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Original article

Factors contributing to poor outcome in patients on warfarin receiving 4-factor prothrombin complex concentrate in critically ill

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Abstract. *Aim:* To compare the demographical profile, indications, efficacy, and contributors to adverse outcome following administration of 4F-PCC in patients on warfarin with supratherapeutic INR. *Methodology:* Retrospective cross-sectional study was performed in a community-based teaching hospital. All patients 18 years and older on warfarin with supratherapeutic INR, who had received 4F-PCC between January 2014 and December 2018 were eligible and included in the study. *Results*: 44 patients were included in the analysis. The mean age of the patients was 79.5 years. The male to female ratio was 1:1. Patients were on warfarin for atrial fibrillation, thromboembolism in 79.5% (N-35), and 20.5% (N-9) respectively. Indications for use of 4F-PCC were active bleeding in 93% (N-41) of patients. The common sites of bleeding were gastrointestinal, intracranial, and musculoskeletal which were seen in 54.5% (N-24), 29.5% (N-13) and 6.8% (N-3) respectively. The median number of doses of 4F-PCC administered was 1 per patient. The mean dose administered was 2,883u. Clinical improvement was documented in 84% (N-37) of patients. Mortality was seen in 16% (N-7) of patients. BMI greater than 30, anemia, hypotension, presence of intracranial bleed, the requirement of blood products, and mechanical ventilation were associated with higher odds for mortality. Hypotension and requirement of mechanical ventilation were statistically significant. *Conclusion:* 4F-PCC continues to be an effective agent in the rapid reversal of warfarin therapy in patients with supratherapeutic INR presenting with major bleeding events. Most patients have clinical improvement with a single, weight-adjusted dose.

Key words: Prothrombin complex concentrate, outcome, predictors

Background

Each year 3.4 million patients are prescribed warfarin in the United States of America. Among these patients, the annual rate of major hemorrhage has been reported to be 1.7% to 3.4% (1)plasma, or the newly approved agent, four-factor prothrombin complex concentrate (4F-PCC. The most common manifestation of the same is acute bleeding requiring 42,000 hospitalizations every year (2,3)multicenter, open-label, noninferiority trial, nonsurgical patients were randomized to 4F-PCC (containing coagulation factors II, VII, IX, and X and proteins C and S. The agents used for a rapid anticoagulation reversal in such patients are supplementation of vitamin K, fresh frozen plasma (FFP) or prothrombin complex concentrate (PCC).(2,4)multicenter, open-label, noninferiority trial, nonsurgical patients were randomized to 4F-PCC (containing coagulation factors II, VII, IX, and X and proteins C and S PCCs are of 2 types namely activated or nonactivated. Nonactivated PCC's are lyophilized concentrates of vitamin K-dependent

coagulation factors containing FII, FVII, FIX, and FX and proteins C and S also known as 4F-PCC. Unlike blood derivatives, it does not carry the risk of vertical transmission of viral infections. It is being used more often for rapid reversal of supratherapeutic international normalized ratio (INR) in patients on vitamin k antagonist (VKA). In this study, we aimed to assess the indications of the use of 4F-PCC among in-patients on warfarin requiring urgent reversal due to bleeding or supratherapeutic INR. We also aimed to assess the various factors contributing to a poor outcome.

Methodology

In this retrospective chart review patients on warfarin who received 4F-PCC either for urgent reversal prior to a procedure or for acute bleeding with supratherapeutic INR were included. This study included patients who had presented to the hospital from January 2014 to December 2018. Supratherapeutic INR was defined as an INR > 2 in keeping with the prior studies. Institutional review board approval was obtained before the initiation of the study. Patients who were 18 years or older were eligible to be included. As per the hospital protocol 4F-PCC had to be ordered by a physician either in the emergency department or in the inpatient setting. Administration of vitamin K occurred before the administration of 4F-PCC. Eligibility for the administration of 4F-PCC was confirmed by a pharmacist prior to administration.(4–12)Kcentra® All consecutive patients receiving 4F-PCC were identified from the hospital electronic database. Patient details including age, gender, risk factors including body mass index (BMI), hypertension (HTN), atrial fibrillation (Afib), coronary artery disease (CAD), anemia, congestive heart failure (CHF), and reason for anticoagulation including arrhythmia, thromboembolic disease, vascular disease, artificial valve were obtained. Reason for warfarin reversal (bleed, prior surgery), details of the type of bleed (intracranial, gastrointestinal, musculoskeletal, others), type of surgery (neurosurgery, cardiothoracic, orthopedic), details of INR (pretreatment, posttreatment), details of 4F-PCC (dose, direction), Vitamin K dose, admission, and nadir hemoglobin/hematocrit, platelet count values, number of blood product support if required red blood cells (PRBCs), fresh frozen plasma (FFP), platelets were obtained by a trained physician. Acute major bleeding was defined as life threatening bleeding, a fall in the hemoglobin of greater than 2 mg/dl, bleeding requiring transfusion of blood products, in keeping with prior guidelines. International Society of Thrombosis and Hemostasis guidelines were used in order to define major nonsurgical and surgical bleeding.(13)risk factors, treatment and the outcome of RPH cases at our medical center.Methods: In this retrospective study, all cases who presented to the emergency room (ER Details of the outcome studied included effective prevention of blood loss defined as achievement of hemostasis by 24 hours, effective INR reversal defined as INR reduction to less than1.3 within 3 hours, the requirement of intensive care admission, the requirement of pressor support and/or ventilator support, duration of stay and mortality.

