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Short Communication

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Fixed-Dose Four-Factor Prothrombin Complex Concentrate for Reversal of Anticoagulation: Evaluation of Efficacy, Safety, and Cost Savings

Amer Al Homssi[a, e], Ryan Lokkesmoe[b], Ryan Powers[a], Benjamin Jung[c], Farheen Chunara[a], Aniko Szabo[a], Lisa Baumann Kreuziger[d]

Abstract

Background: Four-factor prothrombin complex concentrate (4F-PCC) is used for warfarin reversal and off-label management of bleeding in patients taking direct oral anticoagulants (DOACs). Dosing strategies that optimize hemostatic efficacy and cost, such as fixed dosing of 4F-PCC, are still under evaluation. The objective of this study was to retrospectively evaluate the efficacy, safety, and cost savings of fixed-dosing of 4F-PCC (1,500 IU for warfarin, 2,000 IU for DOACs).

Methods: Patients records from October 1, 2018, to April 30, 2021, at three hospitals within the Froedtert Health System were retrospectively reviewed for individuals who received fixed-dosing of 4F-PCC. Safety and efficacy were reflected in 30-day bleeding and thrombosis events, the need for repeat doses, and all-cause mortality. Cost savings were defined as the difference in the cost between the administration of fixed-dosing and the projected weight- and international normalized ratio (INR)-based dosing based on the package insert for warfarin reversal or 50 IU/kg in patients treated with DOACs.

Results: A total of 592 patients received fixed-dosing of 4F-PCC during the prespecified period, of whom 541 received it for warfarin reversal (n = 414) or DOACs (n = 127) management in emergency settings. INR below 2 was achieved in 89% of patients on warfarin. Less than 5% in either group required repeat doses of 4F-PCC. Within 30 days, both groups had similar bleeding (12%) and thrombotic (5%) events. All-cause 30-day mortality rates in patients treated with warfarin and DOACs were 24% and 30%, respectively. The median cost savings of fixed-dosing per patient on warfarin and DOACs were $1,567 and $3,936, respectively, with annualized median hospital cost savings of $176,239 and $146,733, respectively.

Conclusions: Fixed-dosing of 4F-PCC had significantly less cost than adjusted dose and is associated with similar rates of thrombosis and death compared to other studies.

Keywords: 4F-PCC; Kcentra; Warfarin; Anticoagulation; Anticoagulation reversal; Fixed-dosing

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[a]Medical College of Wisconsin, Milwaukee, WI 53226, USA
[b]MetroHealth Medical Center, Cleveland, OH 44109, USA
[c]Froedtert Health, Milwaukee, WI 53226, USA
[d]Versiti Blood Center of Wisconsin, Greenfield, WI 53220, USA
[e]Corresponding Author: Amer Al Homssi, Medical College of Wisconsin, Milwaukee, WI 53226, USA. Email: ameralhomssi@gmail.com

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Introduction

Prescriptions for anticoagulation in the United States reach into the tens of millions annually [1]. The most common indications for oral anticoagulation include atrial fibrillation, venous thromboembolism, and a history of heart valve replacement [2]. In 2012, 87% of US Medicare beneficiaries taking oral anticoagulants received warfarin, a number that fell to 48% in 2017. During the same period, the total number of Medicare beneficiaries receiving direct oral anticoagulants (DOACs, apixaban or rivaroxaban) was 46% [3]. Both warfarin and DOACs are associated with an increased risk of major bleeding [3]. Reversal of anticoagulation is frequently required in severe bleeding and emergent surgical procedures [4].

Four-factor prothrombin complex concentrate (4F-PCC) with vitamin K administration is the first-line therapy in patients taking warfarin who experience significant bleed or undergo an emergent surgical procedure [4]. Dose recommendations are either based on calculations involving weight and international normalized ratio (INR), or a fixed-dose, with one study using 1,000 IU for non-intracranial major bleed or 1,500 IU for intracranial bleed [4]. The 4F-PCC agent used in our study population is Kcentra.

4F-PCC is also used for off-label management of bleeding in patients prescribed DOACs. Data evaluating the efficacy of 4F-PCC on direct factor Xa inhibitor-related major bleeding are of low quality and have largely been drawn from several single-arm case series [5]. The most used dosing is 25 - 50 IU/kg. The American College of Cardiology (ACC) expert consensus decision pathway on management of bleeding in patients on oral anticoagulants concluded that administration of 4F-PCC at a fixed-dose of 2,000 IU for severe or life-threatening bleeding in patients anticoagulated with DOACs is reasonable based on the limited evidence available [4].

The purpose of this study was to retrospectively evaluate

the efficacy, safety, and cost savings of fixed-dosing of 4F-PCC at 1,500 IU for warfarin reversal and 2,000 IU for management of patients taking DOACs with bleeding or need for emergent procedures.

Materials and Methods

In October 2018, three hospitals in the Froedtert and the Medical College of Wisconsin Hospital System transitioned to fixed-dose of 4F-PCC (Kcentra). The protocol was to administer 1,500 IU for warfarin, 2,000 IU for DOACs. The protocol allowed a repeat second fixed-dose of 4F-PCC of 500 IU. We retrospectively reviewed 592 patients who received fixed-dosing of 4F-PCC. We only included the patients taking warfarin (n = 414) or a DOACs (n = 127), who received fixed-dosing for bleeding or to prepare for an emergent procedure from October 1, 2018, to April 30, 2021. The remaining 51 patients received 4F-PCC for other indications and were excluded from the analysis. The Institutional Review Board (IRB) reviewed the proposed study and approved access to the requested data. The study was conducted in compliance with the ethical standards of the responsible institution on human subjects as well as with the Helsinki Declaration. The data were deidentified and included age, sex, weight, indication for anticoagulation, indication for reversal, pre- and post-reversal INR, doses of 4F-PCC administered, and other anticoagulation reversal agents given. The primary outcomes were considered the need for repeat dosing, 30-day hemorrhagic or thrombotic events incidence, 30-day all-cause mortality, and cost savings. Hemostatic efficacy was to be based on the need for repeat dosing and the post-reversal INR to be below 2 (which is the threshold to administer 4F-PCC) or a more stringent criterion of below 1.5. Thirty-day mortality was separated to include or exclude intracranial hemorrhage (ICH), given the higher mortality in patients who present with ICH. Charts were examined for imaging results, blood work, and encounters for 30 days post-4F-PCC administration to report any bleeding, thrombosis, or death. Cost savings were defined as the difference in the cost between the administration of fixed-dosing and weight/INR based-dosing. The cost was estimated at $2 per unit as provided by the institution. The projected weight and INR-based dosing is based on the package insert for warfarin reversal or 50 IU of factor IX/kg in patients treated with DOACs.

Statistical analysis

All statistical analyses were performed using SAS 9.4 (SAS Institute, Carey, NC). Continuous variables were summarized by mean and standard deviation (SD), and categorical variables were summarized by frequencies and percentages. Post-INR thresholds (< 1.5 and < 2) were analyzed as categorical outcomes to assess hemostatic efficacy. The costs associated with weight-based dosing (DOAC) and INR-based dosing (warfarin) were summarized per patient and aggregated annually by year. Differences in costs were evaluated using descriptive statistics, and cumulative costs were calculated for each dosing strategy.

Results

A total of 592 patients received fixed-dosing 4F-PCC during the prespecified period (from October 1, 2018, to April 30, 2021). Of these, 541 patients received 4F-PCC for either warfarin reversal (n = 414) or DOACs (n = 127) hemorrhage management and emergent invasive procedures in emergency settings; these patients were included in the analysis. Situations requiring emergent procedures such as transplant, trauma, hernia or ischemic bowel, vascular repair, cardiac surgeries and catheterization, and line placement were observed. 4F-PCC was administered shortly prior to surgeries. Patient characteristics were similar in both groups. The mean age was 71 years (SD 15), 56% (n = 232) were males, and the mean weight was 87 kg (SD 26) among the warfarin group. The mean age was 74 years (SD 13), 61% (n = 77) were males, and the mean weight was 85 kg (SD 22) among the DOACs group. Atrial fibrillation was the leading indication for anticoagulation, comprising 62% (n = 334) of patients, and venous thromboembolism was the cause in 25% (n = 134) of cases (Table 1). Of note, the protocol was for providers to order 4F-PCC 1,500 (based on factor IX content) for warfarin reversal and 2,000 IU for DOAC management. However, the doses administered were changed by the pharmacy team to the actual units present in the vials used resulting in the slightly higher doses administered as described below.

