Tranexamic acid: a global view

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Aims

• Explore fibrinolysis
• TXA – mechanisms of action
• Trial evidence
• When to use it?
Fibrinolysis
Activation of fibrinolysis during liver transplantation
Taken from Segal et al, Transplantation 1994
t-PA levels in cardiothoracic surgery with or without CPB
Taken from Hunt et al Ann Thoracic Surg 1998
Fibrinolysis in civilian trauma

Graphs showing data on fibrinolysis and related parameters in civilian trauma patients.
Tranexamic acid
a lysine binding analogue

Empirical Formula: $\text{C}_8\text{H}_{15}\text{NO}_2$  Molecular Weight: 157.2
A large placebo controlled trial among 20,000 trauma patients with, or at risk of, significant haemorrhage, of the effects of antifibrinolytic treatment (tranexamic acid) on death and transfusion requirement.

The CRASH-2 trial collaborators

CRASH-2 trial results

TXA reduces death due to bleeding in trauma patients

<table>
<thead>
<tr>
<th>TXA-allocated</th>
<th>Placebo-allocated</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n=10,060)</td>
<td>(n=10,067)</td>
</tr>
<tr>
<td>489 (4.9%)</td>
<td>574 (5.7%)</td>
</tr>
</tbody>
</table>

Risk ratio (95% CI)

0.85 (0.76–0.96) 2P=0.0077

The CRASH-2 Collaborators. The Lancet. 2010; 376(9734):23-32
Effect of TXA on death due to bleeding SBP <90 & Massive Transfusion (MT)

RR (95% CI) \( p=0.9408 \)

- No MT
- MT
- All

0.72 (0.63–0.83)
Time from injury

Risk ratio (99% CI)  \( p=0.11 \)

- \( \leq 1 \) hour
- \( >1 \) to \( \leq 3 \) hours
- \( >3 \) hours

Which groups benefit from TXA worldwide?

<table>
<thead>
<tr>
<th>Number</th>
<th>Preventable trauma worldwide deaths with TA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Those presenting with massive blood loss</td>
<td>20,000</td>
</tr>
<tr>
<td>Those presenting with bleeding but not MBL</td>
<td>100,000</td>
</tr>
<tr>
<td>TOTAL</td>
<td>120,000</td>
</tr>
</tbody>
</table>
Vascular occlusive events in CRASH-2

<table>
<thead>
<tr>
<th>Event</th>
<th>TXA Allocated</th>
<th>Placebo Allocated</th>
<th>Risk Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DVT</td>
<td>40 (0.40%)</td>
<td>41 (0.41%)</td>
<td></td>
</tr>
<tr>
<td>PE</td>
<td>72 (0.69%)</td>
<td>71 (0.70%)</td>
<td></td>
</tr>
<tr>
<td>MI</td>
<td>35 (0.35%)</td>
<td>55 (0.52%)</td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>57 (0.56%)</td>
<td>66 (0.65%)</td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>168 (1.63%)</td>
<td>201 (1.95%)</td>
<td></td>
</tr>
</tbody>
</table>
Implementation

• Message still needs to be delivered again and again
• Tranexamic acid in the English paramedic pack
• The relative risk reduction applies to all patients whether massive blood loss or not
• There are many more bleeding trauma patients without massive blood loss who would benefit from TA than those with massive blood loss
• Lets abandon ”massive transfusion guidelines”
• Tariff to ensure Txa delivered to major trauma patients
TXA use in surgery

Systematic review identified 129 trials between 1972-2011 including 10,488 patients (now over 500 trials!)

Transfusion

RR (95% CI)

TXA better 0.62 (0.58-0.65) TXA worse

Mortality

RR (95% CI)

TXA better 0.61 (0.38-0.98) TXA worse

95 trials

72 trials

Ker et al. BMJ 2012; 344:e3054
Size of Effect
Systematic review, meta analysis & meta-regression of the effects of TXA on surgical blood loss
Ker K, Prieto-Merino D, Robert I
Br J Surg 2013; 100: 1271-9

- 104 RCTS available
- Bayesian linear regression to describe the relationship between blood loss & extent of bleeding
- TXA blood loss by 34% (pooled ratio 0.66, 95% CI 0.65-0.67; P < 0.001)
- % reduction in blood loss with TXA differed by type of surgery, timing of TXA and trial quality but differences were small
- Effect did not vary over the doses assessed (5.5-300mg/Kg)

