Management of Critical Bleeding in the Trauma Patient

What we know
What we wish we knew

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No conflicts of interest to disclose

Portions of this presentation discuss off-label indications for reversal agents. Clinical judgment and evaluation of each agent in the context of patient specific clinical scenarios is warranted.
Objectives

- Briefly describe the pathophysiology of the coagulopathic trauma patient.
- Identify both pharmacologic and non-pharmacologic approaches to managing the critically bleeding patient.
- Evaluate the literature supporting the use of antifibrinolytics and factor products within a massive transfusion protocol.
- Describe the limitations within the literature, as it applies to ideal management of the critically bleeding patient.
Case

- 45 y/o M struck in head
- History significant for DVT on Coumadin
  - INR = 2.0 on admission
- Kcentra 2878 units IV x1 PLUS Vit K 10 mg IV x1
**Coagulation Cascade**

**Intrinsic pathway**

- Kallikrein → Pre-kallikrein
- Factor XII → Factor XIIa
- Factor XI → Factor XIa
- Factor IX → Factor IXa. Factor VIIIa
- Factor X → Factor Xa. Factor Va
- Factor VIII
- Factor V

**Extrinsic pathway**

- Tissue factor. Factor VIIa
- Factor VII
- Factor II (prothrombin) → Factor IIa (thrombin)
- Fibrogen → Fibrin

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Image accessed 8/01/16 via http://www.pathologyoutlines.com/topic/coagulationsuperpage.html
Lethal Triad

- **Acidosis**
  - Low-flow state, excess ionic chloride
  - Impairs plasma protease function
  - Increased degradation of fibrinogen

- **Hypothermia**
  - Impaired protease and platelet function

- **Coagulopathy**
  - Trauma induced
  - Hemodilution ➔ resuscitative fluid is deficient in coagulation factors
  - 1:1:1 [massive transfusion]

Maegele M. *Injury* 2007;38(3):298-304
Cotton, B. J *Trauma* 2008;64(5):1177-1182
Hess JR. *J Trauma* 2008;65:748-754

Coagulopathy of Trauma

Simmons, R. *Annals Surg* 1969;169(4):455-482
Brohi, K. *J Trauma* 2003;54:1127-1130
Borgman, M. *J Trauma* 2007;63:805-813
Coagulopathy of Trauma

- Complexity of trauma-related coagulopathy requires early and targeted strategies to avoid exsanguination
  - Traumatic injury to venous or arterial vessels
- Acquired coagulopathy of trauma associated with increased overall mortality
  - Blood loss and dilution s/p crystalloid resuscitation
  - Coagulation factor and platelet consumption
  - Hypothermic platelet dysfunction
  - Acidosis-induced decrease in coagulation factor activity

Cardenas, J. J Trauma 2014;77(6):839-845
Hess JR. J Trauma 2008;65:748-754
Impact of Platelet Function

- Postulated mechanisms include
  - Impaired platelet adhesion under mild hypothermia, traumatic platelet dysfunction
  - Platelet ADP receptor inhibition, CD62 dysfunction
  - Diminished thromboxane B2
  - Attenuated p-selectin expression upon platelet activation

- 40 trauma patients, 20 non-injured controls
  - Trauma: significantly reduced ADP- and TRAP-mediated platelet aggregation and ADP-mediated CD62 expression
    - Thrombin receptor pathway for future research

Chee, L. Resuscitation 2008;76:129-133
Ramsey, M. J Trauma 2015;80(5):726-733
Hyperfibrinolysis

- Fibrin degradation regulated via
  - Plasminogen activator inhibitors
  - Plasmin inhibitors
  - Rapid hepatic clearance of plasminogen activators
- Fibrinolysis associated with injury
  - Exacerbated by shock and mediated by the disinhibition of tPA through the consumption of PAI-1
- Rapid dissolution of hemostatic fibrin results in excessive or recurrent bleeding
  - Need for re-exploration to identify area of blood loss
  - Increased transfusion requirements

Thrombin – Key to Hemostasis?

- Multiple functions in the coagulation cascade
  - Formation of fibrin to fibrinogen
  - Activation of cofactors V and VIII
  - Activation of factor XIII
  - Activation of platelets via the thrombin receptor
- Generation of thrombin via the prothrombinase complex requires sufficient prothrombin (factor II) as a substrate
  - Unlikely in patients with severe dilutional coagulopathy

Brohi K. J Trauma 2008;65:1211-17
Hess JR. J Trauma 2008;65:748-54
Damage Control Resuscitation

- 80% of deaths in the OR, overall 50% of deaths in the first 24 hours after traumatic injury
  - Unrecognized, undertreated, typically within the abdominal cavity
- Coordinated aggressive hemostatic interventions, while addressing the “lethal triad”
  - Maintain adequate blood pressure [ ≥ 90 mmHg ]
  - Massive transfusion protocol triggers a 1:1:1 ratio plus fibrinogen containing products
- Surgery for definitive control of bleeding and clearing of contamination

