



PROTHROMBIN COMPLEX CONCENTRATE IN EMERGENCY DEPARTMENT

Višnja Neseck Adam^{1,2,3} and Ingrid Bošan-Kilibarda⁴

¹Emergency Department, Clinical Hospital Sveti Duh, Zagreb, Croatia;

²Faculty of Dental Medicine and Health, Osijek, Croatia;

³Libertas Interantional University, Zagreb, Croatia;

⁴Croatian Institute for Emergency Medicine, Croatia

SUMMARY – Coagulation abnormalities are common in bleeding or critically ill patient and hemostatic management remains a major challenge for the emergency physician. Management of bleeding patients consists of bleeding control, restoration of blood volume, and correction of any associated coagulopathy. Traditionally, the fresh frozen plasma (FFP) is used for correction of coagulopathy to manage and prevent bleeding, but today Prothrombin complex concentrates (PCCs) offer an attractive alternative because they offers a number of advantages over FFP, including lower infusion volume, rapid INR normalization, faster availability, lack of blood group specificity, and better safety profile. The aim of the present review is to provide an short overview about using PCC, their indication, efficacy and safety in different bleeding setting's.

Key words: *bleeding, emergency department, prothrombin complex concentrates*

Introduction

Although, fresh frozen plasma (FFP) contains all clotting factors at physiological concentrations and traditionally has been the blood component therapy of choice for the prevention and treatment of bleeding, today we have several different plasma products. These products include single coagulation factor concentrates, such as factor VIII concentrates for the treatment of hemophilia A and factor IX concentrate for the treatment of hemophilia B and prothrombin complex concentrates (PCCs). PCCs are human plasma protein concentrates that contain four vitamin K-dependent coagulation factors, factors II, VII, IX and X and therapeutically effective concentrations of thrombo inhibitors (proteins C and S). PCCs are indicated for the urgent reversal of acquired coagulation factor deficiency from warfarin-induced anticoagulation and

can be used as an alternative to fresh frozen plasma (FFP) for emergency bleeding in patients who are not taking anticoagulants.

In this review, we will discuss PCCs and their indications and safety, focusing on use and effectiveness in an emergency department.

Prothrombin complex concentrates

Prothrombin complex concentrates were originally developed as a source of factor IX (FIX) for the treatment of hemophilia B¹, but in the 1990s, with the availability of high-purity plasma-derived recombinant Factor IX, PCCs are now rarely used in this indication. They come from the cryoprecipitate supernatant of large plasma pools after the removal of anti-thrombin and factor X². Since the 1960s, different PCC products have been available, but today prothrombin complex concentrates contain either three-factor (i.e., factors II, IX and X) or four-factor (i.e., factors II, VII, IX and X) vitamin K-dependent coagulation factors in a concentration about 25 times higher

Corresponding author: *Professor Višnja Neseck Adam MD, PhD*, University Department of Anesthesiology, Resuscitation and Intensive Care, Clinical Hospital Sveti Duh, Zagreb, Croatia, Sveti Duh 64
E-mail: visnja.neseck@hotmail.com

than in normal plasma³ and are standardized regarding their factor IX content. Due to the high concentration of coagulation factors and the prevention of their activation, most PCCs contain heparin. The half-life of coagulation factors is different. The half-life of factor II is 60–70 hours, which is much longer than other factors (6–24 hours). Factor VII has the shortest half-life, only 6 hours³. As a consequence, repeated dosing will lead to an accumulation of factors II and X and increase the risk of thrombotic complication.

PCCs are lyophilized and can be stored at room temperature for several years, allowing administration without warming.

Clinical indication

As mentioned before, PCCs were originally used to treat and prevent bleeding in patients with hemophilia B, but today they are most commonly used for rapid reversal of warfarin anticoagulation⁴, although there is increasing interest in using it to treat other forms of abnormal coagulation. Urgent reversal of acquired coagulation factor deficiency induced by warfarin-induced anticoagulation in patients presenting with major acute bleeding (intracerebral hemorrhage-ICH) or a need for an urgent invasive surgery or procedure⁵ was approved in the United States in 2013 and is the only FDA approved indication for PCCs.

However, off-label use of PCCs occurring in nearly 40%⁶, mostly for the reversal direct oral anticoagulants (DOAC) induced coagulopathy, treatment or prophylaxis of bleeding in congenital deficiency of any vitamin K-dependent coagulation factors, pre-operative to decrease bleeding in patients not taking oral anticoagulants or in a trauma setting with massive transfusions⁵.

