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CASE SERIES OF LOW DOSE FOUR-FACTOR PROTHROMBIN COMPLEX CONCENTRATE FOR ANTICOAGULANT REVERSAL

[1, 2]Waad H. Al-Kathiri and [3]Anas A. Khan

[1]Department of Clinical Pharmacy Services, King Saud University Medical City, King Saud University, Riyadh, Saudi Arabia
[2]Clinical pharmacy Department, College of Pharmacy, King Saud University, Saudi Arabia
[3]Department of Emergency Medicine, College of Medicine, King Saud University, Riyadh, Saudi Arabia

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***Corresponding author:** **Waad H. Al-Kathiri**

ABSTRACT

Introduction: Recent international guidelines recommend the use of 4-factor prothrombin complex concentrate (PCC4) over fresh frozen plasma (FFP) for reversal of oral anticoagulant in life-threatening bleeds. Although, thromboembolic complications were reported in many studies in patients who received PCC4. ***Objective:*** Describe the effectiveness and safety of low weight base dose (25mg/kg) 4-factor prothrombin complex concentrate (PCC4) in controlling bleeds event caused by oral anticoagulant. **Methods:** Retrospective case series included nine patients who visit Emergency department with acute bleeding events controlled with low weight base dose 4-factor prothrombin complex concentrate. Chart review was conducted between January 2017 and December 2018. International Normalized Ratio (INR), thromboembolic events and hypersensitivity reaction were documented. ***Results:*** Baseline mean [±SD] INR ([±5.3] 6.4), Anticoagulant caused Intracerebral hemorrhage in two patients, and Gastrointestinal bleeding was the most complication caused by anticoagulant. PCC4 was given in dosing range 25 unit/kg based on estimated patient weight, mean [±SD] INR ([±0.95] 1.6) was 60 minutes post PCC4, PCC4 contributed significant reduction in INR ($p=0.02$). Six patients reached INR < 1.5, two patients INR <2, and only one patient with INR 4.3. No addition PCC4 doses were needed to control the bleeding event. None of patients experienced a thromboembolic events or hypersensitivity reaction 30 days post PCC4. ***Conclusion:*** Low weight base dose (25 unit/kg) PCC4 contributed to efficient reduction of INR in patients with life-threatening bleeding with low risk of thromboembolism event. We recommend a larger study to evaluate INR rebound and re-bleeding for post PCC4 along with thromboembolism event beyond the 30 days.

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INTRODUCTION

Food and Drug Administration (FDA) approved the use four factors Prothrombin Complex Concentrate (PCC4) in April 2013 (Beriplex, 2014). The approved indication is reversal of Vitamin K antagonist anticoagulant in patients with acute major bleeds and in patients requiring urgent surgeries or invasive procedures (Beriplex, 2014). PCC4 is a concentrated mixture of inactivated vitamin K-dependent coagulation factors (Factors II, VII, IX, and X) derived from human plasma, as well as protein C and protein S. Excipients in the formulation include heparin and antithrombin III (Beriplex, 2014). Recent international guidelines recommend the use of PCC4 over fresh frozen plasma (FFP) for reversal of warfarin in life-threatening bleeds (Ageno *et al.,* 2012; Frontera *et al.,* 2016; Keeling *et al.,* 2011; Spahn *et al.,* 2013; Tran *et al.,* 2013). Compared to FFP, PCC4 has no risk of transfusion-related acute lung injury, hypocalcemia, disease transmission, prolonged time required for infusion, and potential for fluid overload (American Society of Anesthesiologists Task Force of Perioperative Blood Transfusion and Adjuvant Therapies, 2006; Sorensen *et al.,* 2011; Cada *et al.,* 2013; Ferreira *et al.,* 2013; Refaai *et al.,* 2015). Although, thromboembolic complications were reported in many studies in patients who received PCC4. Included deep venous thrombosis, myocardial infarction, and bilateral renal infarcts and intracardiac thrombus (Lankiewicz *et al.,* 2006; Fredriksson *et al.,* 1992; Bolton-Maggs *et al.,* 1994; Gruppo *et al.,* 1983; Warren *et al.,* 2009). Anticoagulant associated with cerebral hemorrhage is worse complication of chronic anticoagulant therapy. Patients on oral anticoagulant at a high risk for hematoma expansion, mortality, and other adverse outcomes compared to those

patients presenting with CNS hemorrhage not associated with anticoagulation (Cucchiara *et al.,* 2008; Flaherty *et al.,* 2008; Flibotte *et al.,* 2004; Hylek *et al.,* 2003; Kuramatsu *et al.,* 2015; Yasaka *et al.,* 2005). Limited studies described the optimal PCC4 dose for patient with Cerebral hemorrhage with low INR reading (Rivosecchi *et al.,* 2016). The effect of INR and hematoma expansion for patients presenting with anticoagulant associated cerebral hemorrhage is controversial. (Kuwashiro *et al.,* 2011; Huttner *et al.,* 2006; Dowlatshahi *et al.,* 2012). Emergency Department of King Saud university medical city initiated a protocol for using PCC4 in Emergency department. In this protocol the initial dose of PCC4 is 25 U/kg for all patients who was diagnosed with life-threatening bleeding, regardless the INR reading. The second dose will be given if the active bleeding wasn't stop after the initial dose of PCC4. The objective of the study was to describe the effectiveness and safety of low dose (25 U/kg) PCC4 in controlling bleeds event caused by oral anticoagulant.

