4-Factor Prothrombin Complex Concentrate for Urgent Reversal of
Vitamin K Antagonists in Patients with Major Bleeding

Running title: Quinlan et al.; 4-factor PCC for VKA-related bleeding

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Vitamin K antagonists (VKA), such as warfarin, are widely used for prevention and treatment of arterial and venous thrombosis. Although oral or intravenous vitamin K and fresh frozen plasma are often used to reverse the anticoagulant effects of warfarin in patients who are bleeding, this approach has important limitations. Restoration of hemostasis with vitamin K relies on the hepatic synthesis of vitamin K-dependent procoagulant proteins -- factors II (prothrombin), VII, IX and X -- a process that takes more than 6 hours. Fresh frozen plasma provides an immediate source of functional vitamin K-dependent clotting proteins, but large volumes are often required to normalize the international normalized ratio (INR). This can be problematic because it takes time to blood type-match, thaw and infuse fresh frozen plasma, and the large volumes can lead to fluid overload, particularly in patients with compromised cardiac or renal function.

Prothrombin complex concentrate (PCC) provides an alternative to fresh frozen plasma for reversal of VKA-induced coagulopathy (Table 1). Originally developed as a source of factor IX for treatment of patients with hemophilia B, 3-factor PCC contains factors II, IX and X, but little or no factor VII. In contrast to 3-factor PCC, 4-factor PCC also contains significant amounts of factor VII. Both 3- and 4-factor PCC contain protein C and protein S and some may also contain small amounts of heparin, which is added to prevent activation of the clotting proteins.

PCC contains the vitamin K-dependent clotting proteins in a lyophilized form and can be stored at room temperature for several years. No thawing or blood type-matching is required and after reconstitution with a small volume of sterile water (20-40 mL), PCC can be rapidly administered without risk of fluid overload. Additional advantages of PCC over fresh frozen plasma include a negligible risk of viral transmission and transfusion-related acute lung injury. Potential disadvantages of PCC are increased cost compared with fresh frozen plasma and a
small risk of thromboembolic complications. Both plasma and PCC require co-administration of vitamin K for sustained warfarin reversal because the half-life of factor VII – a key vitamin K-dependent clotting factor – is only 6 to 8 hours, whereas warfarin has a half-life of several days.

Current guidelines recommend 4-factor PCC for situations where rapid reversal of VKA-induced coagulopathy is needed, such as in patients who require urgent surgery or in those with a life-threatening bleed. If 4-factor PCC is unavailable, 3-factor PCC can be used and some clinicians supplement it with fresh frozen plasma or small amounts of recombinant activated factor VII (factor VIIa) as a source of factor VII. Non-activated PCC is preferred over activated PCC, which contains factor VIIa as well as factors II, IX and X, or recombinant factor VIIa because there is likely to be a lower risk of thromboembolic events with non-activated products. In addition, recombinant factor VIIa only replaces one of the four vitamin K-dependent procoagulant proteins.

What is the evidence supporting the use of PCC for reversal of VKA-induced coagulopathy? Two small randomized controlled trials, which included fewer than 60 patients, suggested that PCC reverses VKA-induced coagulopathy more rapidly than vitamin K or fresh frozen plasma, but were underpowered to show improvement in clinical outcomes. Consequently, until now, most of the evidence supporting the use of PCC for VKA reversal came from observational studies. In this issue of Circulation, Sarode and colleagues report the results of a phase III, open-label, non-inferiority, randomized controlled trial that compared a 4-factor PCC with fresh frozen plasma for urgent reversal of VKA-associated coagulopathy in 216 patients with acute bleeding. Despite the modest sample size and the fact that the trial enrolled 69 centers in the United States and Eastern Europe, the study took more than 2 years to complete. All patients received intravenous vitamin K, and the doses of PCC and number of
units of plasma that were infused were calculated based on individual body weight and baseline INR values. Over 60% of patients presented with gastrointestinal or other sites of non-visible bleeding, and over 10% had intracranial hemorrhage. Co-primary outcomes were the effectiveness of the hemostatic response during the 24-hour period from the start of study treatment and the proportion of patients who achieved an INR value of 1.3 or lower within 30 minutes of completion of the study infusion. Outcomes were independently adjudicated by an expert committee blinded to treatment allocation.

The median duration of PCC administration was 17 minutes compared with 148 minutes in those allocated to fresh frozen plasma, and corresponding infusion volumes were 99.4 mL and 813.5 mL, respectively. The proportion of patients achieving effective hemostasis within 24 hours was similar in the two treatment groups (72.4% versus 65.4%; non-inferiority p=0.0045).

The proportion of patients in the PCC group who achieved an INR ≤ 1.3 within 30 minutes of the end of infusion was 62.2%, which was lower than that the 93% observed in a previous observational study using the same PCC protocol, but still substantially higher than the 9.6% in the plasma group (p<0.002); a difference that remained evident at 24 hours. Among the subgroup of patients with visible or musculoskeletal bleeding, 82.6% of those given PCC achieved effective hemostasis at 4 hours compared with 50% in the plasma group (p=0.02). The safety profiles of PCC and fresh frozen plasma were comparable, as were the rates of thromboembolic events (7.8% and 6.4%, respectively), mean number of units of packed red blood cells transfused (1.4 and 1.2, respectively) and the median length of hospital stay. Patients in the PCC group had a lower rate of treatment-related adverse events than those give plasma (9.7% and 21.1%, respectively). There were 10 deaths in the PCC group and 5 in the group given fresh frozen plasma, but only one death was deemed to be treatment-related.
What are the implications of the Sarode study for clinical practice? First, the finding of more rapid reversal of the INR with a 4-factor PCC than with plasma provides additional support for the guideline that gives preference to PCC over fresh frozen plasma for patients who require urgent reversal of VKA-associated coagulopathy. Although the more rapid anticoagulation reversal achieved with a 4-factor PCC did not translate into more effective hemostasis at 24 hours or to an overall improvement in clinical outcomes, hemostatic improvement in the subgroup of patients with musculoskeletal or overt bleeding and a lower incidence of fluid overload support this conclusion. In line with this recommendation, the United States Food and Drug Agency licensed Kcentra® (CSL Behring), the 4-factor PCC that was used in the study by Sarode et al for urgent reversal of warfarin-associated coagulopathy in patients with acute major bleeding.

