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Fresh Frozen Plasma versus Prothrombin Complex Concentrate for Warfarin Reversal in the Emergency Department: A Retrospective Cohort Study of Clinical Outcomes and Costs

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Abstract

Aim: Rapid reversal of warfarin-associated coagulopathy is a frequent challenge in emergency departments (EDs). Four-factor prothrombin complex concentrates (PCCs) correct the international normalized ratio (INR) more rapidly than fresh frozen plasma (FFP), but their clinical and economic impact in routine practice, particularly in resource-limited settings, remains uncertain.

Materials and Methods: This retrospective cohort study was conducted in the ED of a tertiary university hospital. Adult warfarin-treated patients presenting with INR >1.2 and who received FFP alone or PCC (Cofact) alone for supratherapeutic INR and/or warfarin-associated bleeding were included. Clinical, laboratory, and direct product cost data were abstracted from electronic records. Primary outcomes were INR reduction (ΔINR) and achievement of target INR thresholds (≤1.5 and ≤1.8). Secondary outcomes included acute kidney injury (AKI), hospital and intensive care unit (ICU) length of stay, ED disposition, in-hospital mortality, and direct product costs. Multivariable logistic regression was used to explore independent associations.

Results: We analyzed 119 patients (92 FFP, 27 PCC). PCC was associated with a lower final INR and a greater ΔINR than FFP. PCC-treated patients were more likely to have gastrointestinal bleeding and markers of greater illness severity. AKI occurred more frequently in patients receiving PCC, and PCC use was independently associated with AKI after adjustment for age and presenting INR. PCC recipients had longer hospital stays, higher ICU utilization, and a numerically higher in-hospital mortality, although mortality estimates were imprecise. Both direct product costs and the cost per unit reduction in INR were substantially higher with PCC.

Conclusions: In this real-world ED cohort, PCC achieved superior laboratory reversal compared with FFP but was preferentially used in patients who were clinically sicker. While PCC was associated with higher AKI rates, longer hospital stays, and greater direct product costs, these findings likely reflect baseline illness severity and confounding by indication rather than a direct effect of the reversal agent. Our results are primarily hypothesis-generating and underscore the need for larger prospective, multicenter studies with comprehensive cost-effectiveness and safety analyses.

Keywords: Warfarin, plasma, fresh frozen, prothrombin complex concentrates, emergency service, hospital, acute kidney injury, costs and cost analysis

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Introduction

Warfarin is a long-standing oral anticoagulant widely used in the treatment of cardiovascular disease and in the prevention of thromboembolic events. Its efficacy in reducing morbidity and mortality has been demonstrated in conditions such as atrial fibrillation, mechanical heart valve prostheses, deep vein thrombosis, and pulmonary embolism (1-3). However, because warfarin has a narrow therapeutic window, requires careful dose adjustment, and is subject to numerous drug-drug and drug-food interactions, patients are at increased risk of both thromboembolism and bleeding (1,3,4).

Major bleeding is one of the most important clinical problems in patients presenting with warfarin-associated coagulopathy or supratherapeutic international normalized ratio (INR). Intracranial hemorrhage, gastrointestinal (GI) bleeding, and other bleeding foci that cause massive blood loss may result in death or permanent disability (5,6). Many warfarin-treated patients presenting to the emergency department (ED) are rapidly evaluated for bleeding or urgent invasive procedures, and fast and effective reversal of anticoagulation becomes a priority (5,7).

Fresh- frozen plasma (FFP) has been one of the most commonly used treatments for warfarin reversal. By providing coagulation factors, FFP aims to lower the INR, but it has important limitations, including large infusion volumes, prolonged administration time, volume overload, and transfusion-related reactions (5,6). In recent years, prothrombin complex concentrates (PCCs) have gained prominence as an alternative. Four-factor PCCs contain factors II, VII, IX, and X as well as natural anticoagulants, and have been shown to normalize INR more rapidly and predictably than FFP, with lower volumes and shorter administration times, which may be advantageous in hemodynamically fragile patients (7-10).

Randomized controlled trials and observational studies consistently demonstrate that PCCs are superior to FFP in terms of the speed and extent of INR correction. Some reports also suggest possible advantages in functional outcomes, although clear mortality benefits have not been consistently demonstrated, and concerns remain about thromboembolic complications and higher direct product costs (7,9,11). Given limited healthcare resources and the substantial cost burden of blood products, it is important to evaluate reversal strategies not only in terms of clinical efficacy but also with respect to cost and resource use, particularly in developing countries (5,9).

