Prothrombin Complex Concentrates: An Alternative to Fresh Frozen Plasma

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abstract

Insufficiency fractures are a common cause of morbidity among geriatric patients worldwide. Improved outcomes are known to result from decreased delay to definitive operative fixation and mobilization. Use of warfarin is an important potential cause of delay. The ideal mode of warfarin reversal is currently unknown. Prothrombin complex concentrates (PCCs) offer rapid correction with small infusion volume, both of which are important for elderly patients with multiple comorbidities. The authors present 2 cases of insufficiency fractures occurring in geriatric patients receiving warfarin therapy reversed with a 3-factor PCC. Both patients were independent, community ambulators without significant functional disability and returned to their prior level of functioning. There were no significant bleeding or venous thromboembolic complications. To the authors’ knowledge, no previous reports have described the use of PCC in geriatric patients with fractures. Nonetheless, its potential is well documented in emergency and trauma surgery literature. The use of PCC could potentially allow surgeons and hospitals to avoid complications related to immobility and the associated costs of treatment, extended hospital stay, and readmission. The authors’ limited experience suggests 3-factor PCC preparations may provide adequate correction to allow expeditious surgical treatment. [Orthopedics. 2017; 40(2):e367-e369.]

Oral anticoagulant medications may be one source of treatment delay for elderly patients who sustain fragility fractures. In one series of 2660 patients who underwent hip fracture surgery, early surgery was prevented in 7.8% because of an elevated international normalized ratio (INR).1 Disadvantages of vitamin K and/or fresh frozen plasma use include time needed for preparation, administration of a large volume of fluids, allergic reaction, and risk for disease transmission.

Prothrombin complex concentrates (PCCs) are a pooled plasma product containing varying concentrations of factors II, IX, X, and, in 4-factor preparations, VII.2 Clotting factors are isolated and lyophilized for rapid reconstitution and administration.3 Advantages of PCC include rapid reversal of coagulopathy, low risk of viral transmission, low risk of allergic reaction, decreased total volume of infusion, and straightforward, weight-based dosing.

The authors present 2 cases of insufficiency fractures occurring in geriatric patients receiving warfarin therapy. The patients had no personal or family history of venous thromboembolism or hypercoagulability. They were offered PCC because the time needed to prepare and transfuse fresh frozen plasma would postpone surgery unnecessarily or because medical comorbidities prevented infusion of large volumes of fresh frozen plasma.

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**Case Reports**

**Patient 1**

A 72-year-old man with a past medical history of diabetes mellitus, hypertension, peripheral vascular disease, asthma, chronic kidney disease (stage 3), obstructive sleep apnea, obesity (weight, 158.8 kg; height, 169.4 cm; body mass index, 41.6 kg/m²), and atrial fibrillation requiring anticoagulation with warfarin presented to the authors’ institution following a mechanical fall while carrying groceries into his mobile home. On examination, he had chronic venous stasis ulcers and pitting edema to the level of the knees of the bilateral lower extremities. The right lower extremity was maintained in a shortened and externally rotated posture. Radiographs confirmed diagnosis of a displaced femoral neck fracture. Laboratory analysis revealed an INR of 2.2. Warfarin reversal was obtained using 2000 IU of 3-factor PCC (Profilnine SD; Grifols Biologicals Inc, Los Angeles, California) reconstituted in 20 mL of diluent and administered 10 minutes prior to surgical intervention; the volume of fresh frozen plasma required to obtain adequate correction was deemed excessive. No additional preoperative INR value was obtained because PCC has been used for warfarin reversal in the authors’ institution since 2008 and its effects were well-known.

The patient underwent successful open reduction and internal fixation of the proximal humerus fracture via a deltopectoral approach 17 hours and 56 minutes after admission. Preoperative, postoperative day 1, postoperative day 2, and postoperative day 3 hemoglobin concentrations were 13.4 g/dL, 13.6 g/dL, 13.5 g/dL, and 13.6 g/dL, respectively. There was no interruption to his daily warfarin regimen. He was deemed medically fit for discharge on postoperative day 2; however, this was delayed because of issues obtaining insurance authorization. The patient did not experience wound complications or venous thromboembolism.

**Patient 2**

A 72-year-old man with a history of mechanical aortic valve replacement necessitating warfarin use sustained a ground-level fall while exercising. On presentation, he reported left shoulder pain. Radiographs led to a diagnosis of a 4-part proximal humerus fracture. International normalized ratio on presentation was 2.4, which corrected to 1.4 one hour following administration of 2500 IU of 3-factor PCC reconstituted in 25 mL of diluent.

He underwent successful open reduction and internal fixation of the proximal humerus fracture via a deltopectoral approach late in the afternoon on hospital day 2 and use of PCC provided rapid INR correction, whereas fresh frozen plasma administration would have led to an additional day of delay. Prothrombin complex concentrates provide rapid and reliable reversal of the anticoagulant effects of warfarin. The agent used above can be reconstituted in volumes as low as 5 mL, depending on dose. In comparison, weight-based dosing of plasma products requires 10 to 20 mL/kg. Half-lives of the contained factors vary and this should be considered before multiple dosing. Brushing an additional source of coagulopathy, the correction will last indefinitely provided no additional anticoagulant is administered. For patient 1, his cardiac status and size prevented weight-based plasma dosing, which is protocol at the authors’ institution. Prothrombin complex concentrate was selected to provide correction and avoid large-volume plasma infusion. For patient 2, preoperative cardiac testing prevented earlier surgery. Testing was completed late in the afternoon on hospital day 2 and use of PCC provided rapid INR correction, whereas fresh frozen plasma administration would have led to an additional day of delay.

Many authors have studied vitamin K and/or fresh frozen plasma for the reversal of acquired coagulopathy. However, these agents require time to prepare and administer and may not provide immediate reversal. In comparison, PCCs allow for rapid and predictable INR correction. Some authors have suggested that in cases where urgent reversal of acquired coagulopathy is required, fresh frozen plasma and/or vitamin K may fail to fully and rapidly correct INR when compared with PCC.
Prothrombin complex concentrates are not a panacea. Several studies have suggested an increased risk of venous thromboembolism following administration of PCC when used to treat major bleeding.\textsuperscript{11-13} These events are likely explained by ongoing cessation of anticoagulant therapy rather than PCC administration. In their review of the literature, Leissinger et al.\textsuperscript{14} found 14 studies including 460 patients who received PCC therapy, but only 7 thrombotic complications were observed. Furthermore, a recent randomized controlled trial comparing PCC and plasma for the reversal of vitamin K antagonists showed similar rates of thromboembolic events and deaths.\textsuperscript{15} Nonetheless, surgeons should exercise caution because the rate of venous thromboembolism for patients who undergo fracture surgery after receiving PCC is unknown. Other potential risks include disseminated intravascular coagulation, cerebrovascular accident, myocardial infarction, and mesenteric ischemia.

**CONCLUSION**

To the authors’ knowledge, no prospective study comparing the efficacy of PCC with that of conventional methods of coagulopathy correction for patients with fractures has been performed to date. However, the utility of PCC in emergency and trauma situations is known.\textsuperscript{10,11} The authors’ limited experience suggests 3-factor formulations of PCC are useful for geriatric patients with fractures taking warfarin. It may be considered for use in patients with comorbidities that prevent large-volume plasma transfusion or if delay to definitive surgical fixation can be significantly reduced. Costs of PCC therapy vary by institution. At the authors’ institution, the cost of PCC use is equivalent to that of plasma and associated compatibility testing if greater than 2 U will be required. Additional prospective, randomized trials are necessary to determine the efficacy, cost, and safety of PCC.

**REFERENCES**