Warfarin group

Reversal for patients on warfarin was needed in 65% (n = 269) of cases for bleeding and 32% (n = 134) of cases pre-procedure. The remaining 3% (n = 11) received 4F-PCC for the correction of supratherapeutic INR. Of cases presenting with bleeding, 42% (n = 112) were due to ICH and 30% (n = 81) from gastrointestinal bleeding (GIB). Of the patients, 67% (n = 277) had a pre-reversal INR between 2 and 6, and 20% (n = 84) had an INR greater than 6. The mean dose of 4F-PCC administered was 1,636 IU (SD 367). Of patients treated with 4F-PCC for warfarin, 82% also received intravenous (IV) vitamin K with 4F-PCC, and the remaining patients did not receive any vitamin K. Fresh frozen plasma (FFP) was used in only 18% (n = 74) of the patients treated and was given with 4F-PCC at a median of two units per patient (interquartile range (IQR): 2 - 4) (Table 1).

Post-reversal INR below 2 and 1.5 was achieved in 89% (n = 341) and 56% (n = 215) of patients, respectively (Table 2). Patients who received 4F-PCC, vitamin K, and FFP (15%, n = 64) had a higher mean pre- and post-4F-PCC INR of 5.2 and 1.7, respectively. Patients who received 4F-PCC and vitamin K only (67%, n = 276) had a mean pre- and post-4F-PCC INR of 4.3 and 1.5, respectively. Patients who received 4F-PCC only (15%, n = 64) had the lowest pre- and a similar post-4F-PCC mean INR with 3.0 and 1.6, respectively (Table 3).

Within 30 days, bleeding events occurred in 12% (n = 49) of patients with a mean time to event of 9 days (SD 7). Thirty-day bleeding events occurred in 7% (n = 8) of patients with ICH and 19% (n = 15) of patients with GIB. Thrombotic

Table 1. Patient Characteristics

Characteristics	Warfarin (n = 414)	DOACs (n = 127)
Males (%)	232 (56)	77 (61)
Mean age (SD)	71 (15)	74 (13)
Mean weight (SD)	87 (26)	85 (22)
Anticoagulation indication (%)		
Atrial fibrillation	248 (60)	86 (68)
Venous thromboembolism	100 (24)	34 (26)
Other	66 (16)	7 (6)
Pre-reversal INR (%)		
2 - 4	219 (61)	-
4 - 6	58 (16)	
> 6	84 (23)	
DOACs type (%)	-	
Apixaban		85 (67)
Rivaroxaban		42 (33)
Mean dose of 4F-PCC (SD)	1,636 (367)	2,106 (243)
Reason for administration (%)		
Pre-procedure	134 (32)	15 (12)
Bleed	269 (65)	111 (87)
ICH	112 (42)	70 (63)
GIB	81 (30)	24 (22)
Other	11 (3%)	1 (1%)
IV vitamin K given (%)	340 (82)	-
FFP administered (%)	74 (18)	12 (9)

ICH: intracranial hemorrhage; GIB: gastrointestinal bleed; SD: standard deviation; INR: international normalized ratio; DOACs: direct oral anticoagulants; FFP: fresh frozen plasma; 4F-PCC: four-factor prothrombin complex concentrate; IV: intravenous.

Table 2. Outcomes

Outcomes	Warfarin (n = 414)	DOACs (n = 127)
Post-reversal INR		
< 2	341 (89)	-
< 1.5	215 (56)	
Second dose needed (%)	16 (4)	5 (4)
30-day hemorrhagic event (%)	49 (12)	15 (12)
Mean time to event in days (SD)	9 (7)	8 (6)
30-day thrombotic event (%)	23 (6)	6 (5)
Venous thrombosis (%)	16 (73)	3 (50)
Arterial thrombosis (%)	6 (27)	3 (50)
Mean time to event in days (SD)	10 (8)	9 (11)
30-day mortality		
Non-ICH (%)	54 (18)	14 (25)
All-cause (%)	98 (24)	38 (30)

DOACs: direct oral anticoagulants; SD: standard deviation; ICH: intracranial hemorrhage; INR: international normalized ratio.

events within 30 days occurred in 6% (n = 23), of which the majority were venous thrombi at 73% (n = 16). The average time for thrombus development was 10 days (SD 8). Anticoagulation was resumed in 74% (n = 17) of the patients who developed thrombosis after the thrombi were identified. All-cause 30-day mortality rate, including patients who suffered from ICH, was 24% (n = 98). Excluding ICH, the mortality was 18% (n = 54) (Table 2).

