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Original Article

Prothrombin complex concentrates utility for warfarin-associated hemorrhage

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Abstract: Introduction: Prothrombin Complex Concentrate (PCC) for reversal of warfarin is the main therapeutic option in cases of life-threatening bleeding. Aim of the study was to investigate for using 4-factor PCC brought to the therapeutic levels of International Normalized Ratio (INR) values in cases of life-threatening bleeding in Emergency Department. Methods: This retrospective cohort study was performed in a tertiary care university emergency department. Patients with active bleeding who were taking warfarin with INR levels of ≥1.5, and had received 4-factor prothrombin complex concentrate for treatment were included in to study. Results: A total of 75 patients were included in the study. The median age of the study participants was 68 (minimum 23 to maximum 87) years and 45.3% (*n* = 34) of them were male. INR levels was normalized all patients who were received 4-factor PCC. Red blood cell (RBC) was transfused in 16 patients (21%) because of the low hemoglobin levels. Mean unite of the RBC packet was 2,75. The lengths of hospital stay of receiving 4-factor PCC rate were determined 4.9 ± 8.7 days. No thrombotic complications or adverse drug reactions were observed after 4-factor PCC administration in any of the patients. Conclusions: In our study 4-factor PCC was found to be effective and safe in rapidly reversing the effects of warfarin.

Keywords: Prothrombin complex concentrate, warfarin, hemorrhage

Introduction

Warfarin administration has been a standard means of preventing thromboembolism in patients with atrial fibrillation, prosthetic heart valves, and venous thromboembolism for >50 years [1]. Because of a narrow therapeutic window, as many as 3% to 7% of patients taking warfarin are at risk of major, life-threatening bleeding [2], and it is generally believed that this requires rapid and complete warfarin reversal [3]. The current treatment options for oral anticoagulant therapy reversal include fresh frozen plasma (FFP), vitamin K, recombinant factor-VIIa, and prothrombin complex concentrates (PCC) [4].

FFP combined with vitamin K is the traditionally used regimen to reverse the international normalized ratio (INR). Transfusion of FFP for emergency reversal of anticoagulation in the bleeding patient is not ideal. Risks include transmission of infection, allergic reactions, volume overload, incomplete reversal, and increased time to administration because of thawing requirements [5, 6].

PCC has been used for years in the treatment of hemophilia, but its use has recently expanded to warfarin reversal in patients either actively bleeding or at a high risk of bleeding [2, 7]. PCC use in acute hemorrhage has been hypothesized to be a more effective, beneficial, and cost-effective alternative to currently available therapy. These advantages may result from a more potent, sustainable, and rapid INR reversal when compared to agents such as FFP.

The objective of this study was to show the efficacy and safety of 4-factor PCC concentrates in our emergency departments during the study period. Specifically, we examine adverse effects, time to INR reversal, hospital length of stay, and red cell transfusion requirements.

Table 1. 4-factor PCC concentrates products

Components (IU/mL)	Kaskadil®	Cofact®
Company	LFFB*	Sanquin
Source material	Pooled human plasma	Pooled human plasma
Factor II	37	14-35
Factor VII	25	7-20
Factor IX	25	25
Factor X	40	14-35
Protein C	-	11.1-39
Protein S	-	1-8
Heparin	<5	-
Antithrombin III	-	<0.6

*LFFB: Laboratoire Franc¸ais du Fractionnement et des Biotechnologies, France.

Methods

Study design and setting

This retrospective cohort study was conducted in the emergency department (ED) of a tertiary care university hospital with an annual census of approximately 100 000 adult visits between January 2012 and December 2013. The study was approved by the ethics committee of university hospital.

Patients with active bleeding who were taking warfarin with an INR level of ≥1.5, and had received 4-factor prothrombin complex concentrate for treatment were included in to study.

Kaskadil® and Cofact® 10 ml flacon had been used as 4-factor PCC concentrates in study period (**Table 1**). Four-factor PCC concentrate was administrated 20-30 IU/kg intravenous on patients with active bleeding that were taking warfarin. Advice was given to infuse at an initial speed of 1 mL/min, followed by 2-3 mL/min.

Patient selection

We included active bleeding patients who were ≥18 years of age, were taking warfarin with an INR of ≥1.5, and had received 4-factor prothrombin complex concentrate in the ED.

