

Efficacy of Prothrombin Complex Concentrates for Oral Anticoagulant Therapy-related Major Hemorrhage

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Abstract

In patients admitted to accident and emergency departments for anticoagulant use-related major hemorrhage and requiring urgent surgery or life-saving invasive intervention, the international normalized ratio (INR) value should be rapidly corrected and bleeding should be controlled. With prothrombin complex concentrate (PCC), when used at optimal dose levels, target INR values are achieved within 15 min. In this study, we aimed to discuss the efficacy of the used four-factor PCC in 10 patients who were admitted to the accident and emergency department because of oral anticoagulant use-related major bleeding. Of all the patients to whom PCC treatment was administered, targeted INR levels could not be attained in 2 patients (20%). For our cases with gastrointestinal bleeding, the average baseline INR value was 7.3, while the average INR value after PCC administration was 1.9. For our subdural hematoma cases, the median baseline INR value was 2.5, while the median INR value after PCC administration was 1.3. We believe that PCCs used in eligible patient groups, as in this case series, may provide the desired results at lower doses and that they may be safer with regard to complications. (*JAEM 2015; 14: 37-40*)

Key words: Prothrombin complex concentrates, oral anticoagulant, major hemorrhage

Introduction

Patients with major hemorrhage because of anticoagulant usage admitted to accident and emergency departments require urgent surgery or life-saving invasive intervention. The international normalized ratio (INR) value should be rapidly corrected and bleeding should be controlled. Although fresh frozen plasma (FFP) and vitamin K treatments are successful for the reversal of the effects of oral anticoagulants, long administration durations of these treatments have serious disadvantages. With prothrombin complex concentrates (PCCs), when used at optimal dose levels, target INR values are achieved within 15 min. Further, ease of use and adverse effects fewer than FFP make PCC superior compared with other treatment methods (1).

Oral anticoagulants act by inhibiting vitamin K-dependent coagulation factors. Severe bleedings in organs and tissues are the most severe adverse effects that may develop in patients during this

treatment. Bleeding risk is generally associated with the duration and dosage of the treatment (2).

Vitamin K is recommended to patients who develop coagulopathy related to oral anticoagulant usage and, in the case of major bleeding, FFP treatment is recommended in addition to vitamin K (3).

Prothrombin complex concentrates are used for the reversal of the anticoagulant effect of vitamin K antagonists (4). PCCs contain clotting Factor II, Factor IX, Factor X, varying amounts of Factor VII, and natural anticoagulant protein C and protein (5, 6). Many studies demonstrating the efficacy of PCCs have been reported (7-13).

In order to admit the patient for surgery, INR levels should be corrected at the earliest. In the emergency treatment of these patients, PCC, FFP, and vitamin K are used in order to replace the reduced factor levels and to correct INR values (14).

In this study, we aimed to discuss the efficacy of the four-factor PCC (Cofact®) that we used in 10 patients who were admitted to the accident and emergency department because of oral anticoagulant use-related major bleeding.

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Received: 31.10.2013 **Accepted:** 05.08.2014

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DOI: 10.5152/jaem.2015.37928



Table 1. Data of the patients to whom PCC was administered

| Case Nr: | Age | Gender M, F | Body weight (kg) | Indication oral anticoagulant use | Baseline INR value | INR value after 15 minutes | Indication for PCC use | PCC (Cofact®) dose | Result |
|----------|-----|-------------|------------------|-----------------------------------|--------------------|----------------------------|------------------------|--------------------|---|
| 1 | 71 | M | 75 | MVR | ≥10* | 2.1 | GIS hemorrhage | 10 IU/kg | Discharged after endoscopy |
| 2 | 63 | M | 82 | AF | ≥10* | 1.8 | GIS hemorrhage | 10 IU/kg | Discharged after endoscopy |
| 3 | 79 | F | 70 | AF | 4 | 2.1 | GIS hemorrhage | 10 IU/kg | Discharged after endoscopy |
| 4 | 75 | F | 72 | AF | 7.6 | 1.5 | GIS hemorrhage | 10 IU/kg | Discharged after endoscopy |
| 5 | 52 | F | 75 | AF | 4.9 | 1.8 | GIS hemorrhage | 10 IU/kg | Discharged after endoscopy |
| 6 | 85 | F | 68 | AF | 2.4 | 1.3 | Subdural hematoma | 10 IU/kg | EX on the 148 th postoperative day |
| 7 | 58 | F | 70 | MVR | 4.3 | 1.5 | Subdural hematoma | 15 IU/kg | EX on the 8 th postoperative day |
| 8 | 89 | M | 78 | AF | 2.1 | 1.3 | Subdural hematoma | 10 IU/kg | EX on the 15 th postoperative day |
| 9 | 56 | F | 83 | AF | 2.3 | 1.2 | Subdural hematoma | 10 IU/kg | Discharged on the 6 th postoperative day |
| 10 | 63 | F | 74 | AF | 1.6 | 1.4 | Subdural hematoma | 10 IU/kg | Discharged on the 8 th postoperative day |

