The Haematologist’s view of traumatic coagulopathy

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Medical Director of Thrombosis UK
Twitter @bhwords
Conflicts of interest

- I take no personal monies in any form from pharmaceutical companies
- Co PI on CRASH-2 and currently the WOMAN study, both funded by NIHR/Wellcome Trust, & WOMAN study also funded by the Gates Foundation
- Co writer of European bleeding in trauma guidelines, (funded by CLS Behring)
- Co PI of a trial of fibrinogen supplementation in paediatric cardiac surgery funded by CLS Behring
Plan

- What is traumatic coagulopathy?
- Fibrinogen
- Tranexamic acid
- Divergence & evidence base for international practice
Tranexamic acid
a lysine binding analogue
a synthetic derivative of the amino acid lysine.

Empirical Formula: $C_8H_{15}NO_2$
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 on death and transfusion requirement

The CRASH-2 trial collaborators

DOCTOR IS “REASONABLY CERTAIN” THAT ANTI-FIBRINOLYTIC AGENTS ARE INDICATED.

INELIGIBLE
GIVE ANTI-FIBRINOLYTIC AGENTS;
DO NOT RANDOMISE.

DOCTOR IS “REASONABLY CERTAIN” THAT ANTI-FIBRINOLYTIC AGENTS ARE CONTRA-INDICATED.

INELIGIBLE
DON’T GIVE ANTI-FIBRINOLYTIC AGENTS;
DO NOT RANDOMISE.

Doctor is “SUBSTANTIALLY UNCERTAIN” as to the appropriateness of anti-fibrinolytic agents in this patient

TELEPHONE FOR RANDOMISATION OR PAPER RANDOMISE

TRANEXAMIC ACID

PLACEBO
CRASH-2

9% ↓ in death in-hospital within 4 weeks
15% reduction in bleeding deaths

TXA-allocated  Placebo-allocated
(n= 10,060)     (n= 10,067)
1,463 (14.5%)   1,613 (16.0%)

0.91 (0.85–0.97) 2P=0.0035
Vascular occlusive events in CRASH-2

<table>
<thead>
<tr>
<th>Event</th>
<th>TXA allocated (10,060)</th>
<th>Placebo allocated (10,067)</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>
### Table 2. All-Cause Mortality of Overall and Massive Transfusion Groups Within 24 Hours, Within 48 Hours, and In-Hospital Mortality

<table>
<thead>
<tr>
<th>End Point</th>
<th>Total No. of Patients in Follow-up (Mortality, %)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TXA</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
</tr>
<tr>
<td>&lt;24 h</td>
<td>293 (9.6)</td>
</tr>
<tr>
<td>&lt;48 h</td>
<td>264 (11.3)</td>
</tr>
<tr>
<td>In-hospital mortality&lt;sup&gt;b&lt;/sup&gt;</td>
<td>264 (17.4)</td>
</tr>
<tr>
<td>Massive transfusion</td>
<td></td>
</tr>
<tr>
<td>&lt;24 h</td>
<td>125 (9.6)</td>
</tr>
<tr>
<td>&lt;48 h</td>
<td>112 (10.4)</td>
</tr>
<tr>
<td>In-hospital mortality&lt;sup&gt;c&lt;/sup&gt;</td>
<td>125 (14.4)</td>
</tr>
</tbody>
</table>

Abbreviation: TXA, tranexamic acid.

<sup>a</sup>Statistically significant values (P<.05) are bold.

<sup>b</sup> Mean (SD) follow-up, 15 (13) days.

<sup>c</sup> Mean (SD) follow-up, 16 (13) days.
Tranexamic acid for traumatic bleeding

- Worldwide use would reduce global deaths by 120,000 annum
- To ensure those who should receive TXA receive it, need to write “major” bleeding rather than “massive bleeding” guidelines

Implementation:
- TA in every paramedics pack in England
- English health system reduce funding of Trauma Units unless they use TA in bleeding
- A WHO essential drug

Further trials:
- CRASH-3 TXA in traumatic brain injury
- HALT-IT TXA in 8,000 upper GI haemorrhage
- The WOMAN study TXA in 20,000 women with PPH
Systematic review identified 129 trials between 1972-2011 including 10,488 patients.