METHODS

A cross-sectional retrospective one-year study was conducted between January and December 2018at Emergency Department (ED) of King Khalid University Hospital, King Saud University Medical City, Riyadh, Saudi Arabia. In Aug 2016, KSUMC implemented "The use of PCC4 in ED protocol" which includes PCC4 dose is 25 U/kg for all patients who were diagnosed with life-threatening bleeding, regardless the INR reading. And duo to the cost, 24 -29 U/kg was the acceptable range dosing for vial rounding. Repeated INR to be drawn 60 minutes post the PCC4 infusion for all patients. A fellow up appointment to anticoagulant clinic was given to all patients within 4 weeks post receiving PCC4 for anticoagulant reversal. All patients who presented to Emergency department with acute bleeding events controlled with low dose PCC4 during the study period were included in the study. Exclusion criteria: patient received PCC4 for an indication other than reversal of Anticoagulant agents, patient without initial INR reading, and post INR was drawn more than 2 hour post PCC4 infusion.

Efficacy evaluation: Outcome was stop the bleeding or reducing the International Normalized Ratio (INR) to ≤ 1.5 within 60 minutes post PCC4 among patient with life-threatening bleeding for anticoagulation reversal.

Safety evaluation: Outcomes were 1) thromboembolic events (defined as deep vein thrombosis [DVT], pulmonary embolism [PE], limb ischemia, transient ischemic attack, cerebrovascular accident, non-ST-segment elevation myocardial infarction, ST-segment elevation myocardial infarction, and unexplained sudden death) within 30 days post PCC4 infusion. 2) Hypersensitivity reaction to PCC4 (defined as systemic hypersensitivity reaction required antihistamine, steroids or inotropes). 3) INR rebound (defined as supra-therapeutic INR level)or re-bleeding events within 30 days post PCC4. Data was analyzed using the SPSS® statistical package, Version 20.0 (SPSS Inc., Chicago, IL, USA) for Windows®. With P-value of <0.05 considered statistically significant. Descriptive statistics are reported mean and medians ± standard deviation or as frequencies and percentages, as appropriate. Chi-squared test were used to determine association between qualitative variables. While quantitative data was analyzed by Mann-Whitney U test. The retrieval data was accessible to all DEM staff. Co-investigator was also allowed to access this data. Two independent evaluators (Consultant Physician, Clinical pharmacist) reviewed the patient files.

RESULTS

Patient demographics: A total of 14 patients were received PCC4 for anticoagulant reversal at our ED, 5 patients were excluded (2 patients lacking initial INR reading, 3 patients INR was drawn more than 2 hours post PCC4 infusion). Nine patients were included in the study. Five of the nine evaluated patients were Female, mean age of patients was 53(range between 17 and 83) years old. Most indication for anticoagulation was related to Atrial fibrillation and valve replacement. While one patient was taken anticoagulant for Behcet's Disease. Eight patients were on Warfarin and only one patient was on Rivaroxaban (Table 1).

Table 1. Patients Demographics details

Case No.	Age (years)	Gender	Weight (kg)	Height (cm)	Indication of Anticoagulant	Anticoagulant agent (Dose)	Diagnosis in Emergency Department
1	26	Male	56	165	Metalic Aortic and mitral valve replacement	Warfarin (3 mg po od)	ICH
2	56	Male	60	172	Metalic Aortic and mitral valve replacement	Warfarin (2 mg po od)	High INR
3	72	Female	86	155	Paroxysmal AF	Warfarin (3 mg po od)	Gastrointestinal Bleeding
4	48	Female	60	150	Metalic Aortic and mitral valve replacement ,Atrial fibrillation	Warfarin (alternating 2.5 & 3mg po od))	Gastrointestinal Bleeding
5	83	Female	60	144	Atrial fibrillation	Warfarin (5mg po od)	Gastrointestinal Bleeding
6	55	Male	70	163	Metalic Aortic and mitral valve replacement ,Atrial fibrillation	Warfarin (5mg po od)	Gastrointestinal Bleeding & Epitaxsis
7	17	Male	60	150	Behcet's disease	Rivaroxaban (20 mg po od)	SAH
8	71	Female	70	157	Atrial fibrillation	Warfarin (7mg po od)	Gastrointestinal Bleeding
9	50	Female	72	155	Atrial fibrillation	Warfarin (8 mg po od)	Gastrointestinal Bleeding

