Prothrombin complex concentrate use for urgent warfarin reversal compared to fresh frozen plasma and recombinant factor VIIa

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Abstract

Background:
Agents used to rapidly reverse warfarin include fresh frozen plasma (FFP), recombinant factor VIIa (rFVIIa), and prothrombin complex concentrates (PCCs). The recent approval of PCCs to the health system formulary allowed for a comparison of PCCs to the older agents FFP and rFVIIa. Additionally, limited data comparing rFVIIa and PCCs are available.

Objective:
To compare the effectiveness of PCCs and FFP/rFVIIa for the rapid reversal of warfarin.

Methods:
This retrospective study included hospitalized patients who received 4-factor PCC between July 1, 2013 and April 30, 2014 and those who received rFVIIa and/or FFP between October 19, 2010 and September 30, 2012. All reversals for patients receiving therapy with warfarin were included. The primary outcome was the proportion of reversals achieving INR ≤1.3 within 8 hours. Secondary outcomes included average INR reduction and the median time to INR ≤1.3.

Results:
The PCC cohort included 64 warfarin reversals. The historical cohorts included 394 reversals with FFP and 27 reversals with rFVIIa/FFP. The target INR was reached in 