Conclusions
- TXA reduced blood loss in surgical patients by ONE THIRD.
- A total dose of 1gm appears to be sufficient for most adults.
- There is no evidence to support higher doses
# TXA in coronary artery surgery

## Table 3. Outcomes and Adverse Events.

<table>
<thead>
<tr>
<th>Outcome or Event</th>
<th>Tranexamic Acid Group (N = 2311)</th>
<th>Placebo Group (N = 2320)</th>
<th>Risk Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome: death, myocardial infarction, stroke, renal failure, pulmonary embolism, or bowel infarction — no./total no. (%)</td>
<td>386/2310 (16.7)</td>
<td>420/2320 (18.1)</td>
<td>0.92 (0.81–1.05)</td>
<td>0.22</td>
</tr>
<tr>
<td>Death</td>
<td>26/2310 (1.1)</td>
<td>33/2320 (1.4)</td>
<td>0.79 (0.47–1.32)</td>
<td>0.43</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>269/2310 (11.6)</td>
<td>300/2320 (12.9)</td>
<td>0.90 (0.77–1.05)</td>
<td>0.19</td>
</tr>
<tr>
<td>Stroke</td>
<td>32/2310 (1.4)</td>
<td>35/2320 (1.5)</td>
<td>0.92 (0.57–1.48)</td>
<td>0.81</td>
</tr>
<tr>
<td>Renal failure</td>
<td>98/2309 (4.2)</td>
<td>96/2320 (4.1)</td>
<td>1.03 (0.78–1.35)</td>
<td>0.88</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>15/2309 (0.6)</td>
<td>15/2320 (0.6)</td>
<td>1.00 (0.49–2.05)</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Bowel infarction</td>
<td>8/2309 (0.3)</td>
<td>3/2320 (0.1)</td>
<td>2.68 (0.71–10.09)</td>
<td>0.15</td>
</tr>
<tr>
<td>Primary outcome not including renal failure — no./total no. (%)*</td>
<td>324/2310 (14.0)</td>
<td>362/2320 (15.6)</td>
<td>0.90 (0.78–1.01)</td>
<td>0.14</td>
</tr>
<tr>
<td>Reoperation — no./total no. (%)</td>
<td>32/2310 (1.4)</td>
<td>65/2320 (2.8)</td>
<td>0.49 (0.32–0.75)</td>
<td>0.001</td>
</tr>
<tr>
<td>Due to any cause</td>
<td>32/2310 (1.4)</td>
<td>65/2320 (2.8)</td>
<td>0.49 (0.32–0.75)</td>
<td>0.001</td>
</tr>
<tr>
<td>Due to major hemorrhage</td>
<td>18/2310 (0.8)</td>
<td>48/2320 (2.1)</td>
<td>0.36 (0.21–0.62)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Due to cardiac tamponade</td>
<td>16/2310 (0.7)</td>
<td>23/2320 (1.0)</td>
<td>0.61 (0.32–1.18)</td>
<td>0.19</td>
</tr>
<tr>
<td>Transfusion of red cells during hospitalization — no./total no. (%)</td>
<td>759/2311 (32.8)</td>
<td>1086/2320 (46.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of units of red cells that were transfused during hospitalization</td>
<td>2</td>
<td>2</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Duration of mechanical ventilation — hrt</td>
<td>8</td>
<td>9</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>5–14</td>
<td>6–16</td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<td>Interquartile range</td>
<td>5–14</td>
<td>6–16</td>
<td>0.04</td>
<td></td>
</tr>
<tr>
<td>Length of stay in intensive care unit (initial admission) — hrt</td>
<td>21–62</td>
<td>22–67</td>
<td>0.07</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>25</td>
<td>30</td>
<td>0.07</td>
<td></td>
</tr>
<tr>
<td>Interquartile range</td>
<td>21–62</td>
<td>22–67</td>
<td>0.07</td>
<td></td>
</tr>
<tr>
<td>Length of stay in intensive care unit (total) — hrt</td>
<td>21–62</td>
<td>22–67</td>
<td>0.07</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>28</td>
<td>34</td>
<td>0.08</td>
<td></td>
</tr>
<tr>
<td>Interquartile range</td>
<td>22–65</td>
<td>22–69</td>
<td>0.08</td>
<td></td>
</tr>
<tr>
<td>Length of stay in hospital — days;</td>
<td>8.0</td>
<td>8.0</td>
<td>0.08</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>6.0–13.0</td>
<td>6.0–14.0</td>
<td>0.08</td>
<td></td>
</tr>
<tr>
<td>Seizures — no./total no. (%)</td>
<td>15/2304 (0.7)</td>
<td>2/2327 (0.1)</td>
<td>7.62 (1.77–68.71)</td>
<td>0.0005</td>
</tr>
<tr>
<td>Pneumococcal infection — no./total no. (%)</td>
<td>13/2308 (0.6)</td>
<td>15/2319 (0.6)</td>
<td>0.87 (0.42–1.83)</td>
<td>0.85</td>
</tr>
<tr>
<td>Reintubation during hospitalization — no./total no. (%)*</td>
<td>62/2113 (2.9)</td>
<td>62/2122 (2.9)</td>
<td>1.00 (0.71–1.42)</td>
<td>&gt;0.99</td>
</tr>
</tbody>
</table>

