

Prothrombin Complex Concentrates for Warfarin-Related Intracranial Hemorrhage: Should they Replace Fresh Frozen Plasma?

Farid Sadaka*

Mercy Hospital St Louis/St Louis University, Critical Care Medicine/Neurocritical Care, suite 4006B, St Louis, USA

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Intracranial hemorrhage (ICH) is a medical emergency. Rapid diagnosis and management of patients with ICH is important because rapid deterioration is common in the first few hours after ICH onset. Patients undergoing treatment with oral anticoagulants, mainly warfarin, constitute 12% to 14% of patients with ICH [1,2]. Patients with warfarin-related ICH have a high mortality rate close to 60%, compared to about 40% for nonanticoagulated patients with ICH [3,4]. The poor outcome in warfarin-related ICH is mainly related to volume of hemorrhage and expansion of the hematoma size after admission [2,5]. In addition, early expansion of the hematoma occurs more frequently in anticoagulated (54%) versus nonanticoagulated (16%) patients with ICH [6]. A major predictor of mortality and worse outcome is higher initial international normalized ratio (INR). The general recommendation is thus to correct the INR as rapidly as possible [7]. Vitamin K and fresh-frozen plasma (FFP) have historically been recommended, but recently, prothrombin complex concentrates (PCCs) have emerged as potential therapies.

PCCs are concentrates of the vitamin K-dependent factors II, VII, IX, and X, as well as proteins C and S. PCCs are available with low amounts of factor VII (three factor PCCs, used mainly in the United States) and higher concentrations of factor VII (four-factor PCCs, commonly used in Europe). PCCs have the advantages of rapid reconstitution with high concentrations of coagulation factors in small volumes. PCCs are stored as a lyophilized powder and can be reconstituted in a small volume of sterile water in minutes. The volume of FFP per unit is about 250 ml, thereby; the necessary volume of FFP to correct coagulopathy may exceed 2l depending on the initial INR. The advantages of PCC over FFP include less volume overload, less infectious complications, no Transfusion-related Acute Lung Injury (TRALI), and more rapid administration. However, the main side effect of PCCs is thromboembolic complications, especially since patients with warfarin-related ICH are usually predisposed to thromboembolism due to the underlying medical condition which indicated warfarin therapy such as venous thromboembolism, atrial fibrillation or ischemic stroke. Thromboembolic complications may include ischemic stroke, deep vein thrombosis, pulmonary embolism, myocardial infarction, and disseminated intravascular coagulation (DIC) [8-10]. However, the risk of thromboembolism appears to be low [11,12].

It is usually unnecessary to give adjunctive FFP along with PCC, however, some recommend adding FFP to the three-factor PCC. A study found that the lack of factor VII in some PCC formulations attenuated the ability to reverse the INR [13]. Another recent study showed that reversal of coagulopathy in warfarin-related ICH with three-factor PCC was incomplete and associated with serious adverse events, particularly pulmonary embolism [14]. In another study, the amount of PCC required to correct the INR to the "appropriate level" was not significantly higher in PCC only patients versus the adjunctive FFP group [15]. Studies on PCC in warfarin-related ICH show that PCCs consistently reversed the INR. There is evidence that PCCs may

reverse the INR more rapidly compared to FFPs (particularly the four-factor PCCs) [12].

Guidelines on warfarin reversal in life-threatening hemorrhages remain variable, but more are inclined towards PCC. The Australasian Society of Thrombosis and Hemostasis recommends using PCC in combination with FFP and vitamin K for any "clinically significant bleeding" [16]. The reason for this recommendation is the specific PCC product available in Australia, which is relatively deficient in factor VII. The British Committee for Standards of Hematology, on the other hand, recommends that all hospitals managing patients on warfarin should stock a licensed four-factor PCC (1C), that emergency anticoagulation reversal in patients with major bleeding should be with 25-50 u/kg four-factor PCC and 5 mg intravenous vitamin K (1B), and that FFP produces suboptimal anticoagulation reversal and should only be used if PCC is not available (1C) [17]. The American College of Chest Physicians recommends rapid reversal of anticoagulation with four-factor PCC rather than with plasma (2C), with the additional use of vitamin K 5 to 10 mg administered by slow IV injection rather than reversal with coagulation factors alone (2C) [7]. The American Heart Association/American Stroke association vaguely recommends that patients with ICH whose INR is elevated due to oral anticoagulants should have their warfarin withheld, receive therapy to replace vitamin K-dependent factors and correct the INR, and receive intravenous vitamin K (Class I; Level of Evidence: C). They also 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 of Evidence: B) [18].

In conclusion, albeit variable, the most recent national guidelines recommend the use of four-factor PCCs in addition to Vitamin K for rapid management of warfarin-related ICH, with FFPs as a backup in circumstances where PCCs are not available. However, more prospective randomized controlled studies are needed before definite recommendations can be made.

Conflicts of Interest

The author reports no conflicts of interest.

The author declares that No competing financial interests exist.

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***Corresponding author:** Farid Sadaka, MD, Mercy Hospital St Louis/St Louis University, Critical Care Medicine/Neurocritical Care, 621 S. New Ballas Rd, Suite 4006B, St Louis, MO 63141, USA, Tel: 314-251-6486; Fax: 314-251-4155; E-mail: farid.sadaka@mercy.net

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