Data were obtained from the hospital medical record database by a trained physician. Data analysis was done with the statistical package for social sciences (SPSS version 17). The categorical data were analyzed using frequencies, tables, and percentages, while univariate analysis was used to analyze the relationship between the various risk factors and mortality. Odd's ratio was used to establish the strength of association. P value was obtained using the fisher's exact test and chi-square test. A p - value of less than 0.05 was considered significant. Patient identifiers were removed and access to the collected data was only available to the involved members of the study.

Results

Forty-four patients fulfilled the inclusion criteria and were included in the study. The mean age of the patients was 79.4 years as shown in table 1. 57% (N=25) of the patients were in the age group above 80, and 20% (N=9) of these patients were in the age group above 90. The percentages of male and female patients were almost equal. Risk factors of hypertension, atrial fibrillation, anemia, congestive heart failure, chronic kidney disease, coronary artery disease, and venous embolism was present in 84%, 80%, 73%,48%, 34%, 29.5%, and 23% respectively. 25 % (N= 11) of the

patients were obese. 4F-PCC was used for reversal of bleeding in 93% of patients and was used before surgical intervention in 7% of patients.

The mean hemoglobin at presentation, post treatment and at discharge was 9.3 mg/dl, 9.8 mg/dl and 10 mg/dl respectively. 39% (n=17) of patients had severe anemia, defined as hemoglobin of <8. The mean platelet count at presentation, post treatment and at nadir was 242,000 /uL, 215,000/uL, 214,000/uL respectively. The mean creatinine level was 1.3 mg/dl, and 20% (n=9) of patients had evidence of renal failure (as defined by Acute Kidney Injury Network criteria) at the time of presentation.

The median pretreatment INR was 4.9 (1.50 -18.0) and 89% (N=39) of the patient had an admission INR of > 3. The median post treatment INR was 1.2 (1.0-1.9) with 66% (N= 29) of patients having an INR of 1.3 or less. 82% (N=36) patients received a single dose of 4F-PCC and16% (N= 7) required two doses. The median dose of 4F-PCC infused was 2196. 96 IX units [1008.00-9776.00]. Ninety-five percentage [N=42] of patients received vitamin K before receiving 4F-PCC. The median dose of vitamin K was 10 mg. Additional blood product support in the form of packed red cells, fresh frozen plasma and platelets were required by 57%, 14% and 7% of patients respectively.

Rapid reversal of INR to less than or equal to 1.3 post administration of 4F-PCC was achieved in 66% of patients. Effective prevention of blood loss was achieved in 97% of patients as shown in table 2. 73% [N=32] of patients had a hospital stay of fewer than 7 days. 64% of patients were admitted to an intensive care unit, 25% had hypotension, and 16% required mechanical ventilation respectively. Mortality occurred in 16% of patients.