*Outcome was not prespecified in the trial protocol.
†Data were available for 2318 patients in the placebo group.
‡Data were available for 2304 patients in the tranexamic acid group and 2308 patients in the placebo group.
§ Data include one patient who was randomly assigned to receive placebo and received tranexamic acid postoperatively.
Tranexamic acid use and postoperative outcomes in patients undergoing total hip or knee arthroplasty in the United States: retrospective analysis of effectiveness and safety

Poeran et al, *BMJ* 2014; 349

- Retrospective review of >870,000 patients undergoing hip or knee replacement in US
- Those who received TXA showed:
  - lower rates of transfusion (7.7% v 20.1%), thromboembolic complications (0.6% v 0.8%), acute renal failure (1.2% v 1.6%), &
  - combined complications (1.9% v 2.6%); all P<0.01
NICE Quality Standards for Blood Transfusion Dec 2016

- Offer iron before and after surgery to patients with iron deficiency anaemia.

- Offer tranexamic acid to adults and children undergoing surgery who are expected to have at least moderate blood loss (greater than 500 ml)

- Consider tranexamic acid for children undergoing surgery who are expected to have at least moderate blood loss (greater than 10% blood volume)

- Consider intra operative cell salvage with tranexamic acid for patients who are expected to lose a very high volume of blood (for example in cardiac and complex vascular surgery, major obstetric procedures, and pelvic reconstruction and scoliosis surgery)

- Consider using a system that electronically identifies patients to improve the safety and efficiency of the blood transfusion process
Emerging literature- topical use

TRANX-K (Tranexamic Acid in Total Knee Replacement) RCT of topical (intra-articular) application of TXA on blood loss & transfusion following a knee replacement.

1gm TXA in 50mls saline sprayed into the wound at the end

TXA REDUCED

- Blood transfusion by 15.4% (95% confidence interval [CI], 7.5% to 25.4%; p = 0.001), from 16.7% to 1.3%
- Blood loss by 168 mL (95% CI, 80 to 256 mL; p = 0.0003),
- The length of stay by 1.2 days (95% CI, 0.05 to 2.43 days; p = 0.041)
- Cost per episode by £333 (95% CI, £37 to £630; p = 0.028). (In 2008, £1 = 1.6 U.S. dollars.)
Systematic review of topical TXA
Ker K, Beecher D, Roberts I, Cochrane Jul 2013

29 RCTS involving 2612 pts - 28 involved surgery & 1 epistaxis

• Topical TXA reduced blood loss by 29%
  (pooled ratio 0.71, 95% CI 0.69-0.72, p<0.0001)

• Topical TXA reduced the risk of receiving blood transfusion by 45%
  (RR 0.55, 95% CI 0.55-0.46, p<0.0001)

• Uncertainty on effect of death, myocardial infarction, stroke, DVT & PE
WOMAN Trial Collaborators
Aims and objectives

A randomised, double blind, placebo controlled trial among 20,060 women with a clinical diagnosis of postpartum haemorrhage.

**AIMS**
To determine the effect of early administration of TXA on mortality, hysterectomy and other morbidities in women with clinically diagnosed PPH.

