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Title: Association of Four-Factor Prothrombin Complex Concentrate with Subsequent Plasma Transfusion: A Retrospective Cohort Study

Short title: Association of 4FPC with Plasma Transfusion

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Abstract

Objective: To assess whether patients prescribed four-factor prothrombin complex concentrate (4FPC) received less plasma during the following 24-hour period than those treated for the same indications who received only plasma.

Introduction: It is unclear whether 4FPC is associated with a reduction in subsequent plasma transfusion. This is important for minimizing transfusion-associated risks and for inventory management.

Materials and Methods: We retrospectively studied patients treated for bleeding or coagulopathy. Individuals receiving 4FPC were matched by indication to patients treated with only plasma. Blood products received during 24-hour follow-up were compared between 4FPC and plasma-only patients.

Results: There was no difference in the number of patients receiving additional plasma (19 (21%) 4FPC patients v 31 (34%) plasma-only patients, p=0.07), nor in the median number of additional plasma units received (0 units for both groups, interquartile range [0, 0] for 4FPC

patients v [0, 1] for plasma-only patients, p=0.09). Subgroup analysis comparing patients who received 4FPC for on-label versus off-label indications found no difference in the number of patients receiving plasma nor in the median number of plasma units received.
Conclusion: 4FPC was prescribed to a diverse set of patients and administration was not associated with reduced plasma transfusion at our institution.

Keywords: coagulation factor concentrate, plasma, transfusion therapy

Introduction

Four-factor prothrombin complex concentrate (4FPC) is prepared from human plasma and contains the vitamin K-dependent coagulation factors II, VII, IX, and X, in addition to proteins S and C, heparin, and antithrombin III. In 2013, the Food and Drug Administration (FDA) approved 4FPC for the urgent correction of vitamin K antagonist (VKA) therapy in patients with acute major bleeding. Historically, agents for warfarin correction have included vitamin K and plasma. Plasma is cheaper per dose and provides a more physiologic blend of coagulation factors compared to 4FPC. However, its transfusion requires ABO matching, its effect on international normalized ratio (INR) is slow, and large volumes are required to achieve meaningful doses of coagulation factors. Plasma transfusion also introduces the risk of complications, such as transfusion-associated circulatory overload, transfusion-associated lung injury, transfusion-

transmitted infections, transfusion-related immune modulation, and allergic reactions. 4FPC obviates these risks but remains more expensive per dose. The average wholesale price for 4FPC in the United States was recently quoted at $3 per unit in the Micromedex Red Book (Kcentra: Product Information, 2018), while the most recent National Blood Collection and Utilization Survey of blood collection and transfusion in the United States found that hospitals paid a median price of $54 per unit of plasma (Ellingson, *et al.*, 2017). This means that, for a 70-kilogram (kg) patient with an INR of 3, one dose of 4FPC would cost $5,250 (70 kg x 24 units/kg x $3/unit) using dosing based on the FDA-approved prescribing information (CSL Behring, 2018). Conversely, one dose of plasma for a 70-kg patient would cost $151.20 (70 kg x 10 mL/kg x 1 unit/250 mL x $54/unit) using minimum dosing of 10 mL/kg based on a recent multicenter study of plasma use in the United States (Triulzi, *et al.*, 2015).

The safety and efficacy of 4FPC for urgent VKA correction in bleeding patients have been demonstrated in a prospective, multicenter randomized controlled trial (Sarode, *et al.* 2013). Other studies have examined the use of 4FPC in a variety of patient populations such as those requiring VKA correction prior to urgent surgical or invasive procedures (Goldstein *et al.* 2015), undergoing liver transplant (Arshad *et al.* 2013), recovering from cardiac surgery (Cappabianca *et al.* 2016 and Enter *et al.* 2017), and on warfarin (Rivosecchi *et al.* 2016 and Steiner *et al.* 2016) or direct factor Xa inhibitors (Grandhi *et al.* 2015) who have intracranial hemorrhage. Meta-analyses have concluded that 4FPC is safe and effective for VKA correction in the context of bleeding (Brekelmans *et al.* 2017), and that 4FPC reduced transfusion requirements in patients

undergoing cardiac surgery (Lin *et al.* 2013). In contrast, a Cochrane review examining 4FPC for VKA correction in both bleeding and non-bleeding patients showed that 4FPC does not appear to reduce mortality or transfusion requirement, but does demonstrate the possibility for reversing VKA-induced coagulopathy without requiring plasma (Johansen *et al.* 2015).Overall, the impact of 4FPC on resource utilization has generated mixed conclusions (Khorsand *et al.* 2013 and Jones *et al.* 2016).

