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

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Vitamin K antagonists (VKAs), 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 >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 match blood type and thaw and infuse fresh frozen plasma, and the large volumes can lead to fluid overload, particularly in patients with compromised cardiac or renal function. Nonactivated PCC is preferred over activated PCC, with the fact that the trial enrolled 69 centers in the United States and Eastern Europe, the study took >2 years to complete.15 All of the patients received intravenous vitamin K, and the doses of PCC and number of units of plasma that were infused were calculated on the basis of individual body weight and baseline INR values. More than 60% of patients presented with gastrointestinal or other sites of nonvisible bleeding, and >10% had intracranial hemorrhage. Coprimary 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 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 and 813.5 mL, respectively. The proportion of patients achieving effective hemostasis within 24 hours was similar in the 2 treatment groups (72.4% versus 65.4%; noninferiority \(P=0.0045\)). The proportion of patients in the PCC group who achieved an INR \(\leq 1.3\) within 30 minutes of the end of infusion was 62.2%, which was lower than the 93.0% observed in a previous observational study using the same PCC protocol\(^1\) but still substantially higher than the 9.6% in the plasma group; 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 50.0% 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 given 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 1 death was deemed to be treatment related.

What are the implications of the study by Sarode et al\(^4\) 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.\(^3,4\) 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 US Food and Drug Agency licensed Kcentra (CSL Behring), the 4-factor PCC that was used in the study by Sarode et al\(^4\) for urgent reversal of warfarin-associated coagulopathy in patients with acute major bleeding.\(^16\)

Second, the 7% to 8% overall rate of thromboembolic events and the 3% to 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 fresh frozen 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 fresh frozen 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.\(^17\) Although Sarode et al\(^4\) administered 4-factor PCC at doses of 25 to 50 IU of factor IX per kilogram of body weight, 30 minutes after drug infusion, 37.8% of the patients still had INR values \(>1.3\). It is uncertain whether higher doses of PCC would have resulted in INR correction in a greater proportion of patients. The results of 2 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 (Clinical Trial Registration NCT00618098 and 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 study by Sarode et al\(^4\) has important implications for future research. The introduction of several new oral anticoagulants as alternatives to VKAs 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.\(^18,19\) 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 study by Sarode et al. 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 study by Sarode et al 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 the 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.

Disclosures

None.

References


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