**Transfusion**

- **TXA better**
  - RR (95% CI): 0.62 (0.58-0.65)
- **TXA worse**

95 trials

**Mortality**

- **TXA better**
  - RR (95% CI): 0.61 (0.38-0.98)
- **TXA worse**

72 trials

Ker et al. BMJ 2012; 344:e3054
TXA dose

• Large doses - > 4gm in adults cause neurological events (plasminogen/t-PA are neurotransmitters)

• Surgical studies show no increased benefit from large doses

• In vitro there is a maximal benefit from 2gms (Horrow), TXA is a competitive inhibitor & expect a plateau effect

• Suggest 1gm initially +/- 0.5g/hr
TXA & thrombotic risk

Biologically unlikely

Clinical evidence:
• No increased risk in trauma

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

• Aspirin & TA for Cardiac surgery trial
  www.atacas.org.au

• Could TA reduce the rate of myocardial infarction post surgery?
  Ker & Robert Brit Med J 2014; 349:g4934
BUT North American divergence of practice……

Recommendations that TXA is used only if hyperfibrinolysis on the TEG and/or massive blood loss

NB entry to CRASH-2
Those with significant blood loss or AT RISK of significant blood loss
Effect of TXA on death due to bleeding SBP <90 \& Massive Transfusion (MT)

No MT

MT

All

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

0.72 (0.63–0.83)
Deaths avoided
SBP <90 & Massive Transfusion (MT)

Mortality rate

Absolute number of deaths

Percentage of avoided deaths
Rough guide to which groups benefit from TA 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>
“Hyperfibrinolysis” on TEG/ROTEM = ML30 > 15%

Associated with a high mortality (67-84%) Cotton et al 2012 J Trauma Acute Care Surg
Fibrinolysis & thromboelastometry

303 trauma patients
Compared plasmin-antiplasmin (PAP) with TEG

Raza, J Thromb Haemost 2013
Why is there so much fibrinolytic activation in trauma? i.e what stimulates t-PA release?

In vitro:
Adrenaline
Thrombin
Vasopressin
Hypoxia

i.e surgery/ bleeding/ trauma
High circulating adrenaline levels at admission predict increased mortality after trauma


- 75 adults with trauma
- Circulating adrenaline levels were independently associated with 30 day mortality
- Adrenaline levels correlated with degree of tissue damage (histone complexed DNA) and fibrinolysis (t-PA and D-dimer levels) and increased APTT levels.
THE DEFINITION OF ACUTE TRAUMATIC COAGULOPATHY?

Brohi’s group: definition should be Prothrombin Time Ratio of > 1.2

Extent of coagulopathy related to
• degree of haemorrhagic shock
• severity of injury
But is acute traumatic coagulopathy any different from major bleeding elsewhere?

• Is it different from major perioperative bleeding?

• Is it different from major obstetric haemorrhage?

Similarities
• All due to holes in vascular tree

Differences
• Different amounts of tissue injury
• Time and place of presentation—in general trauma patients managed later so more bled out?
INJURY
INJURY ➞ Adrenaline & vasopressin ➞ Activation of fibrinolysis
Different amounts of tissue injury

Tissue factor
Not present on cells in contact with the blood
Expressed on all other cell
Excreted abluminally by endothelial cells so subendothelial cement is rich in it

More exposure to tissue factor = more activation of coagulation
# Critical haemostatic factors & blood loss


<table>
<thead>
<tr>
<th>Haemostatic factor</th>
<th>Critical level</th>
<th>Blood loss (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelets</td>
<td>50 x 10⁹/l</td>
<td>230 (169-294)</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>1.0g/L</td>
<td>142 (117-169)</td>
</tr>
<tr>
<td>Prothrombin</td>
<td>20%</td>
<td>201 (160-244)</td>
</tr>
<tr>
<td>Factor V</td>
<td>25%</td>
<td>229 (167-300)</td>
</tr>
<tr>
<td>Prothrombin</td>
<td>20%</td>
<td>236 (198-277)</td>
</tr>
</tbody>
</table>
Fibrinogen levels in 517 patients

Fibrinogen levels were associated with:
- Severity score
- Shock
- Prehospital volume
- Predictor of mortality at 24 and 48 hours
Bastion, Afghanistan Factor assays in those with shock (unpublished)

Mean Factor X levels

Mean Factor VII Levels

Mean Factor V levels

Mean Factor II levels
Fibrinogen is vital!

The end point of the coagulation cascade!
Soluble fibrinogen converted to insoluble fibrinogen

AND........
Fibrinogen is the ligand for platelet aggregation
Why does fibrinogen fall in traumatic coagulopathy?