Reversal of anticoagulants

Reversal of vitamin K antagonist

For many years, the vitamin K antagonist (VKA), warfarin has been the cornerstone for thrombosis prevention and treatment. The efficacy of warfarin for prevention and treatment of thrombosis has been studied in a number of clinical studies, but bleeding, particularly in the setting of over-anticoagulation, is still a major concern. The reported incidence of bleed-

ing during therapy with VKAs is highly variable in published studies. The overall incidence of bleeding in anticoagulated patients during long-term VKA therapy is about 10%–17% per year, 2%–5% for major bleeding and 0.5%–1% for fatal bleeding⁷. Previously, FFP and vitamin K were the only options for reversing anticoagulation, but today PCCs offer several advantages over FFP. These advantages include more rapid INR normalization, lower infusion volume (a large volume of FFP is needed to reverse coagulopathy caused by vitamin K antagonism; 10 mL/kg–20 mL/kg), significantly higher amounts of the clotting factors compared to FFP (one dose of a PCC equals 8 to 16 units of FFP)⁵, a lack of blood group specificity, a lower risk of viral transmission, since they undergo viral inactivation, and a better safety profile.

It is very important to point out that both FFP and PCCs need coadministration of vitamin K for warfarin reversal. The half-life of vitamin VII is only 6 to 8 hours, whereas warfarin has a half-life of several days. Although vitamin K is not a direct hemostatic agent, it is a cofactor for the activation of factors II, VII, IX, X, and the anticoagulant proteins C and S⁸. Administrations of vitamin K counteract the long half-life of warfarin. The usual dose is from 5 to 10 mg.

A meta-analysis of 13 studies comparing the use of PCCs and FFP for warfarin reversal showed that PCCs were associated with a significant reduction in all-cause mortality, more rapid INR reduction, (INR, odds ratio [OR] 10.80; 95% confidence interval [CI], 6.12–19.07) and the time to correction was shorter (mean difference – 6.50 h; 95% CI, –9.75 to –3.24), less volume overload (OR 0.27, 95 % CI; 0.13–0.58) and without an increased risk of thromboembolic events⁹. The 17 studies with a total of 2606 participants also showed that PCCs were more effective than FFP in all-cause 90-day mortality and INR reduction with a lower risk of adverse events¹⁰. A meta-analysis by Brekelman et al. showed that the INR within 1 h after PCC administration ranged from 1.4 to 1.9, and after FFP administration from 2.2 to 12 which means that PCC significantly reduced the time to reach INR correction in comparison with FFP¹¹.

The most seriously complication in patients taking oral warfarin is intracranial hemorrhage with still very high mortality. A prospective, observational study showed that PCC adequately corrected INR without any increase in adverse events compared to FFP and

was associated with less major hemorrhage and improved 3-month outcomes in patients with warfarin-associated intracranial hemorrhage¹².

American Heart Association guidelines from do 2010 not recommend any specific reversal protocol for warfarin-associated intraparenchymal hemorrhage¹³ and state that "PCCs have not shown improved outcome compared with FFP but may have fewer complications compared with FFP and are reasonable to consider as an alternative to FFP" (Class IIa, Level B evidence)¹³. However, guidelines from do 2015 state that „PCCs may have fewer complications and the INR more rapidly than FFP and might be considered over FFP (Class IIb; Level of Evidence B)¹⁴. The new recommendation is based on results from phase 3 randomized controlled trial performed on 202 patients with acute bleeding (24 of whom had intracranial hemorrhage)¹⁵. The study showed that PCC is an effective alternative to FFP for urgent reversal of vitamin K antagonist therapy in major bleeding. Rapid INR reduction was achieved in 62.2% of patients receiving PCC versus 9.6% receiving FFP¹⁵.

Reversal of direct oral anticoagulants (DOACs)

Today, direct oral anticoagulants (DOACs) are the treatment of choice to prevent thromboembolic events because of their better overall risk–benefit profile, more predictable pharmacokinetics and pharmacodynamics and fewer interactions with other medications and food, compared to VKA. Their main disadvantage is currently the absence of a specific reversal agent and the fear of bleeding. Although, patients receiving therapy with DOACs have a lower risk of bleeding compared to VKA therapy, they also may present with serious bleeding or a need for unexpected emergency surgery or procedures¹⁶. Because of their very short half-lives compared to warfarin, most episodes of non-life-threatening bleeding can be managed with supportive measures, such as temporarily withholding drugs, blood product transfusions, etc. However, in a life-threatening bleed, and in patients with intracranial bleeding, additional strategies may be required. At present, the treatment of DOAC-associated hemorrhaging is limited. A specific reversal agent for dabigatran, idarucizumab, was approved by the US Food and Drug Administration (FDA) in 2015. In May 2018, andexanet alfa, the antidote for factor Xa (FXa) inhibitors, was also approved by the FDA to reverse

apixaban and rivaroxaban in patients with life-threatening or uncontrolled bleeding¹⁷. However, these specific antidotes, particularly andexanet alfa, are very expensive and not widely available.