Holcomb, J. J Trauma 2007;62:S36-S37
Cotton, B. J Trauma 2005;64:1177-1183
Massive Transfusion Protocol

- **Step 1: Prediction → ABC scoring system**
  - Penetrating injury
  - SBP < 90 mmHg [presenting]
  - BP > 120 BPM [presenting]
  - Positive FAST

- **Step 2: Initiation of MTP**
  - Early delivery of blood component therapy, permissive hypotension, minimization of crystalloid-based resuscitation
  - Requires successful implementation of process via a multidisciplinary approach
    - Reduction of 30-day mortality in both penetrating and blunt injuries

Cotton, B. J Trauma 2010;69:S33-S39
Cotton, B. J Trauma 2008;64(5):1177-1182
### Massive Transfusion Protocol

**Step 1: Prediction**
- Penetrating injury
- SBP < 90 mmHg [presenting]
- BP > 120 BPM [presenting]
- Positive FAST

**Step 2: Initiation of MTP**
- Early delivery of blood component therapy, permissive hypotension, minimization of crystalloid-based resuscitation
- Requires successful implementation of process via a multidisciplinary approach
-Reduction of 30-day mortality in both penetrating and blunt injuries

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**Table 2: Univariate Analyses of Primary and Secondary Outcome Measures**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Pre-TEP (n = 117)</th>
<th>TEP (n = 94)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-d mortality (%)</td>
<td>65.8</td>
<td>51.1</td>
<td>0.030*</td>
</tr>
<tr>
<td>24-h blood product use (units)</td>
<td>39 ± 28</td>
<td>31.8 ± 19</td>
<td>0.017*</td>
</tr>
<tr>
<td>24-h RBC use (units)</td>
<td>19.8 ± 12.8</td>
<td>18.8 ± 11.2</td>
<td>0.695</td>
</tr>
<tr>
<td>24-h FFP use (units)</td>
<td>12.4 ± 12.5</td>
<td>9.9 ± 7</td>
<td>0.595</td>
</tr>
<tr>
<td>24-h PLT use (units)</td>
<td>6.8 ± 7.2</td>
<td>3.1 ± 3.7</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Intraoperative RBC use (units)</td>
<td>11.1 ± 8.5</td>
<td>16 ± 11.4</td>
<td>0.001*</td>
</tr>
<tr>
<td>Intraoperative FFP use (units)</td>
<td>4.3 ± 4</td>
<td>8.2 ± 6.8</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Intraoperative PLT use (units)</td>
<td>1.1 ± 2.6</td>
<td>2.2 ± 2.3</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Intraoperative crystalloid (L)</td>
<td>6.7 ± 4.2</td>
<td>4.9 ± 3.0</td>
<td>0.002*</td>
</tr>
<tr>
<td>Unexpected survivors (%)</td>
<td>5.1</td>
<td>22.3</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Unexpected deaths (%)</td>
<td>22.2</td>
<td>8.5</td>
<td>0.007*</td>
</tr>
</tbody>
</table>

* Statistically significant at p < 0.05.

TEP, trauma exsanguination protocol; RBC, red blood cell; FFP, fresh frozen plasma; PLT, platelets.

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**Fig. 1.** Unadjusted initial 24-hour blood product utilization before and after implementation of TEP. Each bar corresponds to the mean number of units transfused ± standard deviation.

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Cotton, B. J. *J Trauma* 2008;64(5):1177-1182
PROPPPR Trial

- 1:1:1 transfusion ratio versus to 1:1:2 transfusion ratio
  - Phase 3, multi-site, randomized trial
  - Product to bedside delivery within 10 minutes
  - Inclusion: ABC score of 2 or greater
    - 680 patients randomized
  - Primary outcome: Absolute percent group differences for 24-hour and 30-day mortality

