Use of plasma versus coagulation factor concentrates: is there evidence?

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SOME CLINICAL SETTINGS WITH REFRACTOR OR MASSIVE BLEEDING REQUIRING URGENT OR EMERGENT THERAPY

• Coagulopathy of liver disease: acute fulminant hepatitis or cirrhosis
• Trauma
• Postpartum
• Complex surgical procedures: liver transplantation, cardiothoracic surgery
• Gastrointestinal lesions: esophageal varices, diverticulosis
• Sepsis with Disseminated Intravascular Coagulation (DIC)
• Warfarin-associated coagulopathy
The effect of plasma transfusion on morbidity and mortality: a systematic review and meta-analysis

• Very-low quality evidence suggests that plasma infusion in the setting of massive transfusion for trauma patients may be associated with a reduction in the risk of death and multiorgan failure.

• A survival benefit was not demonstrated in most other transfusion populations.

Murad et al. Transfusion 2010; 50:1370-1383
Fig. 4. Should plasma transfusion (vs. no plasma) be used for patients with warfarin anticoagulation–related intracranial hemorrhage? (A) Percentage of panel recommending for or against this intervention. (B) Quality of evidence supporting this intervention, as rated by the panel.
Evidence-Based Practice Guidelines for Plasma Transfusion

Roback JD, et al. Transfusion 2010;50:1227-1239

• ‘Efficacy of plasma to reduce mortality outweighed its potential risks (e.g. TRALI, inventory) in warfarin-treated patients with ICH.’*

* However, the level of recommendation and grading of evidence as ‘low’ may be attributed to ‘too little too late’ (type II error)
SOME CURRENT KNOWN RISKS OF PLASMA THERAPY

• Pathogens transmissible by blood: 1:500,000 (Hepatitis B) to 1:2,000,000 (Hepatitis C, HIV)

• Allergic transfusion reactions: 1-2% for severe, up to 15% for mild

• Transfusion-related volume overload (TACO): 6% in prospective surveillance studies.

• Transfusion-related acute lung injury (TRALI) Estimated to be 1:5,000-10,000 before risk mitigation policies for female plasma donors; reduced to 1:60,000 in 2006, 1:170,000 in 2008.
How we treat warfarin-associated coagulopathy in patients with intracerebral hemorrhage.

Goodnough LT, Shander AS. Blood 2011;117(23):6091-9
Variability in Treatment of Patients on Oral Anticoagulants with Spontaneous ICH

<table>
<thead>
<tr>
<th></th>
<th>1 Hospital</th>
<th>4 Other Hospitals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma</td>
<td>4 of 7 (60%)</td>
<td>2 of 34 (6%)</td>
</tr>
<tr>
<td>PCC</td>
<td>19 of 26 (73%)</td>
<td>1 of 37 (3%)</td>
</tr>
<tr>
<td>No Action Taken</td>
<td>2 of 26 (8%)</td>
<td>23 of 40 (57%)</td>
</tr>
</tbody>
</table>

Sjoblom et al Stroke 2001;32:2567
ED Management and INR Reversal in Warfarin-Associated Coagulopathy

INR Reversed at 24 h

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No (n=12)</th>
<th>Yes (n=57)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median</td>
<td>Median</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(25% to 75%)</td>
<td>(25% to 75%)</td>
<td></td>
</tr>
<tr>
<td>Door to CT time</td>
<td>65 (30 to 90) min.</td>
<td>40 (25 to 85) min.</td>
<td>0.5</td>
</tr>
<tr>
<td>CT to FFP time*</td>
<td>210 (100 to 375) min.</td>
<td>90 (60 to 205) min.</td>
<td>0.02</td>
</tr>
<tr>
<td>Dose of FFP</td>
<td>2 (1 to 5) units</td>
<td>4 (2 to 6) units</td>
<td>0.1</td>
</tr>
<tr>
<td>CT to Vit. K time</td>
<td>245 (37 to 361) min.</td>
<td>87 (25 to 210) min.</td>
<td>0.2</td>
</tr>
<tr>
<td>Any Vit. K given</td>
<td>58%</td>
<td>81%</td>
<td>0.1</td>
</tr>
</tbody>
</table>