**OBJECTIVES**
To provide reliable evidence as to whether TXA reduces mortality, hysterectomy and other morbidities in women with clinically diagnosed PPH; thromboembolic effects on breastfed babies also assessed.
TREATMENT

- Dose 1; 1 gram of tranexamic acid by intravenous injection, or placebo (sodium chloride 0.9%)
- Dose 2; if after 30 minutes bleeding continues, or if it stops and restarts within 24 hours after dose 1

FOLLOW-UP

- Outcome form completed 42 days after randomisation or at discharge or at death, whichever occurs first
- Adverse events reported up to 42 days after randomisation
## Death

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>TXA N=10036 n (%)</th>
<th>Placebo N=9985 n (%)</th>
<th>Risk ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleeding</td>
<td>155 (1.5)</td>
<td>191 (1.9)</td>
<td>0.81 (0.65–1.00)</td>
<td>0.045</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>10 (0.1)</td>
<td>11 (0.1)</td>
<td>0.9 (0.4–2.13)</td>
<td>0.82</td>
</tr>
<tr>
<td>Organ failure</td>
<td>25 (0.3)</td>
<td>18 (0.2)</td>
<td>1.38 (0.7–2.5)</td>
<td>0.29</td>
</tr>
<tr>
<td>Sepsis</td>
<td>15 (0.2)</td>
<td>8 (0.1)</td>
<td>0.25 (0.05–1.17)</td>
<td>0.15</td>
</tr>
<tr>
<td>Eclampsia</td>
<td>2 (0.02)</td>
<td>8 (0.1)</td>
<td>0.99 (0.54–1.85)</td>
<td>0.06</td>
</tr>
<tr>
<td>Other</td>
<td>20 (0.2)</td>
<td>20 (0.2)</td>
<td>0.88 (0.74–1.05)</td>
<td>0.99</td>
</tr>
<tr>
<td>All causes</td>
<td>227 (2.3)</td>
<td>256 (2.6)</td>
<td>0.88 (0.74–1.05)</td>
<td>0.16</td>
</tr>
</tbody>
</table>
Effect of TXA on death due to bleeding: subgroups

<table>
<thead>
<tr>
<th>Time since delivery</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤1 hour</td>
<td>0.80 (0.55–1.16)</td>
</tr>
<tr>
<td>&gt;1–3 hours</td>
<td>0.60 (0.41–0.88)</td>
</tr>
<tr>
<td>&gt; 3 hours</td>
<td>1.07 (0.76–1.51)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Type of delivery</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaginal</td>
<td>0.82 (0.64–1.05)</td>
</tr>
<tr>
<td>Caesarean section</td>
<td>0.80 (0.54–1.18)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Cause of haemorrhage</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uterine atony</td>
<td>0.74 (0.55–0.99)</td>
</tr>
<tr>
<td>Other / unknown</td>
<td>0.90 (0.66–1.21)</td>
</tr>
</tbody>
</table>

All patients: 2-sided p=0.045

Effect of TXA on death due to bleeding: subgroups
Laparotomy for bleeding

Time since delivery
- \( \leq 1 \) hour
  - RR (95% CI): 0.48 (0.29–0.79)
- >1–3 hours
  - RR (95% CI): 0.54 (0.31–0.95)
- >3 hours
  - RR (95% CI): 0.89 (0.59–1.35)

Type of delivery
- Vaginal
  - RR (95% CI): 0.64 (0.42–0.97)
- Caesarean section
  - RR (95% CI): 0.63 (0.44–0.92)

Cause of haemorrhage
- Uterine atony
  - RR (95% CI): 0.63 (0.42–0.95)
- Other
  - RR (95% CI): 0.66 (0.45–0.96)

All causes
  - Two-sided \( p = 0.002 \)
  - RR (95% CI): 0.64 (0.49–0.85)
## Thromboembolic events

