

## Prothrombin complex concentrates in warfarin anticoagulation reversal

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### Introduction

Anticoagulation is very effective for primary and secondary prevention of thromboembolic events. However, questions persist about the risks and management of over-anticoagulation. The annual incidence of major bleeding in trials and cohort studies has been reported to be between 1.1% and 2.3% in patients treated with warfarin to achieve an international normalized ratio (INR) of 2.0 to 3.0. These rates are derived from carefully controlled studies, but in “unselected” outpatients, the risk of bleeding was found to be as high as 4.3% in patients receiving warfarin<sup>(1)</sup>.

For minor bleeding due to Vitamin K antagonists (VKA), discontinuation of anticoagulation therapy (with or without the administration of vitamin K) is sufficient to bring bleeding under control. However, for patients with major bleeding during VKA use, rapid reversal of anticoagulation is desirable, particularly if bleeding is life threatening or an urgent surgical procedure is required. Two products are suitable for increasing the concentration of vitamin K-dependent coagulation factors in these situations: fresh frozen plasma (FFP) and prothrombin complex concentrates (PCC)<sup>(2)</sup>. Both products contain coagulation factors II, VII, IX and X, which are down-regulated during VKA therapy.

PCC present several advantages over FFP, the most significant being the potential to completely reverse warfarin-induced anticoagulation in minutes, as compared with the longer periods required for the issuing of FFP from blood banks, the requirement of pre-transfusion tests, thawing and transfusion. Additional disadvantages of FFP include potential allergic reactions, transfusion-related acute lung injury (TRALI), volume overload and transfusion-transmitted diseases. For these reasons, some guidelines suggest a preferential use of PCC over FFP for warfarin reversal<sup>(3)</sup>. Although all PCC contain factors II, IX and X, there is significant variability in the factor VII content. It has been argued by some that PCC with little factor VII (the so called 3-factor PCC) produce poorer correction of the INR and should not be used for warfarin reversal<sup>(3,4)</sup>.

The aim of the present study was to review the scientific literature on employing PCC for warfarin reversal.

### Methods

A literature search was conducted utilizing Medline and the Cochrane Library, including papers published until May 3<sup>rd</sup> 2012, with the objective of identifying original articles reporting on the use of PCC for warfarin reversal. The following search strategy was used: warfarin and reversal and (“prothrombin complex concentrate” or PCC). In addition, references from these articles were searched for relevant studies addressing these questions. Inclusion criteria for entering this systematic analysis included: (1) original studies in which PCC was used in human subjects, (2) administration of PCC for the immediate reversal of warfarin anticoagulation (major bleeding and emergency surgery) and (3) articles in English.

### Results

A total of 57 articles were identified by the Medline search, of which 39 fulfilled the inclusion criteria. Fourteen reviews were excluded from the systematic review. The Cochrane Library provided no additional papers. In the end, 25 studies were evaluated, of which 20 were retrospective studies and 5 were prospective studies. Thirteen evaluated the use of PCC alone and 10 evaluated both FFP and PCC. Of the prospective studies, 2 were small randomized studies with less than 100 patients<sup>(5,6)</sup>. No large prospective randomized clinical study was found.

One of the first studies comparing the effectiveness of PCC injection and FFP infusion was a retrospective study in 41 patients who required urgent reversal of warfarin therapy due to major bleeding; this research showed that PCC was superior to FFP for INR correction<sup>(7)</sup>.

In this study, complete correction of the INR occurred within 15 minutes in 28 of 29 patients treated with PCC (50 U/kg) versus none of 12 patients given FFP. PCC was also compared to FFP in an open-label randomized trial in 40 patients undergoing urgent cardiopulmonary bypass surgery with INRs ranging from 2.1 to 7.8 at admission. Seven PCC-treated patients versus no FFP-treated patients had an INR < 1.5 fifteen minutes after treatment (p-value < 0.001). No significant difference in surgical bleeding was observed between groups, but of course the study was not powered to detect such a difference<sup>(8)</sup>.

In the context of intracranial hemorrhage in patients under warfarin therapy, PCC was evaluated in 9 studies, three of which compared PCC and FFP. In a small case series of 17 patients with intracranial hemorrhage, the mean INR decreased from 2.83 to 1.22 within 4.8 hours in PCC-treated patients compared to a decrease from 2.97 to 1.74 after 7.3 hours in patients receiving FFP (p-value < 0.001). In addition, a clinical evaluation used to assess the progression of intracranial hemorrhage suggested a better outcome in those receiving PCC compared to FFP (grade 0.2 versus 1.9 on a scale of 1-8)<sup>(9)</sup>. A small randomized study compared the use of FFP plus PCC versus FFP alone. FFP plus PCC (40-50 U/kg; n = 5) was associated with significantly greater rates and shorter times for INR correction in patients with intracranial hemorrhage as compared to FFP alone (n = 8) (p-value < 0.01)<sup>(5)</sup>. Although no difference in neurologic outcomes was observed, 5 of 8 patients treated with FFP monotherapy presented complications related to fluid overload. A case-controlled study of 12 patients with intracranial hemorrhage also found that PCC (50 U/kg) achieved a significantly more rapid and complete INR reversal compared to FFP<sup>(10)</sup>.

