70)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Orthopaedic</td>
<td>298/462</td>
<td>0.55 (0.49 to 0.61)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hepatic</td>
<td>29/54</td>
<td>0.52 (0.39 to 0.68)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Urological</td>
<td>40/60</td>
<td>0.66 (0.48 to 0.91)</td>
<td>0.01</td>
</tr>
<tr>
<td>Vascular</td>
<td>11/19</td>
<td>0.58 (0.34 to 0.99)</td>
<td>0.05</td>
</tr>
<tr>
<td>Gynaecological</td>
<td>17/50</td>
<td>0.86 (0.48 to 1.54)</td>
<td>0.61</td>
</tr>
<tr>
<td>Cranial and orthognathic</td>
<td>52/76</td>
<td>0.63 (0.45 to 0.86)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

Ker K, et al. BMJ 2012; 344
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*

Summary
Background Tranexamic acid can reduce bleeding in patients undergoing elective surgery. We assessed the effects of early administration of a short course of tranexamic acid on death, vascular occlusive events, and the receipt of blood transfusion in trauma patients.

Methods This randomised controlled 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 then infusion of 1 g over 8 h) or matching placebo. Randomisation was balanced by centre, with an allocation sequence based on a block size of eight, generated with a computer random number generator. Both participants and study staff (site investigators and trial coordinating centre staff) were masked to treatment allocation. The primary outcome was death in hospital within 4 weeks of injury, and was 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. This study is registered as ISRCTN86750102, Clinicaltrials.gov NCT00375258, and South African Clinical Trial Register DOH-27-0607-1919.

Lancet 2010; 376: 23-32
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See Comment page 3
*Members listed at end of paper
Correspondence to:
Clinical Trials Unit, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, UK
crash@lshtm.ac.uk
Results:
• Early administration of TXA to trauma patients at risk of significant bleeding reduces the risk of death from haemorrhage.
• No apparent increase in vascular occlusive events.
• All-cause mortality was significantly reduced with TXA.
CRASH-2 Study:

<table>
<thead>
<tr>
<th></th>
<th>Tranexamic acid (n=10 060)</th>
<th>Placebo (n=10 067)</th>
<th>RR (95% CI)</th>
<th>p value (two-sided)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any cause of death</td>
<td>1463 (14.5%)</td>
<td>1613 (16.0%)</td>
<td>0.91 (0.85–0.97)</td>
<td>0.0035</td>
</tr>
<tr>
<td>Bleeding</td>
<td>489 (4.9%)</td>
<td>574 (5.7%)</td>
<td>0.85 (0.76–0.96)</td>
<td>0.0077</td>
</tr>
<tr>
<td>Vascular occlusion*</td>
<td>33 (0.3%)</td>
<td>48 (0.5%)</td>
<td>0.69 (0.44–1.07)</td>
<td>0.096</td>
</tr>
<tr>
<td>Multiorgan failure</td>
<td>209 (2.1%)</td>
<td>233 (2.3%)</td>
<td>0.90 (0.75–1.08)</td>
<td>0.25</td>
</tr>
<tr>
<td>Head injury</td>
<td>603 (6.0%)</td>
<td>621 (6.2%)</td>
<td>0.97 (0.87–1.08)</td>
<td>0.60</td>
</tr>
<tr>
<td>Other causes</td>
<td>129 (1.3%)</td>
<td>137 (1.4%)</td>
<td>0.94 (0.74–1.20)</td>
<td>0.63</td>
</tr>
</tbody>
</table>

Table 2: Death by cause

“The results show that the early administration of tranexamic acid to trauma patients with, or at risk of, significant bleeding reduces the risk of death from haemorrhage with no apparent increase in fatal or non-fatal vascular occlusive events. All-cause mortality was significantly reduced with tranexamic acid.”
Tranexamic acid for preventing postpartum blood loss after cesarean delivery: a systematic review and meta-analysis of randomized controlled trials