Less than 5% (n = 16) required a second dose of 500 IU for bleeding recurrence or to decrease the post-reversal INR further. The median weight of the patients who received a second dose was higher than the entire group at 94 kg (IQR: 83 - 126). Among those patients who received a second dose, the first dose of 4F-PCC ranged from 1,558 to 5,360 IU, with three patients receiving above 1,700 IU. Two patients had an INR above 6 before 4F-PCC administration, and two patients had an INR above 2 after the reversal. Of the patients, 50% (n = 8) requiring a second dose received the agent prior to procedures, while the other half received it for an ICH. Two patients had a hemorrhagic outcome, and two (one who also had a hemorrhagic event) had thrombotic events within 30 days. Thirty-day mortality was high at 56% (n = 9); one from a hemorrhagic event and none from a thrombotic event, and the vast majority (n = 7) presented with an ICH (Table 4).

DOACs group

Administration of fixed-dosing of 4F-PCC for patients in our study taking DOAC occurred for bleeding in 87% (n = 111), of which 63% (n = 70) were for ICH and 22% (n = 24) for GIB. The remaining 13% (n = 16) received 4F-PCC prior to emergent procedures. The mean dose of 4F-PCC administered was 2,106 IU (SD 243) (Table 1).

Within 30 days, bleeding events occurred in 12% (n = 15) of patients with a mean time to event of 8 days (SD 6). Thirty-

Table 3. Warfarin Outcomes Based on Interventions

Outcomes	Mean pre-reversal INR	Mean post-reversal INR
4F-PCC only 15% (n = 64)	3.0	1.6
4F-PCC and vitamin K 67% (n = 276)	4.3	1.5
4F-PCC, vitamin K, and FFP 15% (n = 64)	5.2	1.7

FF: fresh frozen plasma; INR: international normalized ratio; 4F-PCC: four-factor prothrombin complex concentrate.

Table 4. 4F-PCC Repeat Dosing of 4F-PCC 500 IU

	Warfarin (n = 16)	DOACs (n = 5)
Median weight, kg (IQR)	94 (83 - 126)	95 (86-100)
Indication		
Pre-procedure	8	
Bleeding	8 (all ICH)	
Range of first dose of 4F-PCC, IU	1,558 - 5,360	1,637 - 2,252
30-day hemorrhagic event (%)	2 (13)	3 (60)
30-day thrombotic event (%)	2 (13)	0 (0)
30-day mortality	9 (56)	2 (40)

DOACs: direct oral anticoagulants; IQR: interquartile range; 4F-PCC: four-factor prothrombin complex concentrate; ICH: intracranial hemorrhage.

day bleeding events occurred in 7% (n = 5) of patients with ICH and 4% (n = 1) of patients with GIB. Thrombotic events within 30 days occurred in 5% (n = 6), of which 50% (n = 3) were venous thrombi. The average time for thrombus development was 9 days (SD 11). The three patients who developed arterial thrombosis had thrombectomies, while two of the three patients with venous thrombosis had anticoagulation resumed. All-cause 30-day mortality rate, including patients who suffered from ICH, was 30% (n = 38). Excluding ICH, the mortality was 25% (n = 14) (Table 2).

Less than 5% (n = 5) required repeat doses. The median weight of the patients who received a second dose was 95 kg (IQR: 86 - 100). The first dose ranged from 1,637 to 2,252. Patients received the 4F-PCC either for ICH or pre-procedure. Three patients had a hemorrhagic event within 30 days, while no one had a thrombotic outcome. Two of the five patients died within 30 days (Table 4).

Cost savings

Considering the cost of $2 per unit of 4F-PCC (Kcentra) as provided by our institution's pharmacy, the median cost savings of fixed-dosing per patient taking warfarin was $1,567 (IQR $455 - $2,947). The annualized median hospital cost saving was $176,239 (IQR $57,010 - $291,950). The median cost savings of fixed-dosing per patient on DOACs was $3,936 (IQR $2,716 - $5,632). The annualized median hospital cost saving was $146,733 (IQR $68,322 - $202,402) (Table 2).