<table>
<thead>
<tr>
<th>Event Type</th>
<th>TXA (N=10033)</th>
<th>Placebo (N=9985)</th>
<th>Risk ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any event</td>
<td>30 (0.3)</td>
<td>34 (0.3)</td>
<td>0.88 (0.5–1.4)</td>
<td>0.60</td>
</tr>
<tr>
<td>Venous events (DVT, PE)</td>
<td>20 (0.2)</td>
<td>25 (0.3)</td>
<td>0.80 (0.4–1.4)</td>
<td>0.45</td>
</tr>
<tr>
<td> Deep vein thrombosis</td>
<td>3 (0.03)</td>
<td>7 (0.1)</td>
<td>0.43 (0.1–1.6)</td>
<td>0.20</td>
</tr>
<tr>
<td> Pulmonary embolism</td>
<td>17 (0.2)</td>
<td>20 (0.2)</td>
<td>0.85 (0.4–1.6)</td>
<td>0.61</td>
</tr>
<tr>
<td>Arterial events (MI, stroke)</td>
<td>10 (0.1)</td>
<td>9 (0.1)</td>
<td>1.11 (0.4–2.7)</td>
<td>0.83</td>
</tr>
<tr>
<td> Myocardial infarction</td>
<td>2 (0.02)</td>
<td>3 (0.03)</td>
<td>0.66 (0.1–3.9)</td>
<td>0.65</td>
</tr>
<tr>
<td>Stroke</td>
<td>8 (0.1)</td>
<td>6 (0.1)</td>
<td>1.33 (0.4–3.8)</td>
<td>0.60</td>
</tr>
</tbody>
</table>
Death due to bleeding

**Early treatment**
(≤3 hrs)

- PPH: Overall 1.27 (0.96–1.69)
- Trauma: Overall 1.44 (1.12–1.84)
- Overall: PPH 1.07 (0.76–1.51)

**Late treatment**
(>3 hrs)

- PPH: Overall 1.07 (0.76–1.51)
- Trauma: Overall 1.44 (1.12–1.84)
- Overall: PPH 1.27 (0.96–1.69)
Tranexamic acid in PPH

- Reduces death due to bleeding overall by one fifth
- Reduces death due to bleeding within 3 hours by about 1/3
- No effect on other causes of death
- Reduces laparotomy for bleeding by over 35%
- No evidence of adverse effects
Time to treatment: reduction in effectiveness of TXA with increasing treatment delay

The bar highlighted in red shows the estimated treatment effectiveness (90%), with a treatment delay of 15 minutes.

*The Lancet* DOI: (10.1016/S0140-6736(17)32455-8)
Over 10 million people are killed or hospitalised because of traumatic brain injury. Approx 90% of the deaths occur in low and middle income countries. It predominantly affects young adults and many have lasting disability.

This is an RCT of TA 1gm followed by 1gm over 8 hrs vs placebo. 10,000 patients with a 90% power to detect a 15% relative reduction in all cause mortality from 20% to 17%.

Entry criteria: bleeding on scan or if no scan a GCS <12.
Tranexamic acid for the treatment of gastrointestinal bleeding: an international randomised, double blind placebo controlled trial
TXA and thrombotic risk

Biologically unlikely

- No increased risk in trauma
  CRASH-2

- No increased risk in hip and knee replacement
  Poeran et al, Brit Med J 2014; 349: 4829

- No increased risk in cardiac surgery

- No increased risk in post partum haemorrhage
  WOMAN study
What does free plasmin do?

In vitro experiments show:

• It activates platelets


• It can activate/deactivate Factor V

• It binds to endothelial receptors & cause local inflammatory changes

Review of plasminogen receptors. Godier & Hunt JTH 2012

So if plasmin production is blocked by TA there is less activation of platelets, coagulation and inflammation in patients?
“Fits” and tranexamic acid

In paediatric & adult cardiac surgery where
• “high dose” used
• &/or renal dysfunction

Montes FR Ann Card anaes 2012; 15: 6-12

But illogical to use a high dose – no evidence of increased efficacy

Affects GABA receptor & possibly other neurotransmitters, which have lysine binding sites
SUMMARY: is TXA the perfect haemostat?

- Efficacy: In RCTS in surgery & trauma it reduces mortality & bleeding by 1/3
- Safety: No increased thromboses after use: indeed may decrease arterial events
- Safety: no neuro events if use 1-2gm
- Other: May reduce post procedure inflammation?
When should TXA be used?

• When expecting a significant blood loss whatever the cause
• Use as soon as possible

• TXA is NOT suitable
• if TXA allergy
• urological surgery where ureteric obstruction by clot is a possibility
• Not in DIC
The future?
Self-propelled particles that transport cargo through flowing blood and halt hemorrhage. J. R. Baylis et al. Science Advances, 2015; 1 (9): e1500379 DOI: