Plasma vs. Prothrombin Complex Concentrates for Acute Warfarin Reversal

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BACKGROUND
Strategies are undergoing scrutiny regarding the relative role(s) of plasma and prothrombin complex concentrates (PCC) to supplement Vitamin K administration in acute reversal of warfarin-associated coagulopathy.

Plasma Therapy
A recent report published evidence-based practice guidelines for plasma therapy\(^1\). When literature reviewed was limited to Level 1 evidence, outside the setting of trauma, no survival benefit to plasma therapy was found. A “weak” recommendation was given for reversal of warfarin-associated coagulopathy in medical/surgical emergencies, such as intracerebral hemorrhage (ICH), based on the quality of evidence. The level of recommendation and the grading of evidence as “low,” could be in part attributable to two factors: the paucity of studies which support that abnormal coagulation test results predict bleeding; and the delayed administration and inadequate dosing strategies have not shown convincing evidence for a benefit for plasma therapy\(^2\).

Lack of enthusiasm and logistical/technical barriers in this and other settings have led to approaches for plasma therapy that are perhaps “too little, too late”. First, transfusion services must identify the patient’s blood group type before issuing blood type-compatible plasma. For patients unknown to the institution and/or without a historic blood type in the patient record, considerable time (up to 60 minutes) can elapse from presentation until a blood type can be determined. Second, since plasma is stored frozen at -18°C, further time (30 to 45 minutes) is required to thaw and issue plasma. Third, the plasma volume (~ 200mL/unit) represents a challenge regarding volume overload, commonly occurring in an elderly population who have pre-existing co-morbidities. The plasma dose needed to correct the coagulopathy has often been underestimated and, therefore, may be sub-therapeutic. Plasma therapy of 15-30 mL/kg is necessary to restore hemostatic clotting factor levels to 30-50 percent of normal in acute reversal of warfarin toxicity\(^2\).

Prothrombin Complex Concentrates (PCC)
PCCs are either activated (i.e. to bypass inhibitors to Factor VIII or Factor IX in the treatment of hemophilia A or B), or are non-activated (Table 1)\(^2\). The non-activated PCCs are further categorized based on the presence (4 factor) or absence (3 factor) of sufficient levels of factor VII. A four-factor PCC product (Beriplex, CSL Behring, King of Prussia, PA) is undergoing regulatory review in the US for emergency reversal of warfarin coagulopathy in

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**Key Points**
- Institutional clinical care pathways are needed for acute reversal of warfarin coagulopathy.
- Plasma therapy has limitations for effective reversal of warfarin coagulopathy.
- PCCs currently approved in the US have diminished levels of Factor VII and are currently not approved for reversal of warfarin coagulopathy.
- Whether PCCs or plasma are used, administration of Vitamin K is essential for warfarin reversal.
patients with major bleeding and for perioperative management. Three-factor PCCs are approved in the US only for the replacement of Factor IX, and their use for reversal of warfarin is controversial. While they can be demonstrated to normalize INR, one report showed a suboptimal effect in correcting INR due to minimal increase in Factor VII levels. In contrast, four factor PCCs are approved outside the US for replacement of the vitamin K-dependent clotting factors (II, VII, IX, X).

Published guidelines for acute reversal of warfarin coagulopathy are variable in their recommendations (Table 2). One review of emergency warfarin reversal in US neurosurgical patients recommended the concomitant administration of a three-factor concentrate (4000 IU) and rVIIa (1 mg). This lack of consensus on the role of PCC therapy relative to plasma therapy stems from variable clotting factor levels; differing regulatory approval status amongst countries; uncertain availability among hospital formularies - particularly in community hospitals; and potential risks of thrombogenicity.

The safety of PCC concentrates for the emergent reversal of warfarin anticoagulation remains debatable. An estimated 4.6 percent of patients have thrombotic events, but these have been attributed to cessation of anticoagulant therapy for underlying risks of thrombosis. Increased doses (50 IU/kg) of PCC therapy appear to increase the risk of thromboembolism and DIC.

Multinational trials on patients receiving a four-factor PCC product have supported the safety and efficacy of rapid infusion of PCC. A review of eight clinical studies identified a thromboembolic event rate of 0.9 percent with PCC therapy. Studies of optimal dosing strategies for PCC, including fixed versus variable (weight-based) dosage, provide a basis for future research.

Conclusion
Institutional clinical care pathways are needed in order to successfully manage patients with refractory bleeding for acute reversal of warfarin coagulopathy. Close collaboration among emergency medicine, critical care specialists, hematology, transfusion medicine, and neurology/neurosurgery and pharmacy services, is necessary for patient blood management in critical care settings. Physicians need to be encouraged to adapt their clinical practices with sound clinical evidence for use of these products.

References

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Table 1 - Prothrombin Complex Concentrate (PCC) products currently available or under regulatory review** in the US

<table>
<thead>
<tr>
<th>Product (Manufacturer)</th>
<th>II</th>
<th>VII</th>
<th>IX</th>
<th>X</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. PCC’s, Three-factor (II, IX, X)</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>1. Profilnine SD (Grifols)*</td>
<td>≤150</td>
<td>≤35</td>
<td>≤100</td>
<td>≤100</td>
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<tr>
<td>2. Bebulin VH (Baxter)*</td>
<td>24-38 IU/ml</td>
<td>&lt;5 IU/ml</td>
<td>24-38 IU/ml</td>
<td>24-38 IU/ml</td>
</tr>
<tr>
<td>B. PCC’s, Four-factor (II, VII, IX, X)</td>
<td></td>
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<tr>
<td>1. Beriplex (CSL Behring) **</td>
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IU/ml

*Product insert specifies: Indicated for replacement of Factor IX with hemophilia B. Not indicated for treatment of Facto VII deficiency. The values given for factor contents are the number of units present per 100 Factor IX units in each vial.

Table 2 - Published guidelines for reversal of warfarin anticoagulation in patients with intracerebral hemorrhage

<table>
<thead>
<tr>
<th>Society (Year)</th>
<th>Vitamin K</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 mg)</td>
<td>Yes (NS)</td>
<td>AND</td>
<td>Yes (NS)*</td>
</tr>
<tr>
<td>EU Stroke (2006)*</td>
<td>IV (5-10 mg)</td>
<td>Yes (10-40)</td>
<td>OR</td>
<td>Yes (10-50)</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 mg)</td>
<td>Yes (NS) ‡</td>
<td>OR</td>
<td>Preferred (25-50)</td>
</tr>
<tr>
<td>British Standards (2011)§</td>
<td>IV (5mg)</td>
<td>No</td>
<td></td>
<td>Yes (NS)</td>
</tr>
<tr>
<td>ACCP (2012)§</td>
<td>IV (10 mg)</td>
<td>Yes (NS)</td>
<td>OR</td>
<td>Preferred (NS)</td>
</tr>
</tbody>
</table>

**rFVIIa, Recombinant Human Activated VII; NS, Not specified
*If a three-factor PCC is administered, FFP is also recommended as a source of Factor VII
†Use of PCCs or rFVIIa may vary depending on availability
‡Use of plasma only when PCCs not available
Updated from Goodnough LT, Shander AS. Blood 2011;117:6091-9