GIULIANA SIMONAZZI¹, MARIA BISULLI¹, GABRIELE SACCONEn, ELISA MORO¹, ARIELA MARSHALL³,⁴ & VINCENZO BERGHELLA⁵

Acta Obstetricia et Gynecologica Scandinavica 95 (2016) 28–37

<table>
<thead>
<tr>
<th>Study</th>
<th>Risk</th>
<th>Total</th>
<th>Event</th>
<th>Control</th>
<th>Risk Difference</th>
<th>95% CI</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gungorduk 2011</td>
<td>500</td>
<td>206</td>
<td>330</td>
<td>600</td>
<td>215</td>
<td>330 27.4%</td>
<td>2011</td>
</tr>
<tr>
<td>Movafegh 2011</td>
<td>329</td>
<td>0</td>
<td>50</td>
<td>545</td>
<td>0</td>
<td>50</td>
<td>2011</td>
</tr>
<tr>
<td>Senturk 2013</td>
<td>272</td>
<td>143</td>
<td>101</td>
<td>346</td>
<td>189</td>
<td>122 26.5%</td>
<td>2013</td>
</tr>
<tr>
<td>Xu 2013</td>
<td>379</td>
<td>160</td>
<td>88</td>
<td>441</td>
<td>189</td>
<td>86 25.6%</td>
<td>2013</td>
</tr>
<tr>
<td>Shahid 2013</td>
<td>392</td>
<td>166</td>
<td>38</td>
<td>753</td>
<td>244</td>
<td>36 20.5%</td>
<td>2013</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>607</td>
<td>624</td>
<td></td>
<td></td>
<td>100.0%</td>
<td>−136.75 [−217.39, −56.11]</td>
<td>2013</td>
</tr>
</tbody>
</table>

Heterogeneity: $\chi^2 = 58.998$, $p = 0.04$, df = 3 ($n < 0.001$), $I^2 = 91\%$. 
Concern of using TXA in pregnancy remained due to the hypercoagulable state

http://www.cdc.gov/reproductivehealth/maternalinfanthealth/pmss.html
Why the recent focus?

- International WOMAN trial (20,000 participants)
- Endorsed in national PPH bundles for treatment
- Widely used in other surgical specialties
- High-profile reviews and guidelines suggest its use for treatment of PPH
Effect of early tranexamic acid administration on mortality, hysterectomy, and other morbidities in women with post-partum haemorrhage (WOMAN): an international, randomised, double-blind, placebo-controlled trial

WOMAN Trial Collaborators

Summary

Background Post-partum haemorrhage is the leading cause of maternal death worldwide. Early administration of tranexamic acid reduces deaths due to bleeding in trauma patients. We aimed to assess the effects of early administration of tranexamic acid on death, hysterectomy, and other relevant outcomes in women with post-partum haemorrhage.

Methods In this randomised, double-blind, placebo-controlled trial, we recruited women aged 16 years and older with a clinical diagnosis of post-partum haemorrhage after a vaginal birth or caesarean section from 193 hospitals in 21 countries. We randomly assigned women to receive either 1 g intravenous tranexamic acid or matching placebo in addition to usual care. If bleeding continued after 30 min, or stopped and restarted within 24 h of the first dose, a second dose of 1 g of tranexamic acid or placebo could be given. Patients were assigned by selection of a numbered treatment pack from a box containing eight numbered packs that were identical apart from the pack number. Participants, care givers, and those assessing outcomes were masked to allocation. We originally planned to enrol 15 000 women with a composite primary endpoint of death from all-causes or hysterectomy within 42 days of giving birth. However, during the trial it became apparent that the decision to conduct a hysterectomy was often made at the same time as randomisation. Although tranexamic acid could influence the risk of death in these cases, it could not affect the risk of hysterectomy. We therefore increased the sample size from 15 000 to 20 000 women in order to estimate the effect of tranexamic acid on the risk of death from post-partum haemorrhage. All analyses were done on an intention-to-treat basis. This trial is registered with ISRCTN76913190 (Dec 8, 2008); ClinicalTrials.gov number NCT00872469; and BACTR201007000192283.

Lancet 2017; 389: 2105-16
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April 26, 2017
http://dx.doi.org/10.1016/S0140-6736(17)30538-4
This online publication has been corrected. The corrected version first appeared at thelancet.com on May 5, 2017
See Editorial page 2081
*Collaborators listed at end of the report

Correspondence to:
Clinical Trials Unit, London School of Hygiene & Tropical Medicine, London, UK
thewomantrial@LSHTM.AC.UK
In WOMAN trial of PPH, TXA reduced risk of death from hemorrhage but not death by any cause or hysterectomy.

