Prothrombin complex concentrate in the management of major bleeding induced by oral anticoagulant therapy

Mohammed AlSheef, MD, Ghaydaa Kullab, MD, Modhi Alajmi, MD, Ruba Aldhaheri, MD, Sultan Al Baqmi, MD, Haya Alajlan, BSc, Abdul Rehman Z. Zaidi, MD, Amani Abu-Shaheen, MPH.

ABSTRACT

Objectives: To share clinical data on the efficacy of 4F-PCC in the treatment of major bleeding caused by warfarin, dabigatran, and rivaroxaban.

Methods: This is a retrospective study of patients admitted to King Fahad Medical City, Riyadh, Saudi Arabia with major bleeding caused by oral anticoagulants and treated with 4-factor prothrombin complex concentrate (4F-PCC). The International Society of Thrombosis and Hemostasis Scientific and Standardization Subcommittee criteria were used to evaluate the effectiveness of PCCs.

Results: A total of 22 patients were included in the study. Ten of the events were caused by gastrointestinal bleeding (46%). In the majority of patients, anticoagulation was prescribed for stroke prevention, atrial fibrillation, and venous thromboembolism. The median international normalized ratio was significantly lower before and after PCC administration (p<0.001). In patients treated with 4-factor PCC, the rate of thromboembolic events was 0%. The hemostatic effectiveness of PCC was effective in 19 patients. During treatment, no clinically significant bleeding complications occurred.

Conclusion: Prothrombin complex concentrate can effectively reverse the effects of warfarin and rivaroxaban in patients with major bleeding, but only partially reverses the effect of dabigatran.

Keywords: PCC, warfarin, rivaroxaban, ISTH criteria

Saudi Med J 2022; Vol. 43 (2): 213-217
doi: 10.15537/smj.2022.43.2.20210736

Prothrombin complex concentrate (PCC) is a biological product made from pooled human plasma that contains therapeutic levels of factors II, VII, IX, and X.[1] It is advised in the case of major bleeding events (MBEs) caused by warfarin or direct oral anticoagulants (DOAC).[2]

Vitamin K antagonists (VKAs) and DOACs are examples of oral anticoagulant therapies.[3] Direct oral anticoagulants are classified into 2 groups: direct factor Xa inhibitors (such, apixaban, edoxaban, and rivaroxaban) and direct thrombin inhibitors (such, dabigatran), both of which have been used to prevent stroke in non-valvular atrial fibrillation and venous thromboembolism (VTE).[4] Long-term use of oral anticoagulant therapies is linked to major bleeding tendencies, such as intracerebral bleeding, the most feared adverse effect.[5] The International Society on Thrombosis and Hemostasis (ISTH) criteria are used to define a major bleeding event (MBE) in a non-surgical setting.[5] Despite the fact that PCC is increasingly being used in Saudi Arabia to treat life-threatening bleeding caused by oral anticoagulant therapy, there are no studies to back up its efficacy.[6] As a result, we conducted this study to determine the efficacy of PCC in controlling major bleeding caused by oral anticoagulant therapies, as well as the safety of PCC.

Methods. A retrospective review was carried out at a tertiary care hospital in the Internal Medicine Department, King Fahad Medical City (KFMC), Riyadh, Saudi Arabia. Between January 2012 and July 2018, all 43 female and male patients who developed major bleeding and received the first or repeated dose of PCC, which was induced by oral anticoagulant therapy, and met the ISTH criteria, were enrolled in this study retrospectively. The following is the ISTH definition of major bleeding in non-surgical patients: i) Fatal bleeding; ii) Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular, or pericardial, or intramuscular with compartment syndrome; iii) Bleeding resulting in a drop in hemoglobin level of 2 g/dL or more, or necessitating transfusion of 2 or more units of whole blood or red cells.[6] Patients who had pre-operative reversal of oral anticoagulation effects or had previously received other hemostatic agents (rFVIIa or activated PCC) were excluded.