We excluded patients if they were <18 years of age, if there was no documentation that the patient was taking warfarin, if 4-factor prothrombin complex concentrates was administered without an initial INR check, or if they received 4-factor prothrombin complex concentrates within 7 days.

Outcome measures

The primary outcome, incidence of serious adverse events within 30 days of receiving 4-factor prothrombin complex concentrates in the ED, was a composite consisting of the following events: death, ischemic stroke, myocardial infarction, heart failure, venous thromboembolism, and peripheral arterial thromboembolism. Secondary outcomes included time to INR reversal (defined by an INR <1.5), hospital length of stay, and number of units of packed red blood cells transfused within 48 hours.

Primary data analysis

The statistical evaluation of our data was performed using SPSS 20.0 (SPSS Inc., Chicago, IL, USA) software package. Statistical analyses of frequency distributions were performed using chi-square contingency table analysis with the appropriate number of degrees of freedom. Statistical significance was denoted by a value of $P<0.05$ for all tests performed.

Results

Primary outcomes

Our primary outcome was serious adverse events (death, ischemic stroke, myocardial infarction, heart failure, venous thromboembolism, or peripheral arterial thromboembolism) within 30 days.

A total of 75 patients were included in the study. The median age of the study participants was 68 (minimum 23 to maximum 87) years and 45.3% (*n*=34) of them were male. The patients' demographic characteristics are listed in **Table 2**.

In the meanwhile, Kaskadil was administrated in 34 (45.3%) Cofact was administrated in 41 (54.7%) patients.

30-day mortality rate was found 11.8% and 14.6% on patient who were administrated to Kaskadil and Cofact respectively (P=1.000).

Secondary outcomes

Secondary outcomes included time to international normalized ratio reversal, hospital length

Table 2. The demographic features of study patients

Variables	All patients	Kaskadil	Cofact
Patients	75	34	41
Age (median/min-max)	68/23-87	68/40-87	69/23-87
Sex, n (%)			
Male/Female	34 (45.3)/41 (54.7%)	18 (53%)/16 (47%)	23 (56%)/18 (44%)
Warfarin indication, n (%)			
Atrial fibrillation	37 (49.4)	18 (52.9)	19 (46.3)
Heart valve replacement	18 (24)	6 (17.6)	12 (29.3)
Pulmonary embolism	9 (12)	6 (17.6)	3 (7.3)
Deep vein thrombosis	9 (12)	2 (5.9)	7 (17.1)
Others	2 (2.6)	2 (5.9)	0 (0)
Reasons for ED admission, n (%)			
Gastrointestinal system	24 (32)	12 (35.4)	12 (29.2)
Respiratory system	17 (22.6)	7 (20.6)	10 (24.4)
Muscular	9 (12)	3 (8.8)	6 (14.6)
Urinary system	9 (12)	5 (14.7)	4 (9.8)
Intracranial hemorrhage	6 (8)	2 (5.8)	4 (9.8)
Intraabdominal hemorrhage	5 (6.7)	1 (2.9)	4 (9.8)
Others	5 (6.7)	4 (11.8)	1 (2.4)
Complication, n (%)			
Death	10 (13.3)	4 (11.8%)	6 (14.6)
Myocardial infarction	0 (0)	0 (0)	0 (0)
Stroke	0 (0)	0 (0)	0 (0)
Arterial thromboembolism	0 (0)	0 (0)	0 (0)
Pulmonary embolism	1 (1.3)	0 (0)	0 (0)

of stay, and red blood cells transfused within 48 hours.

Subsequent changes in INR values from the previous INR values without being given PCC are shown in **Figure 1** of the patients. Considering the decrease in INR values between these two groups; kaskadil group median value of INR 7.48 (minimum-maximum 2:01, 9:50), the cofactor group 6.03 (minimum-maximum 1:27, 8:38), respectively. The difference between both groups in the decrease in INR value was significant ($P<0.05$).

RBC suspension was administrated only 16 patients (21%) applied an average of 2.75 U.

Average length of hospital stay of patients applied PCC was 4.9 ± 8.7 days. Thromboembolic events were not observed in any patient.

Discussion

PCC are produced by ion-exchange chromatography from the cryoprecipitate supernatant of large plasma pools after removal of antithrombin and factor XI [8]. Different processing techniques involving ion exchangers enable the production of either three-factor (i.e., factors II, IX and X) or four-factor (i.e., factors II, VII, IX and X) concentrates with a final overall clotting factor concentration approximately 25 times higher than in normal plasma [9]. To prevent activation of these factors, most PCC contain heparin. PCC may also contain the natural coagulation inhibitors protein C and protein S.