The aim of this study was to compare the clinical and economic outcomes of FFP versus PCC (Cofact) for anticoagulation reversal in warfarin-treated patients presenting to the ED with warfarin-associated coagulopathy. Specifically, we compared laboratory response (INR reduction), hospital and intensive care unit (ICU) lengths of stay, in-hospital mortality, development of acute kidney injury (AKI), and direct product costs between patients receiving FFP alone and those receiving PCC alone.

Materials and Methods

Study Design and Setting

We conducted a retrospective cohort study in the ED of a tertiary university hospital from 1 January 2015 to 31 December 2017. Using the hospital information system, we identified all adult patients receiving warfarin (Coumadin) whose presenting INR exceeded the laboratory upper reference limit of 1.2. A total of 1,130 warfarin-treated patients with INR >1.2 were identified; 821 did not receive specific reversal with FFP or PCC and were excluded.

Among the remaining 309 patients who received FFP and/or PCC for warfarin-related INR elevation, we included only those who received FFP alone or PCC alone and who had complete clinical, laboratory, and cost data, yielding a final cohort of 119 patients (92 FFP-only and 27 PCC-only). During the study period, the choice between FFP and PCC was not randomized but was left to the discretion of the treating physician; in practice, PCC tended to be used in more clinically severe cases or when rapid INR reversal was considered particularly important.

This study was approved by the Non-Interventional Clinical Research Ethics Committee of Bezmialem Vakıf University (approval date: 02.01.2018, decision/protocol no: 1/12). Due to the retrospective nature of the study, the requirement for informed consent was waived by the ethics committee.

Eligibility Criteria

Patients were eligible if they were aged ≥18 years, were current warfarin users, had a presenting INR>1.2, and received FFP alone or PCC alone in the ED for supratherapeutic INR and/or warfarin-associated bleeding. Warfarin-associated bleeding was defined as any overt bleeding event (e.g., GI, intracranial, genitourinary, or other sites) documented in ED records during warfarin therapy.

Patients were excluded if they were younger than 18 years, had no history of warfarin use, presented with an INR ≤1.2, had a bleeding diathesis without prior warfarin exposure, received both FFP and PCC or other hemostatic products in combination, or had missing key clinical, laboratory, or cost data.

Data Collection and Variables

Data were abstracted retrospectively from the hospital information system and laboratory databases using a standardized form.

For each patient, we recorded age, sex, presenting INR, post-treatment (last) INR, baseline and last serum creatinine levels, the presence of warfarin-associated bleeding and its anatomical location, treatment type (FFP vs PCC) and the units administered, ED disposition (discharge, ward admission, or ICU admission), in-hospital mortality, hospital length of stay, and direct product costs. Economic outcomes were limited to direct product acquisition costs (the price paid by the hospital pharmacy for FFP units and PCC vials). Indirect costs, such as personnel time, laboratory monitoring, and total hospital stay costs, were not included in this analysis.

INR measurements were performed using an Amax 200 Amelung analyzer (Trinity Biotech Plc., IDA Business Park, Bray, Co. Wicklow, Ireland). The "last INR" was defined as the INR value measured within the first 24 hours after initiation of FFP or PCC treatment, or earlier if the patient was discharged or died. Because the exact timing of follow-up INR measurements varied between patients, this value should be interpreted as a pragmatic, real-world indicator of early laboratory response rather than a strictly time-standardized endpoint. As a result, comparisons of the last INR and ΔINR between treatment groups may be influenced by variability in the timing of follow-up measurements. For each patient, we calculated the change in INR (ΔINR = presenting INR, last INR). While vitamin K administration and red blood cell transfusions were part of the standard clinical protocol for warfarin reversal and major bleeding management in our ED, these interventions were inconsistently documented in the electronic records, and therefore could not be included as independent covariates in the multivariable models.

Outcomes and Definitions

The primary laboratory outcome was the magnitude of INR reduction (ΔINR) and the proportion of patients achieving target INR thresholds (≤1.5 and ≤1.8). Clinical outcomes included the development of AKI, hospital and ICU lengths of stay, ED disposition, and in-hospital mortality. Economic outcomes were the total product cost per patient and the cost per unit of INR reduction.