*The value is too high to read. PCC: prothrombin complex concentrate; INR: international normalized ration; GIS: gastrointestinal system; M: male; F: female; MVR: mitral valve replacement; AF: atrial fibrillation; EX: died

Case Presentation

A total of 10 patients required urgent intervention, and for these patients, we preferred to use PCC after obtaining informed consent. Of these, 5 patients were admitted because of anticoagulant use-related acute subdural bleeding and the other 5 patients were admitted because of anticoagulant use-related gastrointestinal (GIS) bleeding. Our target was to achieve INR values below 1.5 for all five of the acute subdural patients who required surgery, and INR values below 2.1 for the rest of the five patients with GIS bleeding who required minor surgery or invasive intervention (1).

The mean age of the patients was 69 years with a range of 56-89 years. Three of the patients were male (30%) and 7 were female (70%).

Of all the patients to whom PCC treatment was administered, targeted INR levels could not be achieved in 2 patients (20%). These two patients were on anticoagulation therapy because of mitral valve replacement, while the other 8 patients with targeted INR levels were treated with oral anticoagulants because of atrial fibrillation (AF). Further, 10 mg vitamin K was intravenously administered to all patients. The average baseline INR value was 7.3 in patients with GIS bleeding before treatment, while it was 1.9 after PCC administration. The mean baseline INR value was 2.5 in patients with subdural hematoma, while it was 1.3 after PCC administration. With these targeted INR values, the patients underwent urgent intervention within the first hour of their arrival, without any waste of time. Three patients died due to sepsis on the 8th, 15th and 148th days of hospitalization. In our study, although half of the recommended doses for Cofact® were used, targeted INR levels could be reached (Table 1).

Discussion

Because of the long administration time and low concentrations of coagulation factors according to PCC, FFP is not a good treatment method for achieving fast reversals in such cases. This long adminis-

tration duration is an essential disadvantage and not in favor of the patient in case of life-threatening bleedings. Furthermore, using single doses of FFP, INR may rarely be corrected to the target level. FFP should be thawed, and its infusion takes a long time. Its other disadvantages include that it may cause blood borne infections because virus inactivation or virus reduction processes are not included in the manufacturing, allergic reactions, and volume overload (8).

PCCs are available as lyophilized solution and do not require blood group compatibility. They contain high concentrations of several factors and provide a rapid onset of intervention, even in small volumes. The peak plasma levels are attained 10 min after the infusion (14).

In an experimental study, PCCs were found to be superior to FFP in many aspects (9). However, no difference in efficiency was observed in a 46-patient study comparing FFP and PCCs for clinical efficiency (10).

There are numerous PCC available worldwide, which have been released as different combinations containing various factors in varying proportions and are licenced under trade names, such as Bebulin®, Beriplex®, Cofact®, and Kaskadil® etc. The PCC (Cofact®) we used in our cases contain 14-35 IU/mL of FII, 7-20 IU/mL of FVII, 25 IU/mL of FIX, 14-35 IU/mL of FX, 11-39 IU/mL protein C, 1-8 IU/mL protein S, and <0.6 IU/mL of antithrombin-III (1). Half-lives of the factors are 40-60 h, 4-6 h, 18-25 h, 30-60 h for Factor II, Factor VII, Factor IX, and Factor X, respectively.