- Death by bleeding:
  - Placebo: 1.9%
  - TXA: 1.5%
  - Relative Risk (RR): 0.81 (0.65-1.00)

- Death by any cause:
  - Placebo: 2.6%
  - TXA: 2.3%
  - RR: 0.88 (0.74-1.04)
Does timing matter?

- Lower rate of laparotomy, and trend toward fewer hemorrhagic deaths in women receiving TXA within 3 hours of delivery
Does it work?

NNT = 250

to prevent one OB hemorrhage death
Does it cause DVTs and PEs?

• Huge RCTs from OB and other fields show no increased clot risk

• Other risks?
  • Higher doses *may* pose risk of seizure or kidney problems

<table>
<thead>
<tr>
<th>WOMEN bleeding</th>
<th>Placebo</th>
<th>TXA</th>
</tr>
</thead>
<tbody>
<tr>
<td>20,060</td>
<td>9,985</td>
<td>10,033</td>
</tr>
<tr>
<td>Thrombotic Events</td>
<td>34</td>
<td>30</td>
</tr>
<tr>
<td>0.3% risk of clot in both arms</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Does it cause complications?

<table>
<thead>
<tr>
<th>Event</th>
<th>TXA (n=10,033)</th>
<th>Placebo (n=9,985)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any thrombotic event</td>
<td>30 (0.3%)</td>
<td>34 (0.3%)</td>
<td>.60</td>
</tr>
<tr>
<td>Venous Events</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- DVT</td>
<td>3 (0.03%)</td>
<td>7 (0.07%)</td>
<td>.20</td>
</tr>
<tr>
<td>- PE</td>
<td>17 (0.2%)</td>
<td>20 (0.2%)</td>
<td>.61</td>
</tr>
<tr>
<td>Arterial Events</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Myocardial Infarction</td>
<td>2 (0.02%)</td>
<td>3 (0.03%)</td>
<td>.65</td>
</tr>
<tr>
<td>- Stroke</td>
<td>8 (0.08%)</td>
<td>6 (0.06%)</td>
<td>.60</td>
</tr>
<tr>
<td>Renal Failure</td>
<td>129 (1.3%)</td>
<td>118 (1.2%)</td>
<td>.51</td>
</tr>
<tr>
<td>Seizure</td>
<td>33 (0.3%)</td>
<td>43 (0.4%)</td>
<td>.24</td>
</tr>
</tbody>
</table>

The WOMAN Trial. Lancet 2017
Does it work?

- For treatment of PPH – highly likely yes
- For prevention of PPH – more research is needed
Tranexamic Acid for the Prevention of Obstetrical Hemorrhage After Cesarean

- A randomized placebo-controlled trial of 11,000 women to assess whether TXA as prophylaxis lowers the risk of PPH in women undergoing a cesarean delivery.

- Participants will be randomized to receive either TXA (1 gram over 10min) intravenously or a placebo

- Primary Outcome - Maternal death or transfusion of packed red blood cells [Time Frame: by hospital discharge or 7 days postpartum, whichever is sooner]

- 12 institutions including U of Utah

- Estimated Completion December 2020

ClinicalTrials.gov Identifier: NCT03364491
Is it available? Cost?

**Availability**
- Probably available
- Common use in ortho/cardiac/ED
- Ask your pharmacist

**Cost**
- $2-$20 per vial
Where does TXA fit in a PPH protocol?

• Consider TXA an adjunctive treatment and NOT a primary treatment for PPH

• TXA 1gm is administered after routine first line PPH drugs but before the need for blood products or additional procedures.

• Within 3 hours of delivery

• Use TXA cautiously in patients with renal impairment; however, with 1g there are no known cases of toxicity

• Repeat 1 gram IV dose if ongoing hemorrhage
  ...after 30 minutes
  ...or up to 24 hours after delivery
  ...and only one repeat dose

WHO Recommendation on TXA for the treatment of postpartum haemorrhage 2017
CMQCC Tranexamic acid (TXA) for Obstetric Hemorrhage July 2017
Quick Reference

1. WHO recommendation on tranexamic acid for the treatment of postpartum hemorrhage. **2017.** World Health Organization.