AKI was defined as an increase in serum creatinine from baseline of ≥0.3 mg/dL or ≥1.5 times the baseline value during hospitalization, consistent with KDIGO criteria. Baseline creatinine was defined as the first measurement obtained in the ED. Due to the retrospective nature of the study, AKI was defined solely based on serum creatinine changes, as hourly urine output data were not consistently available in the electronic medical records to fulfill all KDIGO criteria. Hospital length of stay was calculated as the number of calendar days from ED presentation to discharge or death; same-day discharge was coded as 0 days.

Statistical Analysis

Continuous variables were assessed for normality and summarized as medians with interquartile ranges (IQRs). Categorical variables were summarized as counts and percentages. Comparisons between FFP and PCC groups were performed using the Mann-Whitney U test for continuous variables and the chi-square or Fisher's exact test for categorical variables.

We constructed multivariable logistic regression models to assess the independent association between treatment type (PCC vs FFP) and in-hospital mortality, AKI development, and ICU admission, adjusting for relevant covariates (age, presenting INR, presence of GI bleeding, and/or AKI, as appropriate). Given the limited number of events for mortality (n=5) and ICU admission (n=14), these models are underpowered and should be interpreted as exploratory. In particular, due to the very low number of in-hospital mortality events (n=5), the mortality model was interpreted with extreme caution, given the potential for overfitting and imprecise effect estimates. Two-sided p values <0.05 were considered statistically significant. No formal adjustment was made for multiple comparisons. Analyses were performed using IBM SPSS Statistics, version 25.0.

Results

Patient Characteristics

We included 119 patients who presented to the ED with warfarin-associated coagulopathy. A total of 92 patients received FFP and 27 received PCC (Cofact), each as the sole reversal agent. The groups were similar in age and sex distribution. The median age was 69.0 years (IQR 62.8-77.0) in the FFP group and 67.0 years (IQR 52.5-83.0) in the PCC group (p=0.87). Men constituted 46.7% (43/92) of the FFP group and 59.3% (16/27) of the PCC group (p=0.28) (Table 1).

Baseline serum creatinine values were comparable between groups, with medians of 1.10 mg/dL (IQR 1.10-1.40) in the FFP group and 1.10 mg/dL (IQR 1.05-1.45) in the PCC group (p=0.53). Last creatinine values were significantly higher in the PCC group than in the FFP group, with medians of 1.92 mg/dL (IQR 1.11-2.36) and 1.09 mg/dL (IQR 0.83-1.53), respectively (p=0.008). The change in creatinine was-0.08 (IQR -0.29-0.10) in the FFP group and 0.12 (IQR -0.15-0.99) in the PCC group (p=0.014). AKI occurred in 15.2% (14/92) of FFP-treated patients and 37.0% (10/27) of PCC-treated patients (p=0.026) (Table 1).

GI bleeding was common in both groups, but was more frequent in the PCC group, occurring in 70.7% (65/92) of FFP patients and 92.6% (25/27) of PCC patients (p=0.021).

Table 1. Baseline clinical and cost characteristics by treatment group

Characteristic	FFP (n=92)	PCC (n=27)	p value*
Demographics			
Age (years), median [IQR]	69.0 [62.8-77.0]	67.0 [52.5-83.0]	0.870
Gender			0.280
Male, n (%)	43 (46.7%)	16 (59.3%)	—
Female, n (%)	49 (53.3%)	11 (40.7%)	—
Renal function			
Baseline creatinine (mg/dL), median [IQR]	1.10 [1.10-1.40]	1.10 [1.05-1.45]	0.530
Last creatinine (mg/dL), median [IQR]	1.09 [0.83-1.53]	1.92 [1.11-2.36]	0.008
Creatinine change†, median [IQR]	-0.08 [-0.29-0.10]	0.12 [-0.15-0.99]	0.014
AKI present, n (%)‡	14 (15.2%)	10 (37.0%)	0.026
Coagulation parameters			
Presenting INR, median [IQR]	5.71 [3.52-7.77]	6.38 [4.09-13.39]	0.110
Last INR, median [IQR]	2.23 [1.76-2.91]	1.87 [1.52-2.01]	0.008
INR reduction (ΔINR)§, median [IQR]	3.14 [1.24-5.26]	3.91 [1.94-11.55]	0.039
Bleeding and disposition			
GI bleeding present, n (%)	65 (70.7%)	25 (92.6%)	0.021
Length of stay (days), median [IQR]	1.0 [0.0-6.0]	5.0 [2.5-8.0]	0.014
Discharged from ED, n (%)¶	44 (47.8%)	5 (18.5%)	0.023**
Ward admission, n (%)¶	39 (42.4%)	17 (63.0%)	
ICU admission, n (%)¶	9 (9.8%)	5 (18.5%)	
Mortality			
In-hospital mortality, n (%)	2 (2.2%)	3 (11.1%)	0.076
Product use and direct costs			
FFP units used, median [IQR]	2 [2-4]	—	—
FFP cost per patient (USD), median [IQR]	40 [40-80]	—	—
PCC units used, median [IQR]	—	2 [1-4]	—
PCC cost per patient (USD), median [IQR]	—	260 [130-520]	—
Total FFP cost (USD)	5,680	—	—
Total PCC cost (USD)	—	9,100	—