Holcomb, J. JAMA 2015;313(5):471-482
## PROPPPR Trial

### Table 2. Trial Outcomes by Treatment Group

<table>
<thead>
<tr>
<th>Outcome</th>
<th>1:1:1 Group (n = 338)</th>
<th>1:1:2 Group (n = 342)</th>
<th>Difference (95% CI), %</th>
<th>Adjusted RR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>24-h Mortality, No. (%) b</td>
<td>43 (12.7)</td>
<td>58 (17.0)</td>
<td>-4.2 (-9.6 to 1.1)</td>
<td>0.75 (0.52 to 1.08)</td>
<td>.12</td>
</tr>
<tr>
<td>30-d Mortality, No. (%) b</td>
<td>75 (22.4)</td>
<td>89 (26.1)</td>
<td>-3.7 (-10.2 to 2.7)</td>
<td>0.86 (0.65 to 1.12)</td>
<td>.26</td>
</tr>
<tr>
<td>Achieved hemostasis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. (%)</td>
<td>291 (86.1)</td>
<td>267 (78.1)</td>
<td></td>
<td></td>
<td>.006</td>
</tr>
<tr>
<td>Anatomic, median (IQR), min c</td>
<td>105 (64 to 179)</td>
<td>100 (56 to 181)</td>
<td></td>
<td></td>
<td>.44</td>
</tr>
<tr>
<td>Hospital-free days, median (IQR) c</td>
<td>1 (0 to 17)</td>
<td>0 (0 to 16)</td>
<td></td>
<td></td>
<td>.83</td>
</tr>
<tr>
<td>Ventilator-free days d</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total No. of patients</td>
<td>337</td>
<td>340</td>
<td></td>
<td></td>
<td>.14</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>8 (0 to 16)</td>
<td>7 (0 to 14)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICU-free days d</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total No. of patients</td>
<td>337</td>
<td>340</td>
<td></td>
<td></td>
<td>.10</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>5 (0 to 11)</td>
<td>4 (0 to 10)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incidence of primary surgical procedure</td>
<td>290 (85.8)</td>
<td>284 (83.0)</td>
<td>2.8 (-2.8 to 8.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disposition at 30 d, No. (%) a</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Home</td>
<td>118 (34.9)</td>
<td>105 (30.7)</td>
<td></td>
<td></td>
<td>.37</td>
</tr>
<tr>
<td>Remained hospitalized</td>
<td>82 (24.3)</td>
<td>77 (22.5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other f</td>
<td>59 (17.5)</td>
<td>71 (20.8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morgue</td>
<td>75 (22.2)</td>
<td>89 (26.0)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>4 (1.2)</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glasgow Outcome Scale-Extended score</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total No. of patients</td>
<td>30</td>
<td>28</td>
<td></td>
<td></td>
<td>.11</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>4 (3 to 6)</td>
<td>4.5 (3.5 to 7.0)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Table 3. Adjudicated Cause of Death by Treatment Group and Period From Randomization

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>First 24 Hours</th>
<th>30 Days</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. (%)</td>
<td>Difference (95% CI), %&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Total No. of deaths</td>
<td>43</td>
<td>75</td>
</tr>
<tr>
<td>Cause of death</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exsanguination</td>
<td>31 (9.2)</td>
<td>-5.4 (-10.4 to -0.5)</td>
</tr>
<tr>
<td>Traumatic brain injury</td>
<td>11 (3.3)</td>
<td>-0.3 (-3.2 to 2.7)</td>
</tr>
<tr>
<td>Respiratory, pulmonary contusion, or tension pneumothorax</td>
<td>3 (0.9)</td>
<td>0.6 (-0.9 to 2.4)</td>
</tr>
<tr>
<td>Sepsis</td>
<td>0</td>
<td>0 (-1.1 to 1.1)</td>
</tr>
<tr>
<td>Multiple organ failure</td>
<td>0</td>
<td>0 (-1.1 to 1.1)</td>
</tr>
<tr>
<td>Type of cardiovascular event</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>0</td>
<td>-0.3 (-1.7 to 0.9)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>1 (0.3)</td>
<td>0 (-1.4 to 1.4)</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>0</td>
<td>-0.3 (-1.7 to 0.9)</td>
</tr>
<tr>
<td>Transfusion-related fatality</td>
<td>0</td>
<td>0 (-1.1 to 1.1)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Calculated using exact unconditional methods based on the Farrington-Manning score statistic.

<sup>b</sup> A patient may have had more than 1 cause of death.
Lab Monitoring

- Standard coagulation tests (PT/INR, aPTT) fail to accurately describe trauma-induced coagulopathy
  - In vivo coagulation primarily occurs on the surface of platelets and tissue factor-bearing cells
  - Red blood cells play a significant role in hemostasis
  - No assessment of the quality/strength of the clot or hyper/hypo-fibrinolysis
  - Fibrinogen levels falsely elevated when artificial colloids used (impair fibrin polymerization)

Rotational Thromboelastometry (ROTEM®)

- Postulated benefits
  - Assessment of all phases of coagulation
  - Reduction in transfusion volume and costs
  - Evaluation regarding the effectiveness of different coagulation factors (including fibrinogen)
  - Support the administration of appropriate factor concentrates

- Information provided
  - Hyperfibrinolysis
  - Requirements for anti-fibrinolytics, factor products (PCC), fresh frozen plasma (FFP), cryoprecipitate, fibrinogen or platelet substitution
  - Extent of dilutional coagulopathy
  - Monitoring of heparin and protamine dose

CT (clotting time) – initiation of clotting; thrombin formation; start of clot polymerization

CFT (clot formation time) – Fibrin polymerization; stabilization of the clot with thrombocytes and FXIII

MCF (maximum clot firmness) – increasing stabilization of the clot by the polymerized fibrin, thrombocytes, FXIII

ML (maximum lysis) – stability of the clot (ML<15%) or fibrinolysis (ML >15% within 1 hour)
EXTEM – extrinsic system

INTEM – intrinsic system, presence of heparin

FIBTEM – clot dependent on fibrin formation and fibrin polymerization

APTEM – fibrinolytic process inhibited in vitro – comparison of EXTEM and APTEM allows for detection of hyperfibrinolysis