It has been stated that "while PCC are relatively safe, there is no complete absence of risk, and it was recommended to limit concentrates to the patients with severe, life-threatening hemorrhage that requires urgent surgical intervention" (12). Thromboembolic complications associated with the use of PCC have been reported. These include venous thromboembolism (deep vein thrombosis or pulmonary thromboembolism), myocardial infarction, ischemic stroke, and disseminated intravascular coagulopathy (13, 15). The results of the meta-analysis study covering a total of 27 studies and 1,032 patients determined the average incidence of thromboembolic events

as 1.4% and suggested a low but significant presence of thromboembolic risk (11). Another reason for thrombogenicity is the use of heparin-containing PCCs in patients with heparin-induced thrombocytopenia. Moreover, repeated-dose administrations increase the risk of thromboembolic events (16, 17). In a 160-patient study evaluating the risk of thromboembolism, this adverse effect was observed in 6 (3.8%) patients (95% CI, 1.4%-8%); 3 cases of stroke, 1 case of acute myocardial infarction, 1 case of splenic infarction, and 1 case of deep vein thrombosis were observed (18). In our study, non-heparin containing PCC was used, and repeated-dose administrations were not necessary, and none of our patients developed thromboembolic event.

Nowadays, acute subdural hematoma is one of the fatal intracranial bleedings despite the presence of efficient emergency room services, common use of cranial computed tomography, and fast intracranial pressure monitoring and treatment. Early diagnosis and intervention is essential and life-saving. Moreover, early surgical intervention has been reported to reduce the mortality and morbidity rates, particularly when performed within the first 4 h. In a study, the mortality rate for acute subdural hematoma was reported as 50%-90%, while the rate for functional improvement was reported as approximately 30% (19). There are studies suggesting that warfarin-related major bleeding complications occur most frequently in intracranial area (2). In acute subdural hematoma patients with coagulopathy (INR >1.2), mortality rates are higher than those in patients without coagulopathy; the underlying reasons cannot be clearly explained. However, rapid increase in the hematoma diameter, mass effect, increased intracranial pressure are considered as factors (20). Using PCC in the emergency room, surgery could be performed in all of our cases with subdural hematoma within the first 1 h without delay. In our study, mortality rates were 30% for all the patients, and 60% for the patients who underwent surgery because of acute subdural hematoma. However, these three patients died after a long period of hospitalization and because of sepsis from hospital-borne infection in the intensive care unit. Therefore, we believe that the mortality rates found in our study would not be a measure for the success of the PCC treatment, and the fatalities were not related to PCC treatment.

Based on the results of a 57-patient study, wherein PCCs were used for intracranial hemorrhages (22 patients with intracranial hemorrhage, 13 patients with subdural hematoma, 2 patients with subarachnoid bleeding), the superiority of PCCs over FFP has been demonstrated. In this study, the mean INR value dropped back to 1.4 from 11.7 1 h after 25-50 IU/kg PCC infusion. Only two of 58 patients had an INR >2.0. None of the patients requiring surgical intervention were noted to have excessive bleeding. Four patients developed PCC-related complications (catheter-associated DVT in 1 patient, recurrent DVT in 1 patient, and myocardial infarction without ST elevation in 2 patients) (21).

In our cases, same efficiency was obtained at lower PCC doses than those previously reported, and none of them showed thromboembolic complication. The patients were rescued from coagulopathy disadvantage by reaching the desired INR levels in a short period of time, such as 15 min, and the necessary interventions were quickly provided.

Our study did not comprise many cases and different clinical situations. It would be better to demonstrate the low dose of PCC treatment with a more patients and in different clinical situations; however, this study described a low dose PCC treatment.

Conclusion

We believe that PCCs used in eligible patient groups, as in this case series, may also provide the desired results at lower doses and that they may be safer with regard to complications. More extensive studies determining the most optimal doses of PCCs are required. Moreover, using PCCs more common in emergency patients, a reduction in complications risks and lowering treatment costs would be possible.

Informed Consent: Written informed consent was obtained from patients who participated in this case.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - U.Y.Ç., S.Y.; Design - U.Y.Ç.; Supervision - U.Y.Ç., S.Y.; Materials - S.Y., A.Y.; Data Collection and/or Processing - S.Y., A.Y.; Analysis and/or Interpretation - U.Y.Ç., E.S.; Literature Review - S.Y., E.S.; Writer - U.Y.Ç., S.Y.; Critical Review - U.Y.Ç., E.S.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

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