The recommendation for managing bleeding patients on DOACs was based on limited evidence^{18–22}. Several nonspecific therapeutic strategies have been developed as potential DOAC reversal agents. Treatment options include nonspecific agents, such as fresh frozen plasma, PCCs, recombinant activated factor VII, and antifibrinolytic agents. Evidence regarding the use of PCCs as a potential therapeutic option is increasing.

Data primarily from small case or cohort studies with PCCs in bleeding patients has suggested that PCCs are safe and efficacious in the management of Xa inhibitor bleeding.

The French Working Group on Perioperative Hemostasis (GIHP) in a prospective, cohort registry study of 732 patients treated with direct oral anticoagulants and hospitalized for severe bleeding showed that hemostasis was totally or partially achieved in 44% with 4F-PCCs and 37% with activated PCCs of those who received these agents²³. The UPRATE study, which included two cohorts, one in Sweden²⁴ and one in Canada²⁵ also, found that the use of PCCs for the management of major bleeding in patients on rivaroxaban or apixaban is an effective strategy and supports the use of PCCs for the reversal of activated factor X inhibitors in bleeding patients. PCCs were effective in 69% of patients in the Sweden cohort and 68% in the Canada cohort.

Because specific reversal agents for DOACs are not widely available PCCs, in cases without access to these specific agents, and in situations where the anticoagulant agent is unknown, remain the cornerstones of therapy in patients with DOAC-associated bleeding.

Prothrombin complex concentrate in trauma patients

A resuscitation strategy in trauma bleeding patients have a common aim: to stop bleeding, reestablish hemostasis, restore normal perfusion pressure and prevent acute traumatic coagulopathy (ATC), and improve the outcome of severely injured patients requiring massive blood transfusion²⁶.

Although there is no high-quality study to evaluate the use of PCCs in trauma patients, guidelines in both

trauma and operative settings support the administration of PCCs in bleeding patients to reverse coagulopathy^{27,28}. Several small studies have shown that coagulopathy in trauma patients can be effectively reversed with PCCs and also showed decreased blood product consumption^{29,30}. PCCs increase thrombin generation and may potentially be effective in facilitating hemostasis. A recent meta-analysis that included 17 studies reported similar findings. A resuscitation strategy using both PCCs and FFP transfusion was associated with reduced mortality when compared to a resuscitation strategy involving solely FFP. Also, PCCs reduced the need for RBC transfusions when compared with treatment strategies not involving PCCs³¹. According to recent evidence and discussions on the potential therapeutic role of PCCs in trauma bleeding patients, PCCs may be a good option in the management of hemodynamically unstable trauma patients. But it is important to point out that PCCs do not contain factor V and may not be sufficient as a single agent in traumatic cases requiring massive transfusions⁵.

Conclusion

Data from the literature indicates that PCCs are the therapy of choice for rapid reversal of vitamin K antagonist anticoagulation, and also in situations requiring rapid reversal of anticoagulation by non-vitamin K antagonist, making PCCs a general antidote for oral anticoagulation. For trauma patients the use of PCCs can reduce transfusion requirements and the severity of hemostatic abnormalities, with more rapid restoration of hemostasis.

It has also been shown that not only do PCCs replace deficient clotting factors more rapidly than FFP, but they also minimize the risk of fluid overload and risk of viral transmission. PCC treatment can be the therapy of choice in an emergency anticoagulant reversal setting and can be safely used for rapid hemorrhage control.

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Sažetak

KONCENTRAT PROTROMBINSKOG KOMPLEKSA
U HITNOJ MEDICINSKOJ SLUŽBI*V. Nesek Adam i I. Bošan-Kilibarda*

Poremećaji koagulaciji česti su u kritičnih bolesnika i u bolesnika s krvarenjem, te predstavljaju veliki izazov za sve liječnike koji su uključeni u rad hitne medicinske službe. Liječenje bolesnika s krvarenjem uključuje kontrolu krvarenja, nadoknadu volumena krvi i korekciju koagulopatije. Tradicionalno, za korekciju koagulopatije i sprječavanje krvarenja najčešće se koristi svježe smrznuta plazma (SSP), no danas se kao alternativa sve češće koristi koncentrat protrombinskog kompleksa (engl. prothrombin complex concentrates - PCC) zbog brojnih prednosti u odnosu na SSP, a koje uključuju primjenu manjeg volumena, bržu korekciju INR-a, bržu dostupnost, bolji sigurnosni profil, a također nije potrebna ni krvno grupna specifičnost. Cilj ovog rada je pružiti kratki pregled o osnovnim indikacijama, sigurnosti i učinkovitosti primjene PCC u stanjima krvarenja različite etiologije.

Ključne riječi: *Krvarenja, hitna medicinska služba, koncentrat protrombinskog kompleksa.*