HEPTEM – addition of heparinase degrades heparin present
ROTEM® in Trauma

- Diagnosis and Treatment of Trauma-Induced Coagulopathy [DIA-TRE-TIC] Study
  - Prospective cohort study
  - Fibrinogen deficiency more commonly detected by ROTEM parameters in poly-trauma patients when compared to standard coagulation tests
    - Parameters independently associated with early mortality
      - FIBTEM MCF < 7mm
      - EXTEM CT < 100 secs
      - EXTEM CFT < 200 secs
      - EXTEM MCF < 45mm

Descriptive, systematic review of observational and randomized trials

- 55 studies identified; 38 prospective cohort, 15 retrospective, 2 before and after
- Evaluation of the evidence for ROTEM or TEG
- ROTEM abnormalities predictive of massive transfusion and/or death
  - Increased CFT, decreased MFT, prolonged EXTEM and INTEM CT, prolonged FIBTEM A10, ML >15%, early ML >3%
- ROTEM guided algorithms decreased blood product transfusions without impact on mortality
Ideal Adjunct Agent

- Immediate attenuation of hemorrhage
- No side effects
- Dosing is a breeze
- No storage concerns
- Immediately available
- Doesn’t cost as much as a Ford Focus
Anti-Fibrinolytics

- Synthetic lysine derivatives
  - Tranexamic acid [TXA]
  - ε-aminocaproid acid
- Direct plasmin inhibitor
  - Aprotinin

CRASH-2

- Randomized, placebo-controlled trial
  - Loading dose: TXA 1g IV over 10 min
  - Maintenance: 1g IV over 8 hours
- Primary outcome
  - In-hospital death within 4 weeks of injury
- Secondary outcomes
  - Vascular occlusive events (MI, stroke, PE, DVT), surgical intervention, receipt of blood transfusion, and units of blood products transfused

CRASH-2 trial collaborators. Lancet 2010;376:23-32
## Mortality Outcomes

<table>
<thead>
<tr>
<th></th>
<th>TXA (n=10,060)</th>
<th>Placebo (n=10,067)</th>
<th>RR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</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>Multi-organ 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>

## Vascular Occlusive Events

<table>
<thead>
<tr>
<th>Event</th>
<th>TXA (n=10,060)</th>
<th>Placebo (n=10,067)</th>
<th>RR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular occlusive events</td>
<td>186 (1.7%)</td>
<td>201 (2.0%)</td>
<td>0.84 (0.68-1.02)</td>
<td>0.084</td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>35 (0.3%)</td>
<td>55 (0.5%)</td>
<td>0.64 (0.42-0.97)</td>
<td>0.035</td>
</tr>
<tr>
<td>Stroke</td>
<td>57 (0.6%)</td>
<td>66 (0.7%)</td>
<td>0.86-1.23</td>
<td>0.42</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>72 (0.7%)</td>
<td>71 (0.7%)</td>
<td>1.01 (0.73-1.41)</td>
<td>0.93</td>
</tr>
<tr>
<td>Deep vein thrombosis</td>
<td>40 (0.4%)</td>
<td>41 (0.4%)</td>
<td>0.98 (0.63-1.51)</td>
<td>0.91</td>
</tr>
</tbody>
</table>

Conclusions

- Early administration of TXA in trauma patients with or without the risk of significant bleeding reduces the risk of death from hemorrhage with no apparent increase in fatal or non-fatal vascular occlusive events.
- All-cause mortality was significantly reduced.
  - Most severely injured patients associated with the greatest reduction in the risk of death.
- Exploratory Analysis: Assess the effect of TXA on death due to bleeding.
  - Lingering question from CRASH-2 trial.
    - Which trauma patients should be treated with TXA?
    - Most appropriate place in therapy, timing?
    - With no significant difference found in transfusion requirements, what is the effect of TXA on fibrinolytic assays?

Assess the effect of TXA on death due to bleeding

- Lingering question from CRASH-2 trial
  - Which trauma patients should be treated with TXA?
  - Most appropriate place in therapy, timing?
  - With no significant difference found in transfusion requirements, what is the effect of TXA on fibrinolytic assays?

CRASH-2 Exploratory Analysis

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>All causes of death</th>
<th>Bleeding death</th>
<th>Non-bleeding death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>20,127</td>
<td>0.91 (0.85-0.97); p=0.0035</td>
<td>0.85 (0.76-0.96); p=0.0077</td>
<td>0.93 (0.86-1.02; p=0.13)</td>
</tr>
</tbody>
</table>

MATTERs Trial

- Retrospective, observational
  - Received at least 1 unit of PRBC within 24 hours of admission following a combat-related injury
  - Dosing = 1g IV bolus
- Primary objectives
  - In-hospital mortality at 24 and 48 hours and at 30 days,
- Secondary objectives
  - Transfusion requirements, coagulation parameters (PT, aPTT)
- Other objectives
  - TXA dose/timing, incidence of thrombotic events (DVT or PE)