All data were collected by using a standardized case report form including the medical notes, laboratory results: prothrombin time / international normalized ratio (PT/INR), activated partial thromboplastin time (APTT), hemoglobin at time of presentation to the hospital and 24 hours after receiving the dose of PCC. In addition to any other relevant details, including transfusion records. Data was collected on the patients' demographic characteristics such as age, gender, and weight. The type and the indication for anticoagulants either by using VKA, dabigatran, or

rivaroxaban due to stroke prevention atrial fibrillation, VTE, and stroke. Source of bleeding with or without transfusion, where it might be head/neck, intracranial, thorax, gastrointestinal, abdominal, musculoskeletal, and genitourinary bleeding. Also, the occurrence of thromboembolic events after PCC administration, and death.[7]

In addition, the effectiveness assessment for the PCC in controlling major bleeding was carried out based on the criteria published in the communication letter from the Standardization Subcommittee on the Control of Anticoagulation of the ISTH, for 4 different bleeding types: visible bleeding, nonvisible bleeding, musculoskeletal bleeding, and intracranial hemorrhage (ICH).[7]

Approval for this study was obtained and approved by the Institutional Review Board at KFMC, Riyadh, Saudi Arabia.

Statistical analysis. The SPSS version 21 (SPSS Inc, Chicago, Illinois, USA) was used to enter and analyze data. Descriptive statistics were used in the analysis, which included quantitative data presented as (mean±standard deviation (SD), with a confidence interval (CI) of 95% and qualitative data presented as frequency and percentage. Depending on the type of data, appropriate statistical tests such as the t-test (PCC dose and effectiveness), paired T-test (laboratory data before and after receiving PCC), ANOVA (PCC dose and adverse effects), Fisher exact test (types of oral anticoagulant and their effectiveness), and logistic regression tests were used for comparisons. The cut-off value for statistical significance was set at $p<0.05$.

Results. Our study included 22 patients who received PCCs for the urgent reversal of the anticoagulant effect of warfarin, rivaroxaban, or dabigatran due to an MBE. Twenty-one patients were excluded from further analysis, either because a PCC was given for anticoagulation reversal prior to surgery (n=6) or because the patients were not on oral anticoagulant therapy when they received a PCC (n=13) or because they had missing data charts (n=2).

The study population had a mean age of 58 years and a mean weight of 68.3 kg. The females were (n=18; 82%). Stroke prevention in atrial fibrillation study and VTE were the most common reasons for anticoagulation in the majority of patients (n=10; 46%), respectively. There were 16 MBEs for warfarin patients, 2 MBEs for dabigatran patients, and 4 MBEs for rivaroxaban patients. The most common type of bleeding requiring reversal with a PCC was gastrointestinal (GI) bleeding (n=10; 46%), followed by musculoskeletal bleeding in (n=4; 18%) patients (Table 1).

Before starting PCC treatment, all patients had their INR and APTT levels checked. The APTT and INR were both prolonged in warfarin patients (n=14; 88%) and (n=15; 94%). Furthermore, the INR and APTT were measured 24 hours after receiving the PCC, and their values were significantly lower ($p\leq0.001$) and ($p=0.02$), respectively. Especially in Warfarin-treated patients ($p\leq0.001$). A PCC was given at a dose of 2085.2704.4 IU on average (IQR). Due to the insufficient effect of the initial PCC management, a second PCC dose of 1500-5000 IU (mean 2812.5) was given in 8 cases. Patients were only given BeriplexR of the 4-factor PCCs if it was available at the treating site (Table 2).

A correlation between the weight of the patients in kilograms and PCC dose resulted in a weak positive correlation (r=0.33) ($p=0.13$), where more weight needed higher doses.

Additional management included the transfusion of red blood cell concentrates; (n=11; 61%) patients. Hemoglobin level was measured before and after

Table 1 - Demographic and clinical characteristics of the study population.