* Mann-Whitney U test was used for continuous variables, Fisher's exact test for binary categorical variables, and the chi-square test for the three-category disposition variable. † Continuous variable representing last creatinine minus baseline creatinine. ‡ Coded as 1 for patients who developed AKI and 0 for those who did not. §ΔINR = presenting INR - last INR. ¶Disposition variable: the p value corresponds to the chi-square test for the distribution across the three categories (discharge, ward, ICU). ** Significant difference in the overall distribution of disposition. AKI: Acute kidney injury, ED: Emergency department, FFP: Fresh frozen plasma, GI: Gastrointestinal, ICU: Intensive care unit, INR: International normalized ratio, IQR: Interquartile range, PCC: Prothrombin complex concentrate, USD: United States dollars

Laboratory Response and Clinical Outcomes

INR values tended to be higher in the PCC group, with medians of 5.71 (IQR 3.52-7.77) in the FFP group and 6.38 (IQR 4.09-13.39) in the PCC group; however, this difference was not statistically significant (p=0.11). Final post-treatment INR values were significantly lower in the PCC group [median 1.87 (IQR 1.52-2.01)] compared with the FFP group [median 2.23 (IQR 1.76-2.91)] (p=0.008). The reduction in INR (ΔINR) was greater among PCC-treated patients [median 3.91 (IQR 1.94-11.55)] than among FFP-treated patients [median 3.14 (IQR 1.24-5.26)] (p=0.039).

More PCC-treated patients achieved target INR thresholds, although the differences were not statistically significant. INR ≤1.5 was reached in 7.6% (7/92) of FFP patients and 22.2% (6/27) of PCC patients (p=0.071), and INR ≤1.8 was reached in 26.1% (24/92) and 40.7% (11/27), respectively (p=0.156) (Tables 1 and 2).

Median total hospital length of stay was significantly longer in the PCC group (5.0 days; IQR 2.5-8.0) than in the FFP group (1.0 day; IQR 0.0-6.0) (p=0.014). Among patients with GI bleeding, the median length of stay was 0 days (IQR 0-4) in the FFP group and 5 days (IQR 3-8) in the PCC group (p<0.001), whereas among

those without GI bleeding, the length of stay did not differ significantly between groups. Across the entire cohort, patients who developed AKI had longer hospital stays than those without AKI (5.5 days [IQR 1-9] vs 3.0 days [IQR 0-6]; p = 0.026) (Tables 1 and 2).

Disposition from the ED differed between treatment groups. Among FFP-treated patients, 47.8% (44/92) were discharged directly from the ED, 42.4% (39/92) were admitted to a general ward, and 9.8% (9/92) were admitted to the ICU. Among PCC-treated patients, 18.5% (5/27) were discharged, 63.0% (17/27) were admitted to a ward, and 18.5% (5/27) were admitted to the ICU. The overall distribution of disposition categories differed significantly between groups (p=0.023), with higher rates of ward and ICU admission in the PCC group. ICU admission rates were numerically higher in the PCC group, but did not differ significantly (9.8% vs 18.5%; p=0.305). ICU admission did not differ significantly between patients with and without GI bleeding; however, patients who developed AKI were more likely to require ICU care (25.0% vs 8.4%; p=0.035) (Tables 1 and 2).