<table>
<thead>
<tr>
<th></th>
<th>TXA</th>
<th>No TXA</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;24h</td>
<td>293 (9.6)</td>
<td>603 (12.4)</td>
<td>0.20</td>
</tr>
<tr>
<td>&lt;48h</td>
<td>264 (11.3)</td>
<td>507 (18.9)</td>
<td><strong>0.004</strong></td>
</tr>
<tr>
<td>In-hospital</td>
<td>264 (17.4)</td>
<td>603 (23.9)</td>
<td>0.03</td>
</tr>
<tr>
<td><strong>Massive Transfusion</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;24h</td>
<td>125 (9.6)</td>
<td>196 (14.8)</td>
<td>0.17</td>
</tr>
<tr>
<td>&lt;48h</td>
<td>112 (10.4)</td>
<td>160 (23.5)</td>
<td><strong>0.003</strong></td>
</tr>
<tr>
<td>In-hospital</td>
<td>125 (14.4)</td>
<td>196 (28.1)</td>
<td><strong>0.004</strong></td>
</tr>
</tbody>
</table>

Conclusions

- Observation of improved survival confirms findings from CRASH-2 and extends outcomes to those with wartime injuries
  - Benefit from TXA use rests in those with higher injury severity
- TXA improvement of coagulation markers, resulting in lower mortality

Where does TXA fit?

- Selection bias / exclusion of severely injured patients
- With no difference in transfusion requirements, where is the benefit coming from
- What is the impact regarding the effect on fibrinolytic assays
  - No laboratory monitoring for changes in coagulation function
- Utility in patients with traumatic brain injuries
  - TXA has not been shown effective in patients with SAH
Where does TXA fit?

- Utility in certain environments
  - Areas without massive transfusion protocols
  - Pre-hospital environment (i.e. helicopter and road transport)
    - Greater degree of coagulopathy management prior to hospital arrival
- Early versus late administration following traumatic injury
  - Utility within the first 1-3 hours following injury
- Thrombus generation
  - Dose dependent increase in thrombin formation in animal models, but concerns relatively unsubstantiated in clinical trials
Hemostatic Agents

- Recombinant factor VIIa
  - Induces a platelet-mediated thrombin burst at the site of vascular injury, rapid INR reduction
  - INR is a relatively unreliable surrogate measure for reversal of VKA effects → anticoagulation effects of VKAs dependent on reduced prothrombin, not factor VII
Recombinant FVIIa

- Two parallel, randomized, placebo-controlled, double-blind
  - rFVIIa as adjunctive therapy for control of bleeding in patients with severe blunt or penetrating trauma
- Treatment
  - rFVIIa 200 mcg IV x1 [following 8th unit PRBC], 100 mcg IV x1 and 100 mcg IV x1 [1 and 3 hours after the first dose]
- Primary end-point
  - Units of PRBCs transfused at 48 hours
- Inclusion
  - Age 16 – 65 years
  - Severe trauma defined as: 6 units of PRBCs within 4 hours of admission
- Exclusion
  - Cardiac arrest, GSW head
  - GCS <8
  - Base deficit >15 mEq/L or severe acidosis [pH <7.0]
  - >8 units PRBCs prior to admission
  - ≥ 12 hours since injury

Boffard, K. J Trauma 2005;59:8-18
Recombinant FVIIa

- Blunt trauma: significant reduction [2.6 units at 48 hours, $p = 0.02$]
CONTROL Trial

- Prospective, randomized, double-blind, multicenter, placebo-controlled

- Treatment
  - rFVIIa 200 mcg/100mcg x 2

- Primary endpoint
  - 30-day mortality [superiority]

- Inclusion
  - Received 4 units of PRBCs, but no more than 8 within 12 hours of injury, ages 18 – 70 years

- Exclusion
  - Moribund, TBI, injured >12 hours prior to randomization or >4 hours prior to hospital arrival

Hauser, C. J Trauma 2010;69:489-500
### TABLE 2. Clinical Outcomes (30-d ITT Analysis)