Table 2. The effect of PCC dose on Coagulation profile

Case No.	Initial Coagulation profile			PCC Dose		Vit K Dose	Coagulation 60 minutes post PCC dose		
	INR	PT	APTT	Unit	Unit/kg	mg	INR	PT	APTT
1	1.4	17.50	42.30	1400	25	5	1.23	15.7	33
2	13.46	20.70	64.50	1,500	25	5	1.96	20.20	60.20
3	5.44	49.2	85.9	2500	29	5	1.3	16.6	41.7
4	3.4	34.1	88.2	1500	25	-	1.79	27.1	72.6
5	16	120	180	1500	25	5	4.13	39.7	78.3
6	1.4	17.7	46.6	2000	29	5	1.11	15.20	37.90
7	1.88	22.3	52.4	1500	25	-	1.24	15.7	41.8
8	6.14	56.1	65.6	2000	29	-	1.2	15.9	31.6
9	8.48	72	131.5	2000	28	-	1.23	15.5	38.20

Baseline mean [±SD] INR ([±5.3] 6.4) (Table 2), Anticoagulant caused Intracerebral hemorrhage in two patients, and Gastrointestinal bleeding was the most complication caused by anticoagulant. (Table 1).

Hemostatic effectiveness: PCC4 was given in dosing range 24-29 unit/kg based on estimated patient weight, 5mg Vitamin k was given in combination to PCC4 in five patients. After 60 minutes post-PCC4 dose mean [±SD] INR ([±0.95] 1.6), PCC4 contributed significant reduction in INR (p=0.02). Six patients reached INR < 1.5, two patients INR <2, and only one patient with INR 4.3 (Table 2), (Figure: 1) No addition PCC4 doses were needed to control the bleeding event.

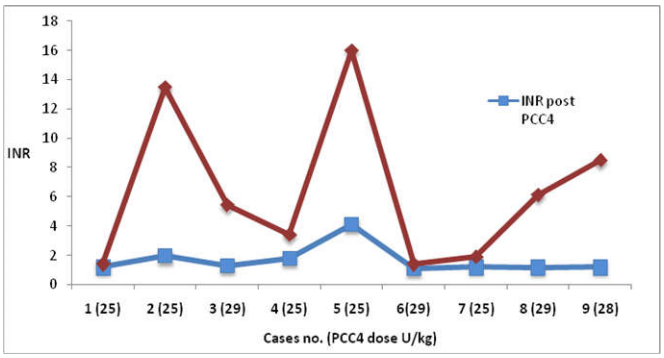

Figure 1. INR pre and post PCC4doses

Safety assessment: None of patients experienced thromboembolic events, hypersensitivity reaction or INR rebound/re-bleeding within 30 days post PCC4.

DISCUSSION

The low dose PCC4 resulted in achieving the primary outcome of hemostatic efficacy in all the patients, although the targeted INR (<1.5) was achieved in 66% of the patientswithin 60 minutes post the PCC4 infusion. The targeted INR was achieved in the consequence INR readings within 24hr post PCC4 infusion in all the patients. The randomized trial comparing PCC4 to FFP showed similar result to our study that there was no difference in hemostatic efficacy for warfarin reversal, while PCC4 has faster INR reduction compared to FFP (Sarode *et al.,* 2013), the use of fixed dose PCC4 compared to low dose PCC4 had shown similar result for hemostatic efficacy in previous studies (Khorsand *et al.,* 2011 & 2012; Varga *et al.,* 2013). The fixed doses PCC4 protocols included Vitamin K 5- 10 mg IV in combination to PCC4 fixed dose, the safety of warfarin resistant was not studied. In our study five patients received vitamin K 5 mg IV in combination to PCC4 low dose the INR average reduction was 53.6% from initial INR, compared to average of 61.8% INR reduction in patients who didn't receive vitamin k. Vit k concomitant to PCC4 has no superior benefit in INR reduction compared to PCC4 alone (p-value was 0.1, statistically insignificant). The American College of Chest Physicians guidelines recommended concomitant vitamin K with PCC4 for reversal of warfarin to prevent the incidence of INR rebound. Our patients who didn't receive vit k in combination to PCC4, did not develop INR rebound during the evaluation period. Our result was against this recommendation. The thromboembolic events and INR rebound evaluation within 30 days post PCC4 was selected rather than 45 days period, which was selected in the previous Randomized control trials (Huttner *et al.,* 2006; Goldstein *et al.,* 2015). Duo to the study nature we could not follow discharged patients for 45 days.

Conclusion

Low weight base dose (25 unit/kg) PCC4 contributed to efficient reduction of INR in patients with life-threatening bleeding with low risk of thromboembolism event. We recommend a larger study to evaluate INR rebound and re-bleeding for post PCC4 along with thromboembolism event beyond the 30 days.

Conflicts of interest: The authors declare that there were no competing interests regarding the content of this article.

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