In-hospital mortality occurred in 2.2% (2/92) of FFP-treated patients and 11.1% (3/27) of PCC-treated patients (p=0.076). In a multivariable logistic regression model including treatment type, age, and presenting INR, PCC treatment was associated with higher odds of mortality (odds ratio (OR) 5.82; 95% confidence interval (CI) 0.86-39.30; p=0.071]. However, this association did not reach statistical significance and had a very wide confidence interval, due to the low number of events (n=5). Age and presenting INR were not independently associated with mortality (Tables 1 and 3).

In the multivariable model for AKI, after adjustment for age and presenting INR, PCC use remained significantly associated with AKI compared with FFP (OR 5.21; 95% CI 1.71-15.86; p=0.004).

Table 2. Subgroup analyses of INR targets, length of stay, and ICU admission

Analysis/subgroup	FFP	PCC (Cofact)	p value*
INR targets			
Reached INR ≤1.5, n/N (%)	7/92 (7.6%)	6/27 (22.2%)	0.071
Reached INR ≤1.8, n/N (%)	24/92 (26.1%)	11/27 (40.7%)	0.156
Length of stay (days), median [IQR]			
GI bleeding present	0 [0-4] (n=65)	5 [3-8] (n=25)	**<0.001**
GI bleeding absent	5 [0-9] (n=27)	4 [2-6] (n=2)	0.759
AKI present	5.5 [1.5-9.0] (n=14)	5.5 [1.25-7.5] (n=10)	0.840
AKI absent	0.0 [0.0-5.0] (n=78)	4.0 [3.0-8.0] (n=17)	**<0.001**
ICU admission, n/N (%)			
By treatment			
FFP	9/92 (9.8%)	—	0.305
PCC	—	5/27 (18.5%)	
By GI bleeding status (entire cohort)‡			
GI bleeding present	10/90 (11.1%)		0.743
GI bleeding absent	4/29 (13.8%)		
By AKI status (entire cohort)‡			
AKI present	6/24 (25.0%)		0.035
AKI absent	8/95 (8.4%)		

*Mann-Whitney U test was used for continuous variables; Fisher's exact test was used for proportions. ‡For the entire cohort (FFP + PCC combined), comparison of ICU admission rates by GI bleeding status (present vs absent) and by AKI status (present vs absent). AKI: Acute kidney injury, FFP: Fresh frozen plasma, GI: Gastrointestinal, ICU: Intensive care unit, INR: International normalized ratio, IQR: Interquartile range, PCC: Prothrombin complex concentrate

Table 3. Multivariable predictors of in-hospital mortality

Variable	OR	95% CI (Lower-Upper)	p value
Treatment: PCC (Cofact) vs FFP*	5.82	0.86-39.30	0.071
Age (per 1-year increase)	0.98	0.93-1.04	0.554
Presenting INR (per 1-unit increase)	0.95	0.76-1.18	0.632

Dependent variable: in-hospital mortality (0 =alive, 1 =death). Model: mortality ~ treatment_cof + age + presenting INR. Model n=119; number of events =5. CI: Confidence interval, FFP: Fresh frozen plasma, INR: International normalized ratio, OR: Odds ratio, PCC: Prothrombin complex concentrate. *Reference category: FFP

However, this association should be interpreted with extreme caution due to the significant potential for residual confounding and indication bias inherent in this non-randomized, retrospective cohort. Specifically, the model could not account for several critical determinants of renal risk such as baseline comorbidities, hemodynamic instability, clinical bleeding severity, total transfusion requirements, or potential nephrotoxic exposures which may have been more prevalent in the PCC group. Regarding other covariates, increasing age was associated with a modest but significant increase in AKI risk (OR 1.04 per year; 95% CI 1.00-1.08; p=0.029), whereas the presenting INR showed only a borderline association (p=0.067) (Table 4). In a separate model evaluating predictors of ICU admission, neither treatment type nor GI bleeding reached statistical significance; however, AKI demonstrated a trend toward significance as an independent predictor of ICU admission (OR 3.25; 95% CI 0.96-11.00; p=0.058) (Table 5).