<table>
<thead>
<tr>
<th></th>
<th>Blunt Trauma</th>
<th>Penetrating Trauma</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>rFVIIa (n = 218)</td>
<td>rFVIIa (n = 44)</td>
</tr>
<tr>
<td></td>
<td>Placebo (n = 242)</td>
<td>Placebo (n = 38)</td>
</tr>
<tr>
<td></td>
<td>p</td>
<td>p</td>
</tr>
<tr>
<td>30-d mortality, n (%)</td>
<td>24 (11.0)</td>
<td>8 (18.2)</td>
</tr>
<tr>
<td></td>
<td>26 (10.7)</td>
<td>5 (13.2)</td>
</tr>
<tr>
<td></td>
<td>0.93*</td>
<td>0.40*</td>
</tr>
<tr>
<td></td>
<td>0.37†</td>
<td></td>
</tr>
<tr>
<td>Durable morbidity*, n (%)</td>
<td>19 (8.7)</td>
<td>1 (2.3)</td>
</tr>
<tr>
<td></td>
<td>23 (9.5)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>0.75</td>
<td>1.00</td>
</tr>
<tr>
<td>Days alive and free from ventilator/RRT through day 30, mean ± SD</td>
<td>17.2 ± 10.3</td>
<td>21.2 ± 11.1</td>
</tr>
<tr>
<td></td>
<td>16.4 ± 10.3</td>
<td>21.9 ± 10.0</td>
</tr>
<tr>
<td></td>
<td>0.31</td>
<td>0.73</td>
</tr>
<tr>
<td>Days alive and free of ICU through day 30</td>
<td>13.7 ± 10.4</td>
<td>18.7 ± 11.2</td>
</tr>
<tr>
<td></td>
<td>12.9 ± 9.9</td>
<td>19.5 ± 10.6</td>
</tr>
<tr>
<td></td>
<td>0.32</td>
<td>0.65</td>
</tr>
<tr>
<td>MOF through day 30§, n (%)</td>
<td>98 (45.0)</td>
<td>10 (22.7)</td>
</tr>
<tr>
<td></td>
<td>129 (53.3)</td>
<td>9 (23.7)</td>
</tr>
<tr>
<td></td>
<td>0.06</td>
<td>0.90</td>
</tr>
<tr>
<td>Days alive and free from MOF through day 30§, mean ± SD</td>
<td>24.6 ± 9.7</td>
<td>24.1 ± 11.6</td>
</tr>
<tr>
<td></td>
<td>24.4 ± 9.4</td>
<td>25.4 ± 10.2</td>
</tr>
<tr>
<td></td>
<td>0.66</td>
<td>0.45</td>
</tr>
<tr>
<td>SOF through day 30, n (%)</td>
<td>214 (98.2)</td>
<td>40 (90.9)</td>
</tr>
<tr>
<td></td>
<td>235 (97.1)</td>
<td>35 (92.1)</td>
</tr>
<tr>
<td></td>
<td>0.49</td>
<td>0.91</td>
</tr>
<tr>
<td>Days alive and free from SOF through day 30, mean ± SD</td>
<td>19.9 ± 8.9</td>
<td>21.9 ± 11.1</td>
</tr>
<tr>
<td></td>
<td>19.5 ± 8.6</td>
<td>23.1 ± 9.8</td>
</tr>
<tr>
<td></td>
<td>0.53</td>
<td>0.50</td>
</tr>
<tr>
<td>Days alive and free of hospital through day 30</td>
<td>4.0 ± 6.9</td>
<td>13.2 ± 10.4</td>
</tr>
<tr>
<td></td>
<td>3.5 ± 6.4</td>
<td>11.3 ± 9.1</td>
</tr>
<tr>
<td></td>
<td>0.39</td>
<td>0.71</td>
</tr>
</tbody>
</table>
Recombinant FVIIa

- 35 randomized, controlled clinical trials (26 involving patients, 9 involving healthy subjects)
  - \( N = 4468 \) (349 healthy volunteers)
  - Seven major bleeding categories
    - Spontaneous CNS (31.3%)
    - Advanced liver (27.8%)
    - Trauma (18.7%)
    - Cardiac surgery
    - Traumatic brain injury
    - Spinal surgery
    - Others

- Three dosing groups
  - Less than 80 mcg/kg
  - 80 – 120 mcg/kg
  - Greater than 120 mcg/kg

### Table 3. Arterial Thromboembolic Events with a Rate Greater Than 0.5%.

<table>
<thead>
<tr>
<th>Variable</th>
<th>rFVIIa (N = 2583)</th>
<th>Placebo (N = 1536)</th>
<th>Odds Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All arterial thromboembolic events</td>
<td>141 (5.5)</td>
<td>49 (3.2)</td>
<td>1.68 (1.20–2.36)</td>
<td>0.003</td>
</tr>
<tr>
<td>Coronary events</td>
<td>76 (2.9)</td>
<td>17 (1.1)</td>
<td>2.39 (1.39–4.09)</td>
<td>0.002</td>
</tr>
<tr>
<td>Acute coronary syndromes</td>
<td>57 (2.2)</td>
<td>11 (0.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased troponin level</td>
<td>19 (0.7)</td>
<td>6 (0.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebrovascular events</td>
<td>45 (1.7)</td>
<td>20 (1.3)</td>
<td>1.27 (0.74–2.17)</td>
<td>0.39</td>
</tr>
<tr>
<td>Cerebral infarction</td>
<td>44 (1.7)</td>
<td>19 (1.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemiparesis†</td>
<td>1 (&lt;0.1)</td>
<td>1 (&lt;0.1)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Objective
- Assess the benefits and harms of PCC compared with FFP for vitamin K antagonist treated bleeding and non-bleeding

Primary outcome
- Overall mortality
- Overall 28-day mortality

Secondary outcome
- Avoidance of blood product transfusion
- Complications: thrombotic episodes [PE, MI, DIC], HIT, TRALI, TACO, sepsis
- Inpatient days
- Mean ICU days
- Other complications [pneumonia, cardiac, renal and/or pulmonary failure

Johansen, M. Cochrane Database 2015(7):CD010555
### Prothrombin Complex Concentrate