*First Dose

Plasma Therapy in Successful Reversal of Warfarin Anticoagulation in Patients with ICH

<table>
<thead>
<tr>
<th>Barrier</th>
<th>Estimated Time Needed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient blood type must be determined</td>
<td>Up to 60 minutes</td>
</tr>
<tr>
<td>Plasma units must be thawed</td>
<td>30-45 minutes</td>
</tr>
<tr>
<td>Plasma volume requires careful management to avoid circulatory overload</td>
<td>30 minutes per unit</td>
</tr>
<tr>
<td>Plasma dosing is underestimated</td>
<td></td>
</tr>
<tr>
<td>Liquid AB plasma available?</td>
<td>5 minutes</td>
</tr>
<tr>
<td>Thawed A plasma available?</td>
<td>5 minutes</td>
</tr>
</tbody>
</table>
Physiologic basis for transfusion therapy in hemorrhagic disorders

“As an initial infusion, 1000mL of normal plasma to an average sized adult is usually required to produce minimum hemostatic levels.”

Paul Aggler
Transfusion 1961;1:71-86
Care of patients receiving long-term anticoagulant therapy

“Volume of plasma required for reversal is almost invariably too large to be infused safely”

Sam Schulman
Use of Factor IX complex in Warfarin-Related ICH

- PT greater than 17 sec. patients (n=13) with:
  - Randomized to FFP alone (n=8) vs. FFP + PCC (n=5)
  - PT, INR Q 2H x 7. Target INR 1.3
  - Vitamin K 10mg sq
  - Plasma infusion, maximum rate tolerated
    CVP monitoring 2-3 liters

FIGURE 2. Mean INRs measured at protocol initiation and 2, 4, and 6 hours after initiation of anticoagulation treatment. Inclusion of FIXCC in the correction regimen reduced the time to normal hemostatic function.
FIGURE 3. Comparison of the time to anticoagulation correction with FFP treatment alone. Groups included patients treated before protocol initiation (n = 6, 25.4 ± 7 h), during the protocol (n = 8, 8.9 ± 1.3 h), and after protocol termination (n = 6, 11.2 ± 4.2 h). An improvement in the time to correction was observed after protocol initiation and persisted after protocol termination.
Toward rational fresh frozen plasma transfusion: The effect of plasma transfusion on coagulation test results.

- Based on the assumption that 30% factor level is adequate, an INR of 1.8 represents minimally acceptable level of coagulation.

Predicted FFP transfusion volume, dose, and expected Factor increment for various target INR values

<table>
<thead>
<tr>
<th>Initial INR</th>
<th>Volume (L)</th>
<th>Dose (mL/kg)</th>
<th>Factor (%)</th>
<th>Volume (L)</th>
<th>Dose (mL/kg)</th>
<th>Factor (%)</th>
<th>Volume (L)</th>
<th>Dose (mL/kg)</th>
<th>Factor (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6.0</td>
<td>4.5</td>
<td>64</td>
<td>45</td>
<td>3.5</td>
<td>50</td>
<td>35</td>
<td>2.5</td>
<td>36</td>
<td>25</td>
</tr>
<tr>
<td>5.0</td>
<td>4.3</td>
<td>61</td>
<td>43</td>
<td>3.0</td>
<td>43</td>
<td>30</td>
<td>2.3</td>
<td>32</td>
<td>23</td>
</tr>
<tr>
<td>4.0</td>
<td>4.0</td>
<td>57</td>
<td>40</td>
<td>2.5</td>
<td>36</td>
<td>25</td>
<td>2.0</td>
<td>29</td>
<td>20</td>
</tr>
<tr>
<td>3.0</td>
<td>3.5</td>
<td>50</td>
<td>35</td>
<td>2.0</td>
<td>29</td>
<td>20</td>
<td>1.5</td>
<td>21</td>
<td>15</td>
</tr>
<tr>
<td>2.0</td>
<td>2.5</td>
<td>36</td>
<td>25</td>
<td>1.5</td>
<td>21</td>
<td>15</td>
<td>0.5</td>
<td>7</td>
<td>5</td>
</tr>
</tbody>
</table>

INR, international normalized ratio.