Discussion

Warfarin group

Three small single-arm studies have evaluated the efficacy, safety, and cost savings of fixed-dosing of 4F-PCC in patients requiring urgent or emergent warfarin reversal [6-8]. In addition, four small comparison studies have evaluated differences in outcomes between fixed-dose and variable dose strategies for such patients [9-12]. In summary, the single-arm studies reported adequate INR reversal and minimal thrombotic risk in most patients treated with 1,500 IU of 4F-PCC [6-8], while the comparison studies showed mixed results due to variability in INR goals and quantity of fixed-dose administered [9-12]. A recent meta-analysis evaluating fixed-dosing vs. variable-dosing 4F-PCC in warfarin reversal concluded that fixed-dosing may be considered effective and safe [13]. It included 10 studies with a total of almost 988 patients. In the variable-dosing groups, mortality was 20%, thrombotic events at < 2%, INR goal achieved in 81%, and 3% required repeat dosing. The fixed-dosing group analysis showed the mortality at 13%, thrombotic events at 2%, INR goal achieved in 70%, and an additional 4F-PCC doses required in 11% of cases. The higher incidence of thrombotic events reported in our study is likely due to the longer follow-up compared to the other studies referenced.

DOACs group

A recent meta-analysis of 25 studies and 1,760 patients with direct factor Xa inhibitor-associated bleeding found a fixed-dosing strategy to be a safe and effective alternative to variable weight-based dosing while reducing 4F-PCC usage [14]. In the variable-dosing groups, mortality was 21%, ICH mortality 29%, thrombotic events at 3%, and hemostatic efficacy at 79%. The fixed-dosing group analysis showed the mortality at 16%, thrombotic events at 3%, and hemostatic efficacy at 74%. Another recent meta-analysis of 36 studies involving 1,832 patients with ICH taking DOACs found similar rates in the overall anticoagulation reversal (4F-PCC: 77%), mortality (4F-PCC: 26%), and thromboembolic event (4F-PCC: 10%) rates among patients receiving 4F-PCC, andexanet alfa, or idarucizumab [15]. In line with our findings, in the control group in the ANNEXA-I study who received usual care (including patients who received PCC), 5.6% of patients had at least one thrombotic event within 30 days [16].

Cost savings

A recent retrospective review compared the projected cost of andexanet to the actual cost of 4F-PCC for the reversal of major bleeding. Most of the patients who would have been candidates to receive andexanet (91% of 46 patients) were given weight-based 50 IU/kg of 4F-PCC with a median actual cost of $5,670 (IQR $2,430 - 8,100). Whereas the actual median cost for patients who received 4F-PCC and would not have been candidates for andexanet (80 patients) was $4,455 (IQR $1,620 - 8,100). The study concluded that weight-based 4F-PCC for reversal was significantly less expensive than the projected cost of andexanet [17]. In our study, the projected median cost of weight-based 4F-PCC per patient was $8,255 (IQR $6,970 - $9,800). The mean weight of patients on the DOACs in our study was 85 kg (SD 22) and we calculated the cost of 4F-PCC based on the unit price of $2; however, no data

on weight nor price per unit were provided by the other study to account for the difference in the median cost.

Limitations

Due to the retrospective nature of our study, the lack of uniform documentation of responsiveness to reversal, and the lack of a control group (weight- and INR-based dosing), we did not have data showing direct efficacy. However, efficacy can be inferred from the post-4F-PCC administration INR < 2 [18] in almost 90% of cases on warfarin, minimal need for repeat doses (4%), and the low 30-day hemorrhagic events (12%).

Conclusions

4F-PCC has many advantages over other reversal agents, including the ability to quickly mix and administer doses. Fixed-dosing further simplifies and streamlines the process, reducing the potential for errors in communication, calculation, and combination of ingredients when compared to variable dosing strategies. Additionally, fixed-dosing may improve cost efficacy without reducing quality of care [18]. Dosing strategies that optimize anticoagulant reversal and cost remain under evaluation, leading to equivocal guideline recommendations [4]. We report real-world outcomes in a cohort of patients managed in academic and community hospitals with fixed-dose 4F-PCC in emergent situations, showing similar outcomes to studies with variable dosing with significant cost savings.

Learning points

Fixed-dosing of 4F-PCC had significantly less cost than adjusted dose. Fixed-dosing of 4F-PCC is associated with similar rates of thrombosis and death compared to other studies.

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Conflict of Interest

None to declare.

Informed Consent

Informed consent was waived by the IRB.

Author Contributions

AA, RL, RP, and LBK contributed to data collection, analysis, writing and editing the manuscript. BJ contributed to data collection and analysis. FC and AS contributed to data analysis, writing and editing the manuscript.

Data Availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Abbreviations

PCC: prothrombin complex concentrate; 4F-PCC: four-factor prothrombin complex concentrate; DOAC: direct oral anticoagulant; INR: international normalized ratio; ICH: intracranial hemorrhage; GIB: gastrointestinal bleed; IQR: interquartile range

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