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Illustrative comparative risks* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>Number of participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall mortality longest follow-up</strong></td>
<td>Study population</td>
<td>RR 0.93 (0.37 to 2.33)</td>
<td>421 (3 studies)</td>
<td>Very low a,b,c,d,e</td>
<td>Effect of the use of PCC on mortality was uncertain. None of the included studies were powered to detect differences in mortality. Large confidence intervals. Few participants and few events</td>
</tr>
<tr>
<td>Control</td>
<td>Control Prothrombin complex concentrate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Assumed risk</td>
<td>Corresponding risk</td>
<td>RR 0.93 (0.37 to 2.33)</td>
<td>421 (3 studies)</td>
<td>Very low a,b,c,d,e</td>
<td></td>
</tr>
<tr>
<td>84 per 1000</td>
<td>78 per 1000 (31 to 195)</td>
<td>RR 0.93 (0.37 to 2.33)</td>
<td>421 (3 studies)</td>
<td>Very low a,b,c,d,e</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>85 per 1000 (34 to 212)</td>
<td>RR 0.93 (0.37 to 2.33)</td>
<td>421 (3 studies)</td>
<td>Very low a,b,c,d,e</td>
<td></td>
</tr>
<tr>
<td>91 per 1000</td>
<td>85 per 1000 (34 to 212)</td>
<td>RR 0.93 (0.37 to 2.33)</td>
<td>421 (3 studies)</td>
<td>Very low a,b,c,d,e</td>
<td></td>
</tr>
<tr>
<td>Number of new occurrences of RBC transfusion</td>
<td>Study population</td>
<td>RR 1.08 (0.82 to 1.43)</td>
<td>376 (2 studies)</td>
<td>Very low a,c,d,e</td>
<td>Number of new occurrences of blood transfusion did not seem to be associated with use of PCC. Large confidence intervals. Few participants and few events</td>
</tr>
<tr>
<td>319 per 1000</td>
<td>344 per 1000 (262 to 466)</td>
<td>RR 1.08 (0.82 to 1.43)</td>
<td>376 (2 studies)</td>
<td>Very low a,c,d,e</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>324 per 1000 (246 to 429)</td>
<td>RR 1.08 (0.82 to 1.43)</td>
<td>376 (2 studies)</td>
<td>Very low a,c,d,e</td>
<td></td>
</tr>
<tr>
<td>300 per 1000</td>
<td>324 per 1000 (246 to 429)</td>
<td>RR 1.08 (0.82 to 1.43)</td>
<td>376 (2 studies)</td>
<td>Very low a,c,d,e</td>
<td></td>
</tr>
</tbody>
</table>
### Prothrombin Complex Concentrate

<table>
<thead>
<tr>
<th>Number of complications probably related to the intervention</th>
<th>Study population</th>
<th>RR 0.92 (0.78 to 1.09)</th>
<th>442 (4 studies)</th>
<th>4</th>
<th>Very low</th>
<th>a,b,c,d,e,f</th>
</tr>
</thead>
<tbody>
<tr>
<td>573 per 1000</td>
<td>527 per 1000</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(447 to 625)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Moderate                                                    |                  |                         |                |        |                |                |
| 563 per 1000                                                | 518 per 1000     |                         |                |        |                |                |
| (439 to 614)                                                |                  |                         |                |        |                |                |

<table>
<thead>
<tr>
<th>Transfusion of RBCs</th>
<th>Mean transfusion of RBCs in the intervention groups was 4.52 lower (80.59 lower to 71.55 higher)</th>
<th>370 (2 studies)</th>
<th>4</th>
<th>Very low</th>
<th>a,c,d,e</th>
</tr>
</thead>
</table>

Assessment of safety was not uniform, which raises concerns of underreporting. Large confidence intervals. Few participants and few events.

Trial sequential analysis of PCC vs FFP on quantity of RBCs transfused from 2 trials led to rejection of an intervention effect of 125 mL based on sparse data and repetitive analyses. Large confidence intervals. Few participants and few events.

Johansen, M. *Cochrane Database* 2015(7):CD010555
Prothrombin Complex Concentrate [3F-PCC]

- Retrospective cohort study
  - Life-threatening warfarin-associated bleeding episodes
- Treatment
  - 3F-PCC 50 units/kg [maximum 4000 units)
  - 1 mg fixed dose rFVIIa
  - Vitamin K 10 mg IV
- Clinical efficacy assessed based on the type of bleeding event
- Complications included any form of VTE, ischemic stroke, MI, HF exacerbation, pulmonary edema, rash or anaphylaxis

Barton, C. Am J Emerg Med 2015;33:1562-1566
### Clinical Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Pre-implementation [n=109]</th>
<th>Post-implementation [n=118]</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intracranial bleeds, n(%)</td>
<td>N = 87</td>
<td>N = 95</td>
<td></td>
</tr>
<tr>
<td>Expansion</td>
<td>22 (25.3)</td>
<td>23 (24.2)</td>
<td>.858</td>
</tr>
<tr>
<td>Stable</td>
<td>61 (70.1)</td>
<td>69 (72.6)</td>
<td></td>
</tr>
</tbody>
</table>