Efficacy of standard dose and 30 ml/kg fresh frozen plasma in correcting laboratory parameters of haemostasis in critically ill patients

- Current guidelines on the use of FFP result in predictably small increments in coagulation factors in critically ill patients and should be reviewed.
- 12.5 ml/kg of FFP lead to relatively small, inadequate increments in factor levels and 30 ml/kg of FFP adequately corrected all factors levels.
- FFP is standardized only for fibrinogen and Factor VIII content.

Urgent reversal of warfarin with prothrobmin complex concentrate: where are the evidence-based data (Editorial)?

• No PCC has received approval from FDA for reversal of elevated INR’s or warfarin-related bleeding.
• No 4 Factor PCC currently available in US Proplex-T (Baxter) removed 2005.
• Does reversal of warfarin-effect require repletion of all four (II, VII, IX, X) or selected Vitamin K-dependent factors?
• INR correction after rVIIa administration probably occurs independently of its hemostatic activity: generation of thrombin ‘burst’ on surface of activated platelets.

Role of Prothrombin Complex Concentrates in Reversing Warfarin Anticoagulation: A Review of the Literature

• In the US, FFP is considered the standard of care for warfarin reversal
• PCC’s offer an alternative to FFP
• However, few prospective trials
• In comparison studies, PCC’s found more effective for INR correction
• Evidence-based treatment guidelines needed

Prothrombin Complex Concentrate (PCC) products available for reversal of warfarin-associated coagulopathy

<table>
<thead>
<tr>
<th>Product (Manufacturer)</th>
<th>Factors Levels</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>II</td>
</tr>
<tr>
<td><strong>Available in the USA:</strong></td>
<td></td>
</tr>
<tr>
<td>PCC’s, Three-factor (II,IX,X)</td>
<td></td>
</tr>
<tr>
<td>Profillnine SD (Grifols)*</td>
<td>≤ 150</td>
</tr>
<tr>
<td>Bebulin VH (Baxter) **</td>
<td>24-38</td>
</tr>
</tbody>
</table>

*The values given for factor contents are the number of units present per 100 Factor IX units in each vial.

**IU/ml

Prothrombin Complex Concentrate (PCC) products available for reversal of warfarin-associated coagulopathy

<table>
<thead>
<tr>
<th>Product (Manufacturer)</th>
<th>II</th>
<th>VII</th>
<th>IX</th>
<th>X</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Available outside the USA:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. PCC’s, Four-factor (II, VII, IX, X)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beriplex (CSL Behring)$^a$</td>
<td>20-48</td>
<td>10-25</td>
<td>20-31</td>
<td>22-60</td>
</tr>
<tr>
<td>Octaplex (Octapharma)$^b$</td>
<td>14-38</td>
<td>9-24</td>
<td>25</td>
<td>18-30</td>
</tr>
<tr>
<td>Cofact (Sanguin)$^c$</td>
<td>14-35</td>
<td>7-20</td>
<td>25</td>
<td>14-35</td>
</tr>
<tr>
<td>Prothromplex T (Baxter)$^d$</td>
<td>30</td>
<td>25</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>PPPSB-Th$^e$</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td><strong>II. PCCs, Three-factor (II, IX, X)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prothromplex HT (Baxter)$^f$</td>
<td>30</td>
<td>-</td>
<td>30</td>
<td>130</td>
</tr>
</tbody>
</table>

$^a$UK, EU  
$^b$UK, Canada, EU  
$^c$EU  
$^d$Austria  
$^e$Japan  
$^f$Australia

Guidelines on Oral Anticoagulation (4th ed) 2011 Update*
in Patients with Major Bleeding