- Consumption in clotting
- Loss
- Fibrinogenolysis
- Relative contribution of each
Fibrinogen supplementation

Available in two forms:
Cryoprecipitate (often pooled)
20 bags will increase fibrinogen by 2g/l
In NZ from high fibrinogen male donors
1.3g/150ml

Fibrinogen concentrate, not licensed for acquired hypofibrinogenaemia in UK or USA, widely available in mainland Europe
INJURY ➔ Adrenaline & vasopressin

⇒ Exposure of tissue factor
INJURY ➔ Adrenaline & vasopressin

Exposure of tissue factor ➔ Activation of coagulation

Activation of fibrinolysis
INJURY

→ Adrenaline & vasopressin

→ Exposure of tissue factor

← Activation of coagulation

← Low fibrinogen

← Activation of fibrinolysis
But this is not the end of the story……. 
Thrombin generation in trauma
Dunbar & Chandler, Transfusion 2009; 49: 2652-60

- 42 trauma patients
- 15 had PT ratio > 1.5
- 25 healthy controls
- Lag times 68% shorter and peak thrombin generation x3 of controls
- Fibrinogen levels were low
INJURY → Adrenaline & vasopressin

- Exposure of tissue factor
  - Activation of coagulation
  - Low fibrinogen → Excess thrombin
  - Activation of fibrinolysis
A lesson from congenital hypofibrinogenenaemia

• 22 year old girl with fibrinogen levels of 0.5g/l
• No bleeding problems from day to day
• Usually had fibrinogen infusions pre operatively
• Had dental extraction without fibrinogen supplementation
• In 7 days she had submassive multiple pulmonary emboli
• Transferred to St Thomas’ thrombosis unit for tertiary care and responded well to fibrinogen supplementation and enoxaparin
Bleeding in congenital hypofibrinogenemia

Local tissue factor expression

↓

Activation of coagulation

↓

Low fibrinogen

↓

Excess free thrombin

 Activation of white cells

 Activation of Protein C

 Platelet activation

 Activation of complement

 Endothelial cell activation
INJURY

Adrenaline & vasopressin

Exposure of tissue factor

Activation of coagulation

Activation of fibrinolysis

Low fibrinogen

Excess thrombin

Activation of white cells

Activation of Protein C

Platelet activation

Activation of complement

Endothelial cell activation
See Cap & Hunt Critical Care 2014; 20:638-45
INJURY → Adrenaline & vasopressin

Exposure of tissue factor

Activation of coagulation

Activation of fibrinolysis

Low fibrinogen

Excess thrombin

Activation of white cells

Activation of Protein C

Platelet activation

Endothelial cell activation

Activation of complement

Disseminated intravascular coagulation

Multiorgan failure

Traumatic coagulopathy with late resuscitation

later
Acute traumatic coagulopathy is multifactorial

Pre-existing factors
- Genetics
- Medical illness
- Medication esp. antithrombotics

TRAUMA

INFLAMMATION
- Loss of haemostatic factors due to
- HAEMORRHAGE
- Activation of FIBRINOLYSIS

Activation of haemostasis & endothelium
- Tissue hypoxia
- Acidosis
- Shock

Resuscitation
- Crystalloid & colloid
- RBC transfusion

Dilutional coagulopathy

TRAUMATIC COAGULOPATHY
North America vs. mainland Europe: what to do in immediate trauma resuscitation
“Our retrospective studies in Iraq make us believe we need to use early FFP in a 1:1 ratio”
Mainland Europe

“Our anecdotal data make us believe we only need to give factor concentrates and tranexamic acid”
# Grading of evidence

From the US Agency of Health Care Policy and Research

<table>
<thead>
<tr>
<th>Level</th>
<th>Type of scientific evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>From meta-analyses of randomised clinical trials</td>
</tr>
<tr>
<td>1b</td>
<td>From at least 1 randomised clinical trial</td>
</tr>
<tr>
<td>IIa</td>
<td>From at least 1 well designed, non-randomised controlled prospective trial</td>
</tr>
<tr>
<td>IIb</td>
<td>From at least one well-designed quasi-experimental study</td>
</tr>
<tr>
<td>III</td>
<td>From well designed observational studies, such as comparative studies, correlation studies of case-control studies</td>
</tr>
<tr>
<td>IV</td>
<td>From documents or opinions of expert committees &amp;/or clinical experience of renown opinion leaders</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Grade</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>One or more RCT with overall good quality and consistency in terms of the specific recommendation i.e level 1a, 1b</td>
</tr>
<tr>
<td>B</td>
<td>Methodologically correct trials that are not RCTs on the topic of the recommendation and includes studies that do not meet A or C criteria i.e levels of scientific evidence are IIa, IIb, III</td>
</tr>
<tr>
<td>C</td>
<td>Documents or opinions of experts &amp;/or clinical experiences of renowned opinion. It indicates the absence of high quality evidence. i.e Level of scientific evidence is IV</td>
</tr>
</tbody>
</table>
This box contains all the Grade A evidence for using fibrinogen concentrates as first line in major bleeding.
Ooooh!
The box contains Grade A evidence for using FFP.
Ooooh!
To determine the effectiveness and safety of transfusing pts with severe trauma & suspected massive bleeding with plasma, platelets & red cells in 1:1:1 & 1:1:2