### Complications

<table>
<thead>
<tr>
<th></th>
<th>Pre-implementation [n=109]</th>
<th>Post-implementation [n=118]</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>13 (11.9)</td>
<td>33 (27.9)</td>
<td>.003</td>
</tr>
<tr>
<td>DVT</td>
<td>3 (2.8)</td>
<td>16 (14.6)</td>
<td></td>
</tr>
<tr>
<td>PEA/Death</td>
<td>1 (0.9)</td>
<td>4 (3.4)</td>
<td></td>
</tr>
<tr>
<td>NSTEMI</td>
<td>1 (0.9)</td>
<td>2 (1.7)</td>
<td></td>
</tr>
<tr>
<td>Intracranial bleeds, any thrombotic</td>
<td>9 (10.3)</td>
<td>25 (26.3)</td>
<td>.006</td>
</tr>
</tbody>
</table>
PCC and ICH: INCH Trial

- Prospective, randomized, multi-center, open-label, blinded-endpoint trial [n=50]
  - Within 12 hours of onset of symptoms, INR >2 on admission
  - Notable exclusion: traumatic or secondary ICH, GCS ≤5

- Treatment
  - 20 mL/kg FFP versus 30 U/kg PCC [4-factor, Octaplex]

- Primary outcome
  - Proportion of patients with INR of 1.2 or lower at 3 hours following start of treatment

Frontera, J. *Neurocrit Care* 2014;21:397-406
Fong, W. *Hong Kong Med J* 2014;20(6):486-494
# PCC and ICH: INCH Trial

<table>
<thead>
<tr>
<th></th>
<th>FFP [n=23]</th>
<th>PCC [n=27]</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary outcome</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>INR ≤1.2 @ 3h</td>
<td>2 (9%)</td>
<td>18 (67%)</td>
<td>OR 30.6 (4.7 to 197.9)</td>
<td><strong>0.0003</strong></td>
</tr>
<tr>
<td><strong>Secondary outcome</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death at 90 days</td>
<td>8 (35%)</td>
<td>5 (19%)</td>
<td></td>
<td>0.14</td>
</tr>
<tr>
<td>Hematoma expansion (mL) @ 3h</td>
<td>23.7 (28.4)</td>
<td>9.7 (20.9)</td>
<td>16.9 (2.5 to 31.3)</td>
<td>0.023</td>
</tr>
</tbody>
</table>

Case

- 45 y/o M struck in head
- History significant for DVT on Coumadin
  - INR = 2.0 on admission
- Kcentra 2878 units IV x1
  PLUS Vit K 10 mg IV x1
Follow up head CT <24 hours from admission
- Status post left frontal parietal craniotomy with evacuation of left epidural
- Left-sided scalp swelling and hemorrhage increased
- Increase in SAH in interpeduncular cistern
- Patient clinical course complicated by severe ARDS, cardiac arrest, enterobacter aerogenes meningitis
- Started to open eyes ~4 weeks following initial trauma, inconsistently follows simple commands
Hemostasis achieved quicker, but to what end?
- Limited consistent data regarding long-term morbidity outcomes, mortality improvement

Data is inconsistent, often do not include the population of interest [i.e. trauma]
- Optimal dosing and timing of administration relatively unknown

Safety: we just don’t know
- Agent related, patient-specific factors
Severity and extent of thrombosis can range from superficial thrombophlebitis to DIC → incidence of such complications unknown

- Variable based on:
  - Content of PCC
  - Dosing strategy utilized, repeat dosing
  - Concurrent use of procoagulants
  - Patient-specific risk factors → example: obesity, hepatic impairment

PCC should not be used routinely in trauma patients not receiving oral VKAs until further safety and efficacy trials are performed with this population

rFVIIa should not be routinely used based on increased risk of thromboembolic complications
Speculated Adjuncts

- DDAVP
  - Increases in circulating FVII, vWF, tPA
  - Utilized in hemophilia A, von Willebrand disease and corrects the impairment of primary hemostasis in patients with uremia and liver cirrhosis

- Tranexamic acid
  - Potential partial correction in arachidonic acid and ADP-induced platelet aggregation
What We Know

- Massive transfusion ratio 1:1:1 ideal
- ROTEM guided MTP should not be employed at this time
- Tranexamic acid should be used early
- PCCs and rFVIIa impact on INR reversal, blood product conservation
- DDAVP should not be used routinely in non-hemophiliacs
- Don’t forget the calcium!
What We Don’t Know

- Laboratory monitoring levels of TIC, NOACs
  - Validated, standard, more widely available assays
- Need for more data for non-VKA bleeding management including non-VKA therapy reversal
  - Time, dose and duration of administration
  - Monitoring for safety, efficacy, long-term outcomes
- Idarucizumab
  - Case reports of treatment failure
Management of Critical Bleeding in the Trauma Patient

What we know
What we wish we knew

GRAZIELLA R. FURNARI, PHARMD, BCPS
CLINICAL PHARMACY SPECIALIST – TRAUMA/CRITICAL CARE
ERIE COUNTY MEDICAL CENTER