- Vit K 5mg IV
- Reversal of over-anticoagulation should be with a 4 Factor PCC, rather than FFP**
- rFVIIa cannot be recommended

*Br J Haematol 2011;154:311-24
**Makris M et al. Thromb Haemostas 1997;77:477
The Relative Efficacy of Infusions of FFP and PCC on Correction of the Coagulopathy

• Results: FFP: INR 10.2 to 2 with 800 mL (n=12)
  PCC: INR 5.8 to 1.3 with 3 Factor (n=13) or 4 Factor (n=16)

• Results: The Factor IX level was 19µ/dl (10-63) following FFP and 68.5µ/dl (31-111) following PCC

• Methods: For FFP cohort, Vitamin K (1-5 mg IV), was given after FFP, simultaneously with 2nd INR
  i.e. 15 minutes after completion of FFP infusion’

• Discussion: ‘It could be argued that the PCC responses were influenced by Vitamin K which was given simultaneously and approximately 15 minutes earlier than in FFP patients.’

## Guidelines for reversal of warfarin anticoagulation in patients with ICH

<table>
<thead>
<tr>
<th>Society (Year)</th>
<th>Vitamin K (mg)</th>
<th>Plasma (ml/kg)</th>
<th>PCC (U/kg)</th>
<th>rFVII</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australian (2004)</td>
<td>IV (5-10)</td>
<td>Yes (NS)</td>
<td>AND</td>
<td>Yes (NS)*</td>
</tr>
<tr>
<td>EU Stroke (2006)</td>
<td>IV (5-10)</td>
<td>Yes (10-40)</td>
<td>OR</td>
<td>Yes (10-50)</td>
</tr>
<tr>
<td>ACCP (2008)</td>
<td>IV (10)</td>
<td>Yes (NS)</td>
<td>OR</td>
<td>Preferred (NS)</td>
</tr>
<tr>
<td>AHA (2010)</td>
<td>IV (NS)</td>
<td>Yes (10-15)</td>
<td>OR</td>
<td>Yes (NS)</td>
</tr>
<tr>
<td>French (2010)</td>
<td>Oral or IV (10)</td>
<td>Yes (NS)‡</td>
<td>OR</td>
<td>Preferred (25-50)</td>
</tr>
<tr>
<td>British Standards (2011)</td>
<td>IV (5)</td>
<td>No</td>
<td></td>
<td>Yes (NS)</td>
</tr>
</tbody>
</table>

PCC, Prothrombin Complex Concentrate; rFVIIa, Recombinant Human Activated Factor VII
NS, Not Specified; IV, Intravenous

*If a three-factor PCC is administered, FFP is also recommended as a source of Factor VII
†Use of PCC or rFVIIa may vary depending on availability
‡Use of plasma only when PCCs not available

Pros/Cons of Plasma vs. PCC

I. **Single Donor Plasma**
1. Time-dependent administration
2. Volume constraints
3. Transmissible disease, known/unknown
4. TRALI

II. **PCC**
1. Thrombogenicity
2. Donor pools: 3,000 to 20,000
3. Transmissible disease, known and unknown pathogens
4. Some preparations lack Factor VII
5. Limited Availability
How We Treat Warfarin-Associated Coagulopathy in Patients with ICH

- Blood type and screen
- Vitamin K 10mg IV over 30 min, Q12h
- Plasma therapy: 15-30 mL/kg, or 4-8 units. First units should be thawed ‘A’ plasma or liquid AB plasma
- INR goal: less than 1.7
- 3 factor PCC is off-label, approved only for replenishment of Factor IX.
How We Treat Warfarin-Associated Coagulopathy in Patients with ICH

• In some countries, 4 Factor PCC is available/approved.
  Doses 25 IU/kg in therapeutic range (TR)
  Doses 35-50 IU/kg greater than TR
• rFVIIa not approved in this setting. 2 mg IV provides 20-40 microgm/kg for 100 kg to 50 kg patients
• rFVIIa: risks of arterial thrombosis