Cost Outcomes

In the cost analysis restricted to product costs, median total cost per patient was 40 United States dollars (USD) (IQR 40-80; mean 61.7±42.3) in the FFP group and 260 USD (IQR 130-520; mean 337.0±245.8) in the PCC group (p<0.001). Total expenditure on FFP was 5,680 USD, whereas total expenditure on PCC was 9,100 USD. The cost per unit of INR reduction was also higher in the PCC group, with a median of 69.1 USD per INR unit (IQR 30.4-157.7; mean 104.3±98.7), compared with 16.0 USD per unit (IQR 8.9-51.1; mean 45.1±68.2) in the FFP group (p<0.001). When stratified by AKI, the median total product cost was 100 USD (IQR 40-130) in patients who developed AKI and 60 USD (IQR 40-120) in those who did not, representing a difference of borderline statistical significance (p=0.082) (Table 6).

Table 4. Multivariable predictors of acute kidney injury

Variable	OR	95% CI (Lower-Upper)	p value
Treatment: PCC (Cofact) vs FFP*	5.21	1.71-15.86	0.004
Age (per 1-year increase)	1.04	1.00-1.08	0.029
Presenting INR (per 1-unit increase)	0.88	0.77-1.01	0.067

Model details: Dependent variable: AKI (0 =no, 1 =yes). Model: AKI ~ treatment_cof + age + presenting INR. Model n=119; number of events = 24. AKI: Acute kidney injury, CI: Confidence interval, FFP: Fresh frozen plasma, INR: International normalized ratio, OR: Odds ratio, PCC: Prothrombin complex concentrate. *Reference category: FFP

Table 5. Multivariable predictors of ICU admission

Variable	OR	95% CI (Lower-Upper)	p value
Treatment: PCC (Cofact) vs FFP*	1.77	0.48-6.56	0.390
AKI present vs absent†	3.25	0.96-11.00	0.058
GI bleeding present vs absent‡	0.63	0.17-2.38	0.493

Model details: Dependent variable: ICU admission (0 =no, 1 =yes). Model: ICU admission ~ treatment_cof + AKI + GI bleeding. Model n=119; number of events =14. AKI: Acute kidney injury, CI: Confidence interval, FFP: Fresh frozen plasma, GI: Gastrointestinal, ICU: Intensive care unit, OR: Odds ratio, PCC: Prothrombin complex concentrate. *Reference category: FFP, †Coded as 1 for AKI present and 0 for AKI absent, ‡Coded as 1 for GI bleeding present and 0 for GI bleeding absent

Table 6. Cost outcomes by treatment and AKI status

Analysis/group	Median [IQR]	Mean ± SD	p value*
Total cost per patient (USD)			
FFP (n=92)	40 [40-80]	61.7±42.3	
PCC (n=27)	260 [130-520]	337.0±245.8	<0.001
Cost per unit INR reduction (USD per INR unit)†			
FFP (n=92)	16.0 [8.9-51.1]	45.1±68.2	
PCC (n=27)	69.1 [30.4-157.7]	104.3±98.7	<0.001
Total cost by AKI status (entire cohort)			
AKI present (n=24)	100 [40-130]	95.0±78.4	0.082
AKI absent (n=95)	60 [40-120]	112.6±156.3	

*Mann-Whitney U test. Total cost = cost of the respective reversal product (FFP or PCC), †Cost per unit INR reduction = total product cost / ΔINR (patients with ΔINR > 0 included). AKI: Acute kidney injury, FFP: Fresh frozen plasma, INR: International normalized ratio, IQR: Interquartile range, PCC: Prothrombin complex concentrate, SD, standard deviation, USD, United States dollars

Discussion

In this retrospective cohort of warfarin-treated patients requiring reversal in a tertiary ED, PCC (Cofact®) achieved greater INR reduction and lower post-treatment INR than FFP, consistent with prior randomized and observational studies (7-11). However, PCC use in our real-world cohort was associated with higher rates of AKI, longer hospital stays, higher direct product costs, and numerically higher, but statistically inconclusive, mortality compared with FFP.

Our findings align with established evidence demonstrating that four-factor PCC provides faster and more complete correction of warfarin-induced coagulopathy than FFP. In the phase IIIb plasma-controlled trial by Sarode et al. (8), most PCC-treated patients achieved target INR within 30-60 minutes, whereas INR normalization was slower and less complete with plasma. Goldstein et al. (10) similarly reported that PCC provided more rapid INR normalization and comparable safety in patients requiring urgent surgical or invasive interventions. In our cohort, PCC recipients had a larger median ΔINR and lower final INR, reinforcing the laboratory advantage of PCC observed in the literature (7-10).