Second, the 7-8% overall rate of thromboembolic events and the 3-4% rate of treatment-related thromboembolism reported in this study underscore the importance of appropriate use of PCC in patients with VKA-associated coagulopathy. Although direct evidence that PCC or plasma causes thrombosis is lacking, there is substantial evidence that reversal of antithrombotic therapy in patients at risk is associated with an increase in thromboembolic events. Consequently, it seems prudent to restrict the use of PCC or plasma to patients with major or life-threatening bleeding or to those requiring urgent surgery.

What are the unresolved issues? First, the optimal PCC dose for reversal of VKA-associated coagulopathy remains uncertain. Although Sarode and colleagues administered 4-factor PCC at doses of 25 to 50 IU of factor IX per kg body weight, 30 minutes after drug infusion, 37.8% of the patients still had INR values above 1.3. It is uncertain whether higher doses of PCC would have resulted in INR correction in a greater proportion of patients. The
results of two recently completed but as yet unpublished trials comparing 4-factor PCC with plasma for reversal of VKA-associated coagulopathy in patients requiring urgent surgery or invasive procedures (NCT00618098, NCT00803101) may help to clarify this issue.

Second, we still need to know whether PCC improves clinical outcomes in patients with VKA-associated coagulopathy who present with serious bleeding. The currently available data are restricted to observational studies, which are subject to confounding and do not provide reliable evidence of efficacy or safety, and to small randomized trials.

The Sarode study has important implications for future research. The introduction of several new oral anticoagulants as alternatives to vitamin K antagonists has focused attention on the need for effective reversal agents to manage patients with major bleeding or those who require urgent surgery or intervention. Specific antidotes have been developed for both dabigatran and oral factor Xa inhibitors, but their efficacy and safety have yet to be demonstrated.\textsuperscript{18,19} Trials of reversal agents in patients with serious bleeding are challenging because consent can be difficult to obtain in the requisite time frame in such patients; a factor that likely contributed to the slow recruitment in the Sarode study. Ideally, studies with reversal agents should not only determine whether treatment results in more rapid normalization of tests of coagulation, but also should evaluate whether this, in turn, improves clinical outcomes. Large clinical trials are needed to show improvements in clinical outcomes. We have yet to see such trials in patients with VKA-associated bleeding and we are even less likely to see them in patients taking the new oral anticoagulants because these agents are associated with less bleeding, particularly intracranial bleeding, than warfarin.

In conclusion, the Sarode study is the first rigorously designed carefully conducted randomized controlled trial to show that 4-factor PCC provides more rapid normalization of the
INR than fresh frozen plasma in warfarin-treated patients who present with acute bleeding. In addition, the study shows an improvement in hemostasis with PCC in a subset of such patients. These results provide further support for current guidelines that give preference to 4-factor PCC over fresh frozen plasma for management of VKA-associated coagulopathy in patients who present with major or life-threatening bleeding. This trial also provides a framework for the future evaluation of reversal agents in patients treated with new oral anticoagulants.

**Conflict of Interest Disclosures:** None.

**References:**


Table 1. Available treatments for reversal of vitamin K antagonist-associated coagulopathy

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Vitamin K</th>
<th>Plasma</th>
<th>3-factor PCC</th>
<th>4-factor PCC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constituents</td>
<td>Vitamin K</td>
<td>All vitamin K-dependent clotting factors</td>
<td>Factor II, IX, X, proteins C and S*</td>
<td>Factor II, VII, IX, X, proteins C and S*</td>
</tr>
<tr>
<td>Route of administration</td>
<td>Oral or intravenous</td>
<td>Intravenous</td>
<td>Intravenous</td>
<td>Intravenous</td>
</tr>
<tr>
<td>Dose</td>
<td>5-10 mg</td>
<td>10-15 mL/kg</td>
<td>25-50 IU of factor IX/kg</td>
<td>25-50 IU of factor IX/kg</td>
</tr>
<tr>
<td>Onset of effect</td>
<td>6-8 hours</td>
<td>Duration of infusion†</td>
<td>15-30 minutes†</td>
<td>15-30 minutes†</td>
</tr>
<tr>
<td>Adverse effects</td>
<td>Rare anaphylaxis</td>
<td>Fluid overload; febrile and allergic reactions; viral transmission; transfusion-related acute lung injury</td>
<td>Possible increase in thromboembolic complications</td>
<td>Possible increase in thromboembolic complications</td>
</tr>
<tr>
<td>Cost</td>
<td>Minimal</td>
<td>Moderate</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Other</td>
<td>Intravenous administration produces more rapid reversal</td>
<td>Requires co-administration of vitamin K to sustain reversal</td>
<td>Requires co-administration of vitamin K to sustain reversal; may require co-administration of plasma or recombinant factor VIIa as a source of factor VII</td>
<td>Requires co-administration of vitamin K to sustain reversal</td>
</tr>
</tbody>
</table>

*Some preparations also contain antithrombin and small amounts of heparin.
†Onset can also be affected by the dose administered.
PCC indicates prothrombin complex concentrate.
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