Variables	Total
Age, years (mean±SD)	57.8±19.4
Weight, kg (mean±SD)	68.3±20.5
Gender	
Female	18 (82)
Male	4 (18)
Previous major bleeding	
Yes	7 (32)
No	15 (68)
Indication for anticoagulant	
Stroke prevention atrial fibrillation	10 (46)
Venous thromboembolism	10 (46)
Stroke	1 (4)
Valve replacement	1 (4)
Most common bleeding site	
GI	10 (45)
Musculoskeletal	4 (18)
ICH	3 (14)
Genitourinary	3 (14)
Abdominal	2 (9)

Values are presented as numbers and percentages (%). GI: gastrointestinal, SD: standard deviation, ICH: intracranial hemorrhage

Disclosure. Authors have no conflict of interests, and the work was not supported or funded by any drug company.

treatment with a PCC, and it resulted in significant improvement (p=0.004) after transfusion.

Patients on warfarin showed significant effectiveness when received a PCC dose of (2196±573.3 IU) compared with patients who received a PCC dose of (1000±707.1 IU) (p=0.02) (Table 3). The hemostatic efficacy of PCC for the management of warfarin, dabigatran, and rivaroxaban-related MBE was assessed as effective in 19 patients (86%) and ineffective in 3 patients (14%). When analyzed according to the anticoagulant type, the hemostatic effectiveness of PCC was assessed as effective in 14 of the 16 patients on warfarin and 1 of the 2 patients on dabigatran, and all 4 patients on rivaroxaban.

Two (67%) of the 3 patients with ineffective hemostasis after treatment with a PCC on warfarin had ICH as the indication for reversal, and their treatment was ineffective due to delayed diagnosis and suboptimal dosing. One patient on dabigatran had GI bleeding, as the indication for reversal, and treatment was ineffective due to multi-organ (renal) failure and suboptimal dosing.

Safety analysis was performed for all the patients with no serious adverse events were observed. The incidence of thromboembolic events was 0% in patients treated with 4-factor PCC.

Death occurred in 8 (36%) patients within (1-3 months) of the MBE, with 5 patients having GI bleeding. Two of the 8 patients had ICH, while the other had genitourinary bleeding. The direct effect of ICH was the cause of death in 2 cases, and 2 patients died of multiorgan failure after GI bleeding, 2 patients had cardiac arrhythmia and were arrested, one patient died from PE, and the other from disseminated intravascular coagulation (DIC). The cause of death in all of these cases was determined to be unrelated to PCC treatment.

Discussion. In this study, we report the results from a cross-sectional study of patients treated with PCCs for the management of MBEs associated with warfarin, rivaroxaban, and dabigatran.

The main findings are that PCC is generally effective in reversing major bleeding without causing complications or serious adverse events such as pulmonary embolism or even death. Major bleeding event on anticoagulants have a high morbidity and mortality rate. Most bleeding events on oral anticoagulants can be managed conservatively with hemodynamic support and blood product transfusion. However, in some cases, a specific DOAC and VKA reversal agent is required to safely and effectively reverse the bleeding. Several clinical trials

Table 2 - Comparison between the lab results before and 24 hours after treatment with PCC.

Variables	Before	After	*P*-value
All patients on oral anticoagulants before and after 24 hours after treatment with PCC (n=22)			
International normalized ratio	7.9±5.3	2.1±1.6	<0.001
Activated partial thromboplastin time	89.1±46.6	59.7±49.0	0.03
Hemoglobin	8.5±3.4	10.7±2.7	0.004
Patients on warfarin before and after 24 hours after treatment with PCC (n=16)			
International normalized ratio	7.38±5.3	1.6±0.6	0.001

Values are presented as mean±SD. PCC: prothrombin complex concentrate

Table 3 - Relationship between anticoagulant type and the effectiveness of prothrombin complex concentrate and the dose.