Despite superior INR correction, PCC has not consistently translated into clear survival or functional benefits over FFP. Randomized trials generally showed comparable mortality and thromboembolic event rates between PCC and plasma, with the main benefit of PCC being faster and more reliable reversal (8-11). Meta-analytic data also suggest that PCC is safe and effective for vitamin K antagonist reversal, with no substantial absolute increase in thromboembolic complications, though careful patient selection is emphasized, especially in high-risk individuals (7,11). In our study, the small number of deaths limited statistical power and yielded wide confidence intervals for the mortality estimate. PCC-treated patients had a numerically higher mortality, but this association did not reach conventional statistical significance and may reflect confounding by indication, with PCC preferentially used in more severely ill or high-risk patients.

One of the most notable findings in our cohort was a higher incidence of AKI among PCC-treated patients; this association remained statistically significant even after adjustment for age and presenting INR. However, this finding must be interpreted with caution due to substantial confounding by indication. In our clinical practice, treatment allocation was not randomized, and PCC was preferentially selected for patients perceived to be more severely ill. This is evidenced by the significantly higher prevalence of GI bleeding in the PCC group (92.6% vs 70.7%, p=0.021) and by a trend toward higher presenting INR values (median 6.38 vs 5.71).

Rather than indicating a direct nephrotoxic effect of the product, these baseline differences specifically the greater hemodynamic instability and clinical complexity associated with extensive bleeding are primary drivers of both pre-renal and intrinsic kidney injury. Since the retrospective nature of our study precluded adjustment for all markers of physiological stress and transfusion requirements, the observed incidence of AKI likely reflects illness severity in patients requiring urgent reversal with PCC. We emphasize that this indication bias is an inherent limitation of the non-randomized, retrospective design and cannot be fully eliminated by statistical adjustment. Only a randomized comparison could determine whether the observed differences between PCC and FFP reflect a true treatment effect rather than being due to the baseline severity of patients selected to receive PCC.

Warfarin-associated bleeding and shock states, as well as underlying comorbidities and concurrent nephrotoxic medications, are recognized contributors to AKI in this population. The literature does not generally implicate PCC as intrinsically nephrotoxic; instead, AKI is more often related to the severity of illness and hemodynamic instability (7). The strong association between AKI and both longer hospital stays and higher ICU admission rates further supports the interpretation of AKI as a marker of overall illness severity rather than a consequence of the treatment choice itself.

Our data also showed substantial differences in direct product costs between FFP and PCC. Economic considerations are increasingly important in decisions about warfarin reversal strategies. PCC is substantially more expensive per unit than FFP, yet may reduce overall costs by shortening the length of stay and reducing transfusion-related resource use, particularly in high-risk subgroups, such as patients with intracranial hemorrhage. Khorsand et al. (9), using a Dutch health system perspective, suggested that the higher acquisition costs of PCC might potentially be offset by reductions in transfusion requirements and hospitalization-related resource utilization when broader healthcare costs are considered. In our study, the economic analysis was restricted to direct product acquisition costs-the price paid by the hospital pharmacy for FFP units and PCC vials. From this limited perspective, both the total cost per patient and the cost per unit reduction in INR were markedly higher in the PCC group. However, it must be clarified that this represents a restricted cost comparison rather than a comprehensive cost-effectiveness analysis. By excluding broader healthcare expenses such as personnel time, laboratory monitoring, and specifically

the costs associated with ward and ICU stays, we could not fully capture the potential cost-offset profile of PCC (7,9,11,12). Given that PCC recipients in our cohort experienced significantly longer hospitalizations, any potential economic advantage from faster INR correction may have been outweighed by the costs of managing patients who were more clinically complex and more severely ill. These findings underscore the necessity for future studies to incorporate total hospital costs and complication-related expenses to provide a more definitive economic evaluation. Because PCC recipients in our cohort had longer hospital and ICU stays, the true difference in overall care costs between PCC and FFP cannot be determined from acquisition costs alone, and our cost findings should therefore not be interpreted as evidence that PCC is less cost-effective than FFP overall.