Table 1. Baseline demographic parameters

Number of patients	44 [100%]
Demographics	
Age (Years)	79.4 [52-98]
Gender	
Male	23
Female	21
Body Mass Index (Kg/m^2)	
<30	33 [75%]
<40	10 [23%]
>40	1 [2%]
Risk factors	
Hypertension	37 [84%]
Afib	35 [80%]
Embolism	10 [23%]
CAD	13 [29.5%]
PVD	9 [20%]
Anemia	32 [73%]
CHF	21 [48%]
CKD	15 [34%]
Prosthetic valve	2 [4%]
Treatment details	
Reason for reversal	
Bleed	41 [93%]
Prior to surgery	3 [7%]
Type of bleed	
Intracranial	13 [32%]
Gastrointestinal	25 [61%]
Others	3 [7%]
Pretreatment INR > 3	39 [89%]
Post treatment INR >1.5	4 [9%]
Requirement of products	
Total	29 [66%]
FFP	6 [14%]
Platelets	3 [7%]
Packed red cells	25 [57%]
PCC dose	
Single	36 [82%]
>1 dose	8 [18%]

M: Male, F: Female, Afib: Atrial fibrillation, CAD: Coronary artery disease, PVD: Peripheral vascular disease, CHF: Congestive heart failure, CKD: Chronic kidney disease, INR: International Normalized Ratio, FFP: Fresh frozen plasma, PCC: Prothrombin complex concentrate.

Table 2. Showing Outcomes of the patients in the study

Effective prevention of blood loss	43 [97%]
Rapid reversal of INR	29 [66%]
Duration of stay	
< 3 days	11 [25%]
4 - 6 days	21 [48%]
7 - 10 days	6 [14%]
> 10 days	6 [14%]
Requirement of Mechanical ventilation	7 [16%]
Hypotension	11 [25%]
ICU stay	28 [64%]
Death	7 [16%]

INR: International Normalized Ratio, ICU: Intensive Care Unit

Risk factors of heart failure, chronic kidney disease, presence of hypotension, the requirement of mechanical ventilation and ICU stay were higher among the patients with mortality. The odds ratio for poor outcome was 11.8 for mechanical ventilation, 5.7 for hypotension, 4.094 for the requirement of ICU stay, and 3.15 for the presence of chronic kidney disease respectively. Among these, the presence of hypotension and the requirement of mechanical ventilation were statistically significant (Table 3).

Table 3. Table showing predictors of worst outcome among patients

Variables	Mortality [N-7]	No mortality [N-37]	p- value
Age			
>80	6 [86%]	19 [51%]	.092**
<80	1 [14%]	18 [49%]	
HTN (37, 84%)			
Present	7 [100%]	30 [81%]	-
Absent	0	7 [19%]	
Afib (35, 80%)			
Present	7 [100%]	28 [76%]	-
Absent	0	9 [24%]	
CAD (13, 29.5%)			
Present	1 [14%]	12 [32%]	0.35*
Absent	6 [86%]	25 [68%]	
Anemia (32, 73%)			
Present	4 [57%]	28 [76%]	.321*
Absent	3 [43%]	9 [24%]	
CHF (21, 48%)			
Present	4 [57%]	17 [46%]	0.588*
Absent	3 [43%]	20 [54%]	
CKD (15, 34%)			
Present	4 [57%]	11 [30%]	.207*
Absent	3 [43%]	26 [70%]	
Requirement of products (29, 66%)			
Yes	3 [43%]	26 [70%]	.207*
No	4 [57%]	11 [30%]	
Severe anemia [Hb <8 mg/dl] (17, 38%)			
Yes	2 [29%]	15 [40%]	.689**
No	5 [71%]	22 [60%]	
Mechanical ventilation (7, 16%)			
Yes	6 [86%]	1 [2.7%]	.000*
No	1 [14%]	36 [97.3%]	
ICU stay (28, 64%)			
Yes	6 [86%]	22 [59.5]	.39*
No	1 [14%]	15 [40.5]	
Hypotension (11, 25%)			
Yes	4 [57%]	7 [19%]	.05*
No	3 [43%]	30 [81%]	

**p value is obtained from Fisher's exact test; **p value is obtained from Chi- square test; HTN: Hypertension, Afib: Atrial fibrillation, CAD: Coronary artery disease, PVD: Peripheral vascular disease, CHF: Congestive heart failure, CKD: Chronic kidney disease, Hb: Hemoglobin, ICU: Intensive care Units*