In this study, we aimed to determine whether 4FPC was associated with a clinically important reduction in plasma transfusion compared to plasma alone for similar indications. We hypothesized that patients receiving 4FPC would receive less subsequent plasma than indviduals receiving only plasma for a similar indication.

Materials and Methods

After approval by our institutional review board, we conducted a retrospective chart review of patients who received 4FPC (Kcentra, CSL Behring, King of Prussia, PA) between 3/1/2016 and 6/15/2016 (Figure 1). Demographic information, clinical characteristics, laboratory data, and the number and types of blood products administered were gathered, as well as whether vitamin K was given. For patients whose charts indicated a diagnosis of liver disease, Model for End-stage Liver Disease (MELD) scores, which predict survival using a formula that incorporates serum bilirubin, creatinine, sodium, and INR values (Kamath, *et al.* 2007), were calculated. Note was made of patients who died during admission or within 30 days of admission. A single indication

for 4FPC administration was assigned to each patient based on a list of indication codes developed by one of the authors (SJR) after review of pilot data (Appendix).

Control subjects were identified by matching patients who received 4FPC to individuals who were treated only with plasma for the same indication between 10/1/2015 and 12/31/2016. This time frame was expanded beyond the time frame used for the 4FPC patients due to the large number of potential control patients needed to identify a sufficient number of plasma-only patients with matching indications. We recorded blood product transfusion for the 24 hours following the administration of either 4FPC administration (4FPC cohort) or after two units of plasma (plasma-only cohort). For plasma-only patients, blood products were only counted after the first two units of plasma so that both cohorts received a similar initial dose of coagulation factors. Thus, when comparing plasma transfusion in the 24 hours following intervention, the intervention for the 4FPC patients was the administration of 4FPC, and the intervention for the plasma-only patients was the administration of the first two units of plasma, per our study protocol (Figure 1).

In order to evaluate whether the indication for 4FPC administration impacted subsequent plasma transfusion, we performed a subgroup analysis examining the same parameters but comparing two groups within the 4FPC cohort. These groups were based on whether patients received 4FPC for an "on-label" indication versus an "off-label" indication, with "on-label" indications considered to be those listed in the FDA package insert for 4FPC (Appendix).

To summarize demographic and baseline characteristics, we used count and percentage (n,%) for categorical variables. For normally distributed continuous variables, we used mean and standard deviation (mean±SD), and for non-normally distributed continuous variables, we used median and interquartile range (median, [Q1, Q3]). For comparing these values between the 4FPC patients and plasma-only patients, we used chi-squared tests, t-tests, or Mann-Whitney U tests, as appropriate. Additionally, the number of patients requiring transfusions and the median plasma received in the 24-hour follow up period were also compared using chi-squared and Mann-Whitney U tests respectively. We used similar tests for the same variables in the subset comparing the "on-label" and "off-label" uses of 4FPC. P-values less than 0.05 were considered statistically significant. All statistical analysis was conducted in R version 3.5.1 (R Core Team (2018). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/.)

Subjects Studied

Ninety patients received 4FPC and were matched to a corresponding patient who received plasma for the same indication. We were unable to match six additional 4FPC patients (five patients received 4FPC for warfarin correction for intracranial hemorrhage and one for coagulopathy correction prior to cardiothoracic surgery). Five of the 90 4FPC patients received two doses of 4FPC within 24 hours of the initial dose, and one patient received three doses. Dosing of 4FPC is based on weight and pre-treatment INR, per the FDA-approved prescribing

information (CSL Behring, 2018), and in our group ranged from 1,096 to 3,354 units (2,402±783 units).

Results

Demographic and baseline clinical and laboratory characteristics were largely similar between groups (Table 1) except that 4FPC patients were older (66±16 v 62±14 years, p=0.02) and, for those who had MELD scores calculated, 4FPC patients had higher scores (39±7, n=21 v 26±9, n=25, p< 0.01). The number of patients who received vitamin K in addition to 4FPC or plasma was not significantly different between groups (43 (47.8%) for 4FPC patients v 45 (50%) for plasma-only patients, p=0.88).