- RCT of 680 pts at 12 US trauma centres
- Intervention 1:1:1 (338) vs 1:1:2 (342) on usual Rx
- Primary outcome: 30 day mortality

**METHOD**

- Within 10 mins of arrival a box would arrive from transfusion lab.
- 1:1:1 = 6u FFP, 6u plts, 6 RBCs Give plts first & alt FFP & RBC.
- 1:1:2 = 3uFFP, 0u plts, 6U RBC & 2uRBC alt with FFP.
# PROPPPR patient details

<table>
<thead>
<tr>
<th></th>
<th>1:1:1</th>
<th>1:1:2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age median (IQR)</strong></td>
<td>34 (25-51)</td>
<td>34 (24-50)</td>
</tr>
<tr>
<td><strong>Male</strong></td>
<td>78%</td>
<td>83%</td>
</tr>
<tr>
<td><strong>Glasgow coma score</strong></td>
<td>14 (3-15)</td>
<td>14 (3-15)</td>
</tr>
<tr>
<td><strong>Systolic BP</strong></td>
<td>102 (81-126)</td>
<td>102 (80-125)</td>
</tr>
<tr>
<td><strong>Diastolic BP</strong></td>
<td>70 (53-90)</td>
<td>68 (50-91)</td>
</tr>
<tr>
<td><strong>HR</strong></td>
<td>115 (97-135)</td>
<td>113 (93-130)</td>
</tr>
<tr>
<td><strong>Blunt/penetrating</strong></td>
<td>55%/45%</td>
<td>50%/50%</td>
</tr>
<tr>
<td><strong>Massive transfusion</strong></td>
<td>45%</td>
<td>47%</td>
</tr>
<tr>
<td><strong>Plt</strong></td>
<td>213 (164-261)</td>
<td>212 (164-264)</td>
</tr>
</tbody>
</table>
## PROPPPR results

<table>
<thead>
<tr>
<th></th>
<th>1:1:1</th>
<th>1:1:2</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>24 hr mortality (%)</td>
<td>43 (12.7)</td>
<td>58 (17)</td>
<td>0.12</td>
</tr>
<tr>
<td>30 d mortality (%)</td>
<td>75 (22.4%)</td>
<td>89 (26.1)</td>
<td>0.26</td>
</tr>
<tr>
<td>Achieved haemostasis</td>
<td>291 (86)</td>
<td>267 (78)</td>
<td>0.06</td>
</tr>
<tr>
<td>ICU-free days</td>
<td>337</td>
<td>340</td>
<td>0.1</td>
</tr>
<tr>
<td>Home at 30 days</td>
<td>34.9%</td>
<td>30.7%</td>
<td></td>
</tr>
<tr>
<td>Still hospitalised</td>
<td>24.3%</td>
<td>22.5%</td>
<td></td>
</tr>
<tr>
<td>Morgue</td>
<td>22.4%</td>
<td>26%</td>
<td></td>
</tr>
<tr>
<td>Death due to exsanguination</td>
<td>9.2</td>
<td>14.6</td>
<td>0.03</td>
</tr>
<tr>
<td>Use of plasma/plts</td>
<td>7 units/12 units</td>
<td>5 units/6 units</td>
<td>0.001</td>
</tr>
</tbody>
</table>
IMMEDIATE: If severe blood loss give FFP: RBCs in ratio >1:2
Give TXA
FOLLOWING: monitor with regular FBCs & coagulation testing

Triggers for using blood products:
- PT/APTT > 1.5 give FFP
- Fibrinogen < 1.5 give cryoprecipitate
- Platelets < 50 x 10⁹/l give platelets
Thromboprophylaxis (TP) for trauma patients

Barrera LM1, Perel P, Ker K, Cirocchi R, Farinella E, Morales Uribe CH.
Cochrane Database Syst Rev. 2013 Mar 28;3:CD008303

- 16 studies. Four compared TP vs. no TP
- TP reduced DVT (RR 0.52; 95%CI 0.32-0.84)
- Mechanical reduced risk < pharmacological (RR = 0.43; 95% CI 0.25-0.73 vs. RR 0.48; 95% CI 0.25-0.95). 
- Both mechanical & pharmacological (RR 0.34; 95% CI 0.19-0.6)
- No evidence it reduced mortality but numbers studied & strength of evidence was not high
• Up to 1:1000 people are affected by VTE in the UK each year and up to 1:10 people who suffer a PE will die if not treated.
• Venous thromboembolism is the most common cause of preventable hospital deaths in the UK.

Download the new GSTT Thrombosis App today!