Discussion

Though very effective in the prevention and treatment of venous thromboembolism, warfarin leads to the largest number of adverse drug reactions requiring emergency treatment in patients over 65 years. The most common manifestation is acute bleeding requiring thousands of hospitalizations every year.(14–16) Recently prothrombin complex concentrate (PCC) has been used for rapid anticoagulation reversal along with vitamin K. PCCs are lyophilized concentrates of vitamin K-dependent coagulation factors (F) either activated or nonactivated. Recent trials have established the safety and the efficacy of four factor prothrombin complex concentrate [4F-PCC] versus plasma for vitamin K antagonist reversal.(2,12,17)multicenter, open-label, noninferiority trial, nonsurgical patients were randomized to 4F-PCC (containing coagulation factors II, VII, IX, and X and proteins C and S These trials have used nonactivated 4F-PCC containing FII, FVII, FIX, FX, and proteins C and S, which is manufactured and marketed as Kcentra© by CSL Behring GmbH and distributed by CSL Behring LLC.(5,18)Kcentra® Administration of 4F-PCC requires prior administration of vitamin K. The median duration and volume of 4F-PCC administered have been reported to be 17 minutes and 100 ml as compared to 148 minutes and 814 mL of fresh frozen plasma in prior studies. Small observational studies have also shown it to be effective in the urgent reversal of direct oral anticoagulants (DOACs) as well.(19,20) an unclear safety profile, and imparts a substantial financial burden. This has led to the off-label use of four-factor prothrombin complex concentrates (4F-PCC Unlike FFP it can be administered rapidly via the intra-

venous route. In a recent report, it is been successfully administered intraosseous route as well.(21) Despite the rapidity of administration, in clinical trials comparing FFP with 4F-PCC rapid reversal of INR has not been shown to have better clinical outcomes, lesser mortality.(16,22) However, it is superior in terms of fewer episodes of fluid overload. Unlike blood derivatives, it does not carry the risk of vertical transmission of viral infections as well.(23)but observational studies suggest that it is associated with transfusion-related adverse reactions (e.g., volume overload To date, most of the studies on 4F-PCC have been observational. These studies mostly include patients with severe life-threatening bleed.(9,24)requiring urgent neurosurgical procedures, from January, 2014 (implementation of 4-PCC therapy The first randomized clinical trial included 216 patients for 2 years. This study reported that the most common site of bleeding for which 4F- PCC was administered was gastrointestinal (60%) as in our study. The same was administered for intracranial bleeding in 10 to 20% of patients requiring 4F-PCC. (1,2,21)plasma, or the newly approved agent, four-factor prothrombin complex concentrate (4F-PCC

We intended to study the indication, and outcome of 4F-PCC in a community based tertiary care center. The most common indication for 4F-PCC use in this study was a major bleed. Similar to previous studies the most common indication of VKA use was atrial fibrillation, thromboembolism. The most common medical comorbidities as shown in previous studies were hypertension, atrial fibrillation, and anemia. (6,25) Alike previous studies the most common site of bleed was gastrointestinal in origin. Table 4 depicts the role of 4F- PCC, as mentioned in the literature. It is been successfully used in patients with multiple non-surgical, surgical indications. As mentioned, it has also been reported to be effective in achieving hemostasis in patients on various anticoagulants. Its efficacy has been shown among neonates, children and other special subgroups of patients.(18) In view of its efficacy, it's off label use is extending to various populations subgroups.(25–28)safety and dosing for off-label indications are limited, but they are included in massive bleeding protocols.\nMETHODS: This was a retrospective review of cases treated with four-factor PCCs (4F-PCCs In our study, 56% of patients were over the age group of 80 years as compared to 40% in previous studies. One could infer that 4F-PCC could be safely used in the elderly population.

Table 4. Role of 4F-PCC as mentioned in literature.

Number	Group	Subgroup
1.	Anticoagulants	Vitamin K agonist - Warfarin - Rodenticide poisoning Direct Oral Anticoagulants - Apixaban - Rivaroxaban - Endoxaban - Dabigatran Injectables - Fondaparinux
2.	Nonsurgical causes	Central Nervous System bleed - Subdural - Subarachnoid - Intra-parenchymal Gastrointestinal bleed Musculoskeletal Intraabdominal Genitourinary Hematoma Pericardial Others
3.	Surgical	Central Nervous System - Subdural - Subarachnoid - Intra- parenchymal - Traumatic Cardiac Abdominal Orthopedic Spinal Urgent procedures Perioperative bleeding Trauma Fractures Transplant - Liver - Cardiac (Adult, Paediatric) Devices - Left ventricular Assist Devices - Mechanical Heart Valve Others
4.	Special population	Neonates Children Pregnancy Jehovah's witness Liver disease

The proportions of patients achieving effective hemostasis within 24 hours have been reported to be