Plasma transfusion in the 24 hours following intervention

Less than half of patients in each group received additional plasma in the 24 hours following either 4FPC or the equivalent dose of plasma (19 (21%) 4FPC patients v 31 (34%) plasma-only patients, p=0.07). Of the 59 plasma-only patients who only received the initial two-unit dose of plasma and did not require additional plasma transfusion, 19 received a total of one unit, and 40 received a total of two units, including the first unit after admission and a second unit within 24 hours of transfusion of the first. The median number of units of additional plasma received by both the 4FPC and plasma groups was 0 units ([0, 0] for 4FPC patients v [0, 1] for plasma-only patients, p=0.09). The 4FPC group included two outliers that received 18 and 31 units of plasma in the 24 hours following 4FPC administration (Figure 2). The largest number of additional

plasma units received in the plasma group was 11. No statistically significant differences were noted between groups in terms of how many patients required red blood cell transfusion (25 (28%) 4FPC patients v 35 (39%) plasma-only patients, p=0.15) or platelet transfusion (20 (22%) 4FPC patients v 24 (27%) plasma-only patients, p=0.60) in the 24 hours following intervention, nor in terms of the median numbers of units of transfused red blood cells (0, [0, 1] for 4FPC patients v 0, [0, 2] for plasma-only patients, p=0.22) or platelets (0, [0, 1] for 4FPC patients v 0, [0, 1] for plasma-only patients, p=0.47).

First post-intervention INR and mortality

The 4FPC patients (n=78) had a lower median first post-intervention INR compared to the plasma-only patients (n=66) (1.5, [1.3, 2.0] v 1.7, [1.5, 2.1], p<0.01). There was no difference in overall mortality between groups (33 (37%) 4FPC patients v 21 (23%) plasma-only patients, p=0.07).

Subgroup analysis

Subgroup analysis comparing patients who received 4FPC for on-label indications (n=22, 24%) to patients who received 4FPC for off-label indications (n=68, 76%) demonstrated no statistically significant difference in the percentage of patients who received plasma in the 24 hours following 4FPC administration (4 (18%) on-label patients v 15 (22%) off-label patients, p=0.93). The median number of units of plasma received by both the groups was 0 units ([0, 0] for on-label patients v [0, 0] for off-label patients, p=0.64). Significantly more patients in the on-

label group received vitamin K in addition to 4FPC (17 (77%) v 26 (38%), p<0.01). While patients in both groups had similar INR values prior to 4FPC administration (2.5, [2.3, 3.0], n=22 on-label patients v 2.8, [2.3, 3.7], n=63 off-label patients, p=0.95), patients who received 4FPC for on-label indications had a lower median first post-intervention INR (1.3 [1.2, 1.5], n=21 v 1.6 [1.3, 2.1], n=57, p=0.01). The off-label group had a considerable prevalence of liver disease (21 (31%)), while the on-label group did not include any patients with liver disease.

Discussion

We did not find a reduction in subsequent plasma usage at our institution for individuals who received 4FPC compared to patients treated with two units of plasma for a similar indication. Seventy-nine percent of 4FPC patients and 66% of plasma-only patients did not receive additional plasma following administration of either 4FPC or equivalent dose of plasma. While most patients in both groups did not require additional plasma, 19 4FPC patients did receive plasma in addition to 4FPC. These patients may have demonstrated progressive coagulopathy, requiring additional intervention within 24 hours of 4FPC administration. Two patients in the 4FPC group were massively transfused in the 24 hours following 4FPC administration. Both patients had a history of cirrhosis. One was admitted for toxic epidermal necrolysis and received 4FPC and plasma transfusion in the setting of hemorrhagic shock following a dressing change. The other received 4FPC and plasma transfusion intraoperatively during liver transplant surgery. These patients demonstrate that 4FPC is administered in a variety of clinical scenarios and patient groups, complicating its association with plasma transfusion. No institutional protocols

governing the administration of 4FPC were in effect during the time frame of this retrospective review; varying clinical practice patterns may have contributed to subsequent plasma transfusion in some 4FPC patients.