Types of anticoagulants	Effective n (%) (M±SD)	Ineffective n (%) (M±SD)	Total (n,%)	*P*-value
VKA PCC dose	14 (88) 2196±573.3	2 (12) 1000±707.1	16 (100)	0.02
Dabigatran PCC dose	1 (50) 2000	1 (50) 2500	2 (100)	
Rivaroxaban PCC dose	4 (100) 2156±986.2	0	4 (100)	

PCC: prothrombin complex concentrate

indicate that PCCs may be effective in the treatment of warfarin-induced bleeding.[9,10] The Food and Drug Administration approved PCC in 2013 for the urgent reversal of warfarin.[9] According to the results of a phase IIIb multicenter no inferiority trial, 4F-PCC is an effective alternative to plasma for the urgent reversal of VKA therapy in MBE.[10]

The hemostatic effectiveness of PCC for the management of a rivaroxaban-related MBE was assessed as effective management in all the cases. This is similar to other studies that showed the significant effect of PCC in reversing the bleeding induced by rivaroxaban.[6,7,11]

Despite the fact that this study discovered that PCC is partially effective in reversing major bleeding caused by dabigatran, clinical trials evaluating dabigatran reversal with 4F-PCC produced mixed results. At least 2 studies show that 4F-PCC has no effect on the anticoagulant action of dabigatran.[12,13] While other studies support its efficacy.[11,14] Furthermore, activated PCC (APCC) has been studied in the reversal of major bleeding caused by dabigatran and may be a better option,[15] and the specific antidote idarucizumab should be the most effective reversal agent. Three of the patients in our study had an ineffective hemostatic effect of PCC. Two of these patients had an ICH, which is associated with poor outcomes and a high mortality rate. The last one had ineffective hemostasis with GI bleeding, and treatment was ineffective due to multiorgan (renal) failure and inadequate dosing. As a result, the ineffective hemostatic outcome of PCCs observed in these 3 cases.

The mortality rate in this study is lower than that in Pahs et al's[7] retrospective review of patients admitted with hemorrhage caused by dabigatran or rivaroxaban.

Thromboembolic events occurred in 3.6% of patients receiving PCC for the treatment of MBEs on factor Xa inhibitors.[6] Thromboembolism rates were low, but there was a quantifiable risk of thromboembolism in VKA-treated patients receiving PCCs for anticoagulation reversal.[9] In our study, no thromboembolic events were observed in patients receiving 4-factor PCC. The sample size, however, was small.

The inclusion of patients who received an anticoagulant dose within 24 hours of PCC administration, as well as the use of standardized ISTH criteria for assessing PCC effectiveness, add to the study's strength. Due to their efficacy and low rates of adverse events, PCCs are a viable alternative for the management of MBEs on warfarin and rivaroxaban.

Based on our findings, we recommend starting patients with MBEs on warfarin or rivaroxaban with a PCC dose of 2000 IU, which can be increased if the effect is suboptimal. Such an approach appears to be associated with an acceptable balance of PCC efficacy and safety.

Study limitation. The major limitations of our study are the lack of a control group, the small sample size, the retrospective design, and some missing data from the patients' charts. To assess the efficacy and safety of PCC in the reversal of DOACs, we recommend larger multi-center studies in Saudi Arabia with a prospective cohort design and a larger sample size.

In conclusion, PPC can quickly and effectively reverse the effects of warfarin and rivaroxaban in patients with major bleeding, but it only has a limited effect on dabigatran reversal.

Acknowledgment. *The authors gratefully acknowledge King Fahad Medical City, Riyadh, Kingdom of Saudi Arabia and their Research Center & International Review Board for their tremendous support. The authors would also like to thank ENAGO (www.enago.com) for English language editing.*

Received 13th September 2021. Accepted 7th December 2021.

From the Medical Specialties Department (AlSheef), from the Internal Medicine Department (Kullab), from the Research Center (Abu-Shaheen), King Fahad Medical City; from the Internal Medicine Department (Kullab, Zaidi), Dr. Sulaiman Al Habib Medical Group, Riyadh; from the College of Medicine (Al Baqmi), King Saud Bin Abdulaziz University for Health Sciences; from the College of Health and Rehabilitation Sciences (Alajlan), Princess Noura Bint Mohammed University, Riyadh; from the College of Medicine (Alajmi), Imam Abdulrahman Bin Faisal University, Dammam; and from the College of Medicine (Aldhaheri), King Abdulaziz University, Jeddah, Kingdom of Saudi Arabia.