72.4% similar to this study. Mortality in our study was higher as compared to the prior studies. A previous randomized control study comparing the efficacy and safety of 4F-PCC with plasma reported a mortality of 9.7 % vs 4.6 % at the end of 45 days.(2)multicenter, open-label, noninferiority trial, nonsurgical patients were randomized to 4F-PCC (containing coagulation factors II, VII, IX, and X and proteins C and S Mortality in our study was higher at 16% and the factors associated with mortality were the presence of severe anemia, intracranial bleed, the requirement of blood products; hypotension and the requirement for mechanical ventilation. Among these, the presence of hypotension and the requirement of mechanical ventilation were statistically significant. We did a literature search of factors associated with poor outcome following 4F- PCC administration, and have classified these into host, disease, and treatment related factors in Figure 1 (4–12)Kcentra®.

In a study of 81 patients by Huang et al, comparing the efficacy of 4F- PCC among patients with and without liver disease, poor outcome was observed in patients with liver disease. Risk factors among patients with liver disease were concomitant anticoagulation use, ICU stay, not achieving post treatment target INR.(5,18)Kcentra® Among our patients, hypotension and ICU stay were associated with higher mortality. In a study including 62 patients on DOAC requiring urgent reversal following traumatic intracranial hemorrhage, higher mortality was reported in the 65-79 age group.(6) However, in our study, this association was not found.

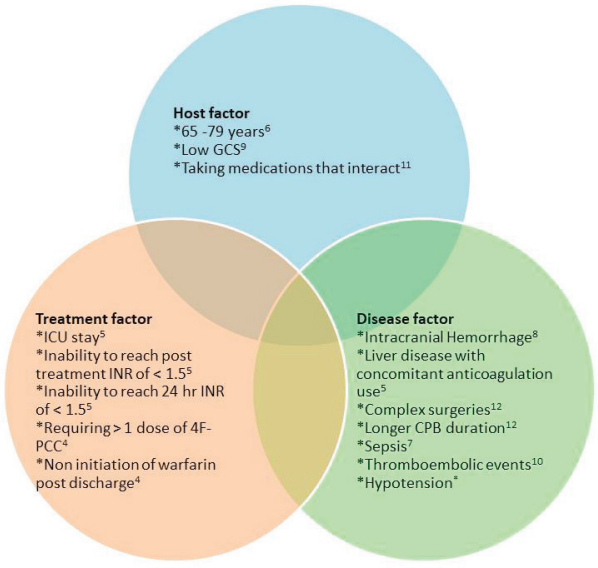

Figure 1. Factors contributing to poor outcome in patients on 4F-PCC

Studies comparing 4F-PCC to plasma have shown to have similar incidences of any adverse event, a severe adverse event, thromboembolic events, and deaths. No episodes of thromboembolic events were reported among our patients. (10,29)patients require emergent warfarin reversal due to active bleeding, supratherapeutic international normalized ratio, or emergent diagnostic or therapeutic interventions. Various agents can be used for emergent warfarin reversal, including fresh frozen plasma (FFPLimitations of this study were small sample size, the retrospective nature of the study, lack of details of the total cost incurred, uniformity in obtaining post treatment INR, and details of long-term outcomes. (30,31)However, the strength of this study is in establishing the efficacy and safety of 4F-PCC in community-based health care centers.

In conclusion, 4F- PCC is a safe and effective agent for reversal of INR among all patients receiving vitamin K antagonists requiring an urgent reversal including the elderly. Most commonly it is used for patients with supratherapeutic INR and symptomatic bleed. Most patients have clinical improvement with a single, weight-adjusted dose. Various host, disease, treatment related factor influence the outcome in these patients (32). As most of these factors have been obtained from retrospective studies, future prospective and randomized trials are needed to validate and prognosticate these.

Lessons for Practice

- 4F- PCC is a safe and effective agent for reversal of INR among all patients receiving vitamin K antagonists requiring an urgent reversal including the elderly
- Hypotension and requirement of mechanical ventilation are independent risk factors associated with higher mortality, despite reversal of coagulopathy.
- Most patients have clinical improvement with a single, weight-adjusted dose of 4F- PCC

Conflicts of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

Institutional Ethics Approval: Approved by Metrowest Medical Center Institutional Review Board; IRB#2019-052

Authors contribution: AKM, KS were instrumental in data collection. AKM, AL were involved with data analysis and manuscript writing. AKM, AL were involved with formatting of the manuscript. AL, SG were involved with editing and finalizing. All the authors confirm that they had access to the data and a role in writing the manuscript

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