Prior studies have reported conflicting conclusions on whether 4FPC is associated with decreased plasma transfusion. Several studies have suggested that 4FPC administration may decrease plasma transfusion in specific clinical scenarios, including in the setting of warfarin-related intracranial hemorrhage (Boulis *et al.* 1999) and in the peri-operative period surrounding heart transplant (Enter *et al.* 2017) and other surgeries requiring cardiopulmonary bypass (Demeyere *et al.* 2010). While a Cochrane review examining the use of 4FPC for VKA correction in bleeding and non-bleeding patients also supported the potential for 4FPC to reduce plasma use, it did not find sufficient evidence to support the claim that 4FPC lowers overall transfusion requirements (Johansen *et al.* 2015). A published audit of plasma use concluded that plasma use remains "inappropriately high" in the setting of warfarin correction, despite the implementation of 4FPC (Shih *et al.* 2015). Our study reviewed 4FPC use for a wide variety of clinical indications and found that, when examining multiple indications together, 4FPC did not appear to be associated with reduced plasma transfusion at our institution.

Of the patients with an INR documented in the medical record following administration of 4FPC or the equivalent dose of plasma, the 4FPC patients had a median first post-intervention INR of 1.5, compared to 1.7 in the plasma-only patients. Several prior studies have reported a higher percentage of patients in the 4FPC group achieving an INR $\leq$ 1.3 at 0.5 hours post-intervention

when compared to patients in the plasma-controlled group (Sarode *et al.* 2013, Goldstein *et al.* 2015, and Kushimoto *et al.* 2017). One study of 4FPC use during cardiopulmonary bypass found that a higher percentage of patients in the 4FPC group achieved a target INR of ≤ 1.5 at 15 minutes, but that there was no difference in the percentage achieving target INR at 1 hour (Demeyere *et al.* 2010); while another study of 4FPC use for intracranial hemorrhage found a difference in INR values between 4FPC and plasma groups for up to 6 hours post-intervention (Boulis *et al.* 1999). Most of our patients had first post-intervention INR values documented more than 0.5 hours post-intervention, and our findings support that the lower INR noted in the 4FPC patients is sustained beyond 0.5 hours post-intervention.

Notably, when 4FPC patients were divided into subgroups based on whether 4FPC was received for on-label versus off-label indications, it became apparent that the vast majority, over three-fourths, received 4FPC for off-label indications. Subgroup analysis comparing patients who received 4FPC for on-label indications to patients who received 4FPC for off-label indications did not demonstrate a significant difference in plasma transfusion between groups, with approximately one-fifth of patients in both on-label and off-label groups receiving plasma in addition to 4FPC. This finding was unexpected based on the assumption that, for on-label indications, 4FPC would be used instead of plasma rather than in addition to it. The absence of an institutional protocol to standardize transfusion of plasma subsequent to 4FPC administration may have led to variations in clinical practice, possibly contributing to the lack of a difference in plasma transfusion between groups.

We did find a difference both in percentage of patients who received vitamin K and in first post-intervention INR between groups. A greater percentage of patients in the on-label group received vitamin K in addition to 4FPC. This finding may reflect more standardized practice patterns in the on-label group; i.e., clinicians prescribing 4FPC for on-label indications were more likely to co-administer vitamin K, as outlined in the package insert. However, as described above, a similar percentage of patients in the on-label and off-label groups received plasma in addition to 4FPC, which may belie variation in clinical practice patterns in both the on-label and off-label groups. While patients in both groups had similar baseline INR values, those in the on-label group had a median first post-intervention INR of 1.3, compared to 1.7 in the off-label group. The lower median INR noted in the on-label group may be attributed to the more frequent co-administration of vitamin K. Alternatively, this finding may suggest that 4FPC is more efficacious for INR correction for certain indications (Appendix). To our knowledge, no other studies have directly compared INR in patients who receive 4FPC for on-label versus off-label indications. However, the efficacy of 4FPC for many of the on-label indications has been supported individually in several studies examining single indications. These indications include VKA correction in the setting of acute hemorrhage (Sarode *et al.* 2013) and specifically for intracranial hemorrhage (Rivosecchi *et al.* 2016 and Steiner *et al.* 2016), VKA correction prior to surgery or invasive procedures (Goldstein *et al.* 2015), intra-operatively during liver transplantation (Arshad *et al.* 2013), and post-operatively following cardiac surgery (Cappabianca *et al.* 2016 and Enter *et al.* 2017).