Clinically, FFP is disadvantaged by the need for larger infusion volumes, longer administration times, and the risk of transfusion-associated circulatory overload and acute lung injury (5,7). PCC, in contrast, can be administered rapidly in much smaller volumes, offering pragmatic advantages for unstable ED patients and those with limited cardiac reserve. Our data do not include systematic documentation of transfusion reactions, volume overload, or thromboembolic events, limiting our ability to compare safety profiles comprehensively. As such, our conclusions regarding safety are based mainly on AKI, length of stay, and ICU utilization, all of which are heavily influenced by baseline severity of illness rather than by the reversal product alone (7,11,12).

Study Limitations

This study has several limitations that warrant consideration. First, its retrospective single-center design and modest sample size particularly in the PCC group limit both internal validity and generalizability. Second, treatment allocation was not randomized, leading to substantial confounding by indication, as PCC was preferentially used in clinically more severe cases. Because PCC recipients differed systematically from FFP recipients in baseline illness severity, our comparative findings on AKI, length of stay, and costs may not be generalizable to settings in which treatment selection is less strongly linked to clinical severity. Furthermore, detailed information on baseline comorbidities and precise bleeding severity scores was not systematically available. Notably, the inconsistent documentation of vitamin K administration and red blood cell transfusions represents a critical limitation. Since these interventions are standard components of warfarin reversal and major bleeding management, their omission from the multivariable models may have influenced the observed rates of INR correction and clinical recovery. Finally, the economic analysis was restricted to direct product acquisition costs and did not account for the broader financial impact of ICU stays or of the management of complications.

We also lacked systematic data on thromboembolic events, transfusion reactions, and volume overload; therefore, the safety comparison between FFP and PCC is necessarily incomplete. AKI assessment was limited to serum creatinine-based criteria because urine-output data and complete KDIGO staging parameters were not consistently available in the retrospective electronic medical records. The economic analysis was restricted to direct product acquisition costs of FFP and PCC excluded ward or ICU stays, procedures, imaging, or readmissions. Multiple outcomes and subgroup analyses were performed without adjustment for multiple comparisons; therefore, secondary findings should be interpreted as exploratory and hypothesis-generating.

Conclusion

Among warfarin-treated patients presenting to the ED with supratherapeutic INR and/or warfarin-associated bleeding, 4-factor PCC (Cofact®) achieved more rapid and pronounced INR correction than FFP, consistent with previous randomized and observational studies. In this real-world ED cohort, 4-factor PCC achieved superior laboratory reversal compared with FFP but was administered to clinically sicker patients and was associated with higher AKI rates, longer hospitalizations, and greater direct product costs. Given the small number of in-hospital mortality events, our findings were underpowered to detect definitive survival differences and should therefore be interpreted with caution. The observed association between PCC treatment and AKI is likely driven by confounding by indication and baseline illness severity rather than a direct nephrotoxic effect of the reversal agent. These findings are primarily hypothesis-generating and underscore the need for larger prospective, multicenter studies with comprehensive cost-effectiveness and safety analyses to clarify the clinical impact of PCC across different warfarin-related bleeding scenarios.

Given the retrospective, non-randomized design, modest sample size particularly in the PCC group and incomplete data on key clinical confounders and safety endpoints, these findings should be interpreted with caution and regarded primarily as hypothesis-generating. Decisions to use PCC versus FFP in the ED should balance the need for rapid INR normalization with the patient's baseline clinical status, renal risk, bleeding site, and local economic constraints. Larger prospective multicenter studies with standardized treatment protocols and comprehensive cost-effectiveness and safety analyses are needed to clarify the clinical and economic impact of PCC in different warfarin-related bleeding scenarios.

Ethics

Ethics Committee Approval: This study was approved by the Non-Interventional Clinical Research Ethics Committee of Bezmialem Vakıf University (approval date: 02.01.2018, decision/protocol no: 1/12).

Informed Consent: Due to the retrospective nature of the study, the requirement for informed consent was waived by the ethics committee.

Author Contributions

Concept: H.İ.Ç., E.S. Design: E.S., B.G., Data Collection or Processing: H.İ.Ç., Y.U., Analysis or Interpretation: H.İ.Ç., S.B., E.S., Literature Search: H.İ.Ç., M.Ş., B.G., B.T., Writing: H.İ.Ç., B.T., B.G.,

Footnotes

Conflict of Interest: Bahadır Taşlıdere is an Associate Editor of the Eurasian Journal of Emergency Medicine but had no role in the editorial process. Independent editors evaluated the manuscript. The other authors declared no conflicts of interest.

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