More recently, a single-arm prospective multinational study evaluated the use of PCC in 43 patients with an INR > 2 (median INR = 3.2) and requiring immediate anticoagulation reversal due to emergency surgery or acute bleeding. In this study, the PCC was dosed according to the INR, with doses of 25, 30 or 50 IU/kg being given to patients with INR of 2-3.9, 4-6 or > 6, respectively. After 30 minutes, all patients had an INR < 1.4, factors II, IX and X were above 75% of normal, and factor VII was around 50% of normal. Regarding safety, one possibly PCC-related fatal thromboembolic event (pulmonary embolism) occurred in a patient with metastatic gastrointestinal cancer and atrial fibrillation after a second dose of PCC<sup>(11)</sup>.

## Discussion

PCC appear to offer several advantages over FFP for the emergency reversal of anticoagulation with VKA. Despite the absence of large randomized clinical trials comparing PCC and FFP, and the lack of a demonstration that PCC improves clinically relevant and robust endpoints, available studies demonstrate that PCC provide more rapid and complete factor replacement as evaluated by laboratory endpoints. In addition, PCC offer other advantages such as lower infusion volumes, lower risks of viral transmission and TRALI, and a potentially faster issuing time. Together, these advantages led the British Committee for Standards in Hematology (BCSH)<sup>(3)</sup> and the American College of Chest Physicians (ACCP)<sup>(12)</sup> to issue recommendations favoring the use of PCC and intravenous

vitamin K for warfarin reversal in the context of major bleeding. However, one should note the significantly different strength of these recommendations (BCSH: grade 1B; ACCP: grade 2C), highlighting the relative weakness of evidence in the field.

The studies reviewed by us clearly show that PCC is capable to reverse the laboratory coagulation parameters in VKA-treated patients, with several advantages over FFP. Considering that prothrombin and factor II, VII, IX and X levels are robust surrogate markers of coagulation in these patients, it is tempting to conclude that the normalization of these parameters translates into normalization of hemostasis. However, while a normal prothrombin time (TP) is sufficient to indicate minimum hemostatic levels of vitamin-K dependent factors, it does not provide information on a potential alteration of the hemostatic balance towards a hypercoagulable state. Consequently, questions remain about the minimum and maximum doses of PCC required for anticoagulation reversal, as well as on the safety of the rapid infusion of vitamin K dependent factors in patients with an increased thrombotic risk at baseline. It thus seems fair to favor individualized doses, based on the INR and body weight, as opposed to fixed doses of PCC.

Nonetheless, based on historical reports in other patient groups, concerns about the occurrence of thromboembolic events in PCC-treated patients are still an issue<sup>(13)</sup>, highlighting the need for additional clinical data on the thromboembolic risk of PCC. In a pooled analysis of 14 studies with 460 patients, no evidence of consumptive coagulopathy could be demonstrated, but seven other thromboembolic events were reported<sup>(14)</sup>. More recently, a meta-analysis of 27 studies with 1032 VKA-treated patients that required anticoagulation reversal with PCC revealed an incidence of thromboembolic events of 1.8% (95% CI 1.0-3.0) in patients treated with 4-factor PCC, indicating a low but quantifiable risk of thromboembolism in this context<sup>(15)</sup>.

In fact, the occurrence of thromboembolic events in these patients should not be considered a surprise, given their high baseline risk and the adequate reversal of anticoagulation provided by PCC. In fact, there are no systematic evaluations of the occurrence of these events in patients treated with FFP either, but it is very likely that these complications may also occur. Furthermore, any added thromboembolic risk of PCC compared with FFP will have to be analyzed in the context of other immediate benefits such as a lower risk of volume overload and TRALI. In the end, the importance of long-term prospective clinical studies will be to demonstrate the net effect of all these variables on robust clinical outcomes or mortality. While these data are available, the use of either FFP or PCC should be reserved to patients that really require immediate anticoagulation reversal, for whom any increased thromboembolic risk are justified.

Another important limitation of the evidence in the field is the lack of demonstration of improvement in clinical outcomes. Only one study evaluated clinical outcomes in patients with intracranial hemorrhage, and found no significant differences<sup>(5)</sup>. However, this should not be regarded as a critical limitation of PCC, since no such evidence is available for FFP either.

In conclusion, several advantages favor the use of PCC over FFP for the reversal of VKA anticoagulation. It is important however to acknowledge the lack of high quality data on the

thromboembolic risk of adequate anticoagulation reversal, either with FFP or with PCC. These risks should be weighed against the clear advantages of PCC. Accumulating evidence from widespread use of these agents and long-term prospective studies should help clarify these issues.

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