Approximately one-third of the off-label group comprised patients with liver disease, compared to no patients with liver disease in the on-label group. These patients with liver disease may have contributed to the higher post-intervention INR noted in the off-label group. A recent study examining the safety and efficacy of 4FPC in patients with liver disease found that these patients demonstrated suboptimal coagulopathy correction and hemostasis compared to patients without liver disease (Huang *et al.* 2017). As most of the patients who received 4FPC received it off-label, studies are needed to determine if its off-label use provides benefits and what the appropriate dose is, if any; or, its off-label use should be reconsidered.

Several limitations to our study warrant consideration. Our study was conducted at a single institution, which may limit the generalizability of our findings. Inherent to our retrospective study design is a limited ability to control for potential confounders. Further, our study did not directly assess the severity of patients' clinical scenarios. Although our study captured mortality information, we did not explore bleeding and clotting complications and how these may have contributed to mortality, since these factors were outside the scope of our study. Another limitation is the fact that most of our plasma-only patients received only 1-2 units of plasma, indicating that plasma was not always dosed according to weight-based dosing of at least 10 ml/kg as supported by a recent study (Triulzi, *et al.* 2015). Finally, the high incidence of off-label prescribing led to a small sample size for on-label use, which may explain why our results differ from prospective randomized controlled trials.

In conclusion, we did not find evidence that 4FPC administration was associated with reduced plasma use at our institution. We did find that 4FPC was prescribed to a diverse patient population, including a subset with liver disease and high MELD scores, which may have complicated our study of the association between 4FPC and subsequent plasma transfusion. We also found that the vast majority of patients received 4FPC for off-label indications. Other possible contributors to the lack of association between 4FPC and subsequent plasma transfusion might include the absence of an institutional protocol for 4FPC use and individual patient scenarios demonstrating progressive coagulopathy or hemorrhage. Our findings highlight the need for stricter institutional guidelines and clear corresponding policies for administering 4FPC to optimize its use for on-label indications. Further studies are warranted to clarify the effectiveness and proper use of 4FPC for both on- and off-label indictions.

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Figure Legends

Figure 1. Workflow of study group selection and data collection.

Figure 2. Number of units of plasma received by 4FPC patients versus plasma-only patients in the 24 hours following either 4FPC or the equivalent dose of plasma. The median number of units received during the 24-hour follow-up period was the same for both groups. The distribution differed somewhat; more plasma-only patients than 4FPC patients received 1-2 additional plasma units, while two 4FPC patients received massive plasma transfusion (18 and 31 units). Bolded line=median; box=interquartile range; whisker=greatest non-outlier observation; dot=outlier (any point less than 25th percentile minus 1.5 times the interquartile range or greater than 75th percentile plus 1.5 times the interquartile range).

Table 1. Demographic and baseline clinical and laboratory characteristics.

Characteristic	4FPC group		Plasma group		p value
	Mean	SD	Mean	SD	
Age (yrs)	66 (n=90)	16	62 (n=90)	14	0.02
Body weight (kg)	86	22	85	23	0.69
	Number	Percent	Number	Percent	
Sex (female)	35	38.9	35	38.9	1.00
Warfarin use	45	50.0	47	52.2	0.88
History of liver disease	21	23.3	27	30.0	0.40
Received vitamin K	43	47.8	45	50.0	0.88
	Median	IQR	Median	IQR	
INR prior to intervention	2.8[a]	1.6	2.2[a]	1.4	0.09
Hgb within 2h prior to intervention (g/dL)	10.0[b]	4.0	9.7[b]	3.4	0.78
Platelet count within 2h prior to intervention (# $x10^9$/L)	167[c]	168	187[c]	131	0.86
MELD score	39[d]	7	26[d]	15	<0.01

4FPC: 4-factor prothrombin complex concentrate; SD: standard deviation; IQR: interquartile range; INR: international normalized ratio; Hgb: hemoglobin; MELD: Model for End-stage Liver Disease

a) 4FPC n=85, plasma n=85

b) 4FPC n=44, plasma n=31

c) 4FPC n=39, plasma n=27

d) 4FPC n=21, plasma n=25