Address correspondence and reprints request to: Dr. Mohammed AlSheef, Internal Medicine Consultant, King Fahad Medical City, Riyadh, Kingdom of Saudi Arabia. E-mail: malsheef@kfmc.med.sa
ORCID ID: https://orcid.org/0000-0003-1651-1158

References

1. Gaston C, Sokn E. Procoagulant Therapy for bleeding associated with acquired bleeding disorders - adult - inpatient clinical practice guideline. ***UWSMPH*** 2018; 1-30.
2. Holbrook A, Schulman S, Witt DM, Vandvik PO, Fish J, Kovacs MJ, et al. Evidence-based management of anticoagulant therapy: antithrombotic therapy and prevention of thrombosis: American College of Chest Physicians evidence-based clinical practice guidelines. ***Chest*** 2012; 141: e152S-e184S.
3. Schulman S, Kearon C. Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. ***J Thromb haemost*** 2005; 3: 692-694.
4. Levy JH, Ghadimi K, Quinones QJ, Bartz RR, Welsby I. Adjuncts to blood component therapies for the treatment of bleeding in the intensive care unit. Transfusion medicine reviews. 2017; 31: 258-263.
5. Lauer A, Pfeilschifter W, Schaffer CB, Lo EH, Foerch C. Intracerebral haemorrhage associated with antithrombotic treatment: translational insights from experimental studies. ***Lancet Neurol*** 2013; 12: 394-405.

6. Majeed A, Ågren A, Holmström M, Bruzelius M, Chaireti R, Odeberg J, et al. Management of rivaroxaban-or apixaban-associated major bleeding with prothrombin complex concentrates: a cohort study. *Blood* 2017; 130: 1706-1712.
7. Pahs L, Beavers C, Schuler P. The Real-World Treatment of Hemorrhages Associated with Dabigatran and Rivaroxaban. *Crit Pathw Cardiol* 2015 ; 14: 53-61.
8. Khorsand N, Majeed A, Sarode R, Beyer-Westendorf J, Schulman S, Meijer K, Subcommittee on Control of Anticoagulation. Assessment of effectiveness of major bleeding management: proposed definitions for effective hemostasis: communication from the SSC of the ISTH. *J Thromb Haemost* 2016; 14: 211-214.
9. Visweshwar H, Srikanthan K. Intracranial hemorrhage secondary to oral anticoagulant therapy: insight into pathogenesis, prognosis and management – a review. *J Hematologica Dis Therapies* 2016; JHGT102: 1-6.
10. Sarode R, Milling TJ, Refaai MA, Mangione A, Schneider A, Durn BL, et al. Efficacy and safety of a four-factor prothrombin complex concentrate (4F-PCC) in patients on vitamin K antagonists presenting with major bleeding: a randomized, plasma-controlled, Phase IIIb study. *Circulation* 2013; 128: 1234-1243.
11. Tran H, Joseph J, Young L, McRae S, Curnow J, Nandurkar H, et al. New oral anticoagulants: a practical guide on prescription, laboratory testing and peri-procedural/bleeding management. *Intern Med J* 2014; 44: 525-536.
12. Kahn MR, Amara RS, Halperin JL. Risks to Reversal of Anticoagulation: The Cardiology Perspective. *Am J Gastroenterol Suppl* 2016; 3: 22-28.
13. Eikelboom J, Merli G. Bleeding with direct oral anticoagulants vs warfarin: clinical experience. *Am J Med* 2016; 129: S33-S40.
14. Milling TJ, Fromm C, Ganetsky M, Pallin DJ, Cong J, Singer AJ. Management of major bleeding events in patients treated with dabigatran for nonvalvular atrial fibrillation: a retrospective, multicenter review. *Ann Emerg Med* 2017; 69: 531-540.
15. Schulman S, Ritchie B, Goy JK, Nahirniak S, Almutawa M, Ghanny S. Activated prothrombin complex concentrate for dabigatran-associated bleeding. *Br J Haematol* 2014; 164: 308-310.