Initially developed to treat hemophilia B, they are licensed and approved in Europe, Australasia, and Canada for warfarin reversal. Because PCC are infrequently used for hemophilia, much of this use must be for warfarin reversal [10, 11]. Four-factor PCC were used in this study.

There are many studies that have shown the efficiency of PCC at providing normal hemostasis at different doses. In our study, the PCC doses used were within the range of 25 to 50

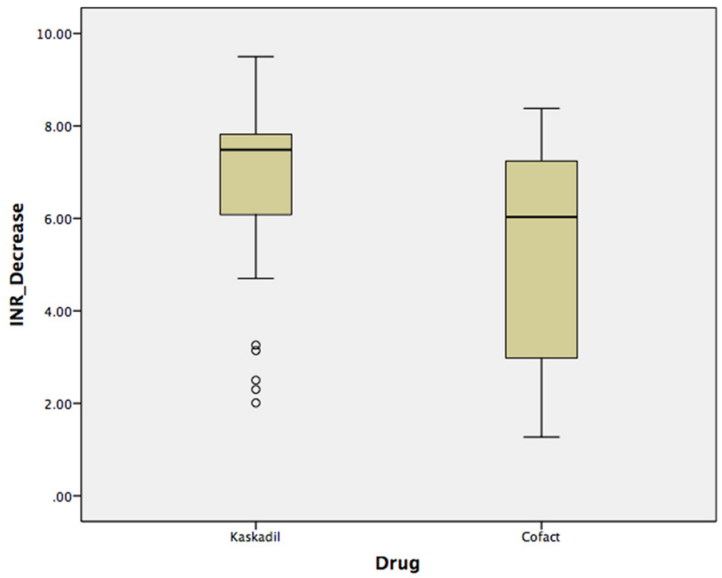

Figure 1. PCC without the patient being given by the previous INR values between subsequent changes in INR values.

IU/kg according to the Australasian guidelines [12] and the dose was given to infuse at an initial speed of 1 mL/min, followed by 2-3 mL/min. We used to same doses and infusion rates in this study. INR values were decreased all study patients. In subgroup analysis there was a statistically significant difference between Cofact and Kaskadil groups ($P<0.05$).

Reported thromboembolic complications of PCC include both venous and arterial thromboembolism, and include ischemic stroke, venous thromboembolism (deep vein thrombosis or pulmonary embolism), myocardial infarction, and disseminated intravascular coagulation [13]. Infectious transmission of viruses including hepatitis A, B and C, HIV, HTLV-1, and parvovirus B19 is a possibility [14]. Other potential adverse effects include allergic reactions including life-threatening anaphylaxis, transfusion reactions, and a theoretical risk of heparin-induced thrombocytopenia due to the small amounts of heparin contained in PCC. No significant hemodynamic changes have been reported [14]. In our study, no thrombotic complications or adverse drug reactions were observed after PCC administration in any of the patients.

There are many studies comparing the efficacy and safety of PCC with FFP. They concluded that treatment of PCC could be done faster, easer and the less volume than FFP treatment. PCC treatment also is not required ABO and subgroups incompatibility. Prothrombin complex concentrates produce more rapid and complete anticoagulation reversal than fresh frozen plasma [15-26] with most studies showing PCC reversal of the INR to less than 1.5 in 10 to 30 minutes [27]. Prothrombin complex concentrates are reconstituted at the bedside and can be infused rapidly. Time to INR correction is 3 to 5 times faster with prothrombin complex concentrates than fresh frozen plasma [19, 21]. We did not include FFP group in this study because of the many studies in the literature.

Only 5 patients (6.6%) died because of the intracranial hemorrhage due to warfarin use in study period in ED. In the literature, the incidence of major bleeding (intracranial hemorrhage) that can lead to that use of warfarin is 1.2-8.1% [28].

Limitations

The most important limitation of our study was the retrospective design and dependence on the quality of electronic medical record documentation. Another limitation of our study concerns the time of the first INR monitoring after administration of PCC.

Conclusions

INR values quickly and reliably achieved the desired INR values with usage of PCC on the study patients in ED. In our study four-factor-PCC was found to be effective and safe in rapidly reversing the effects of warfarin.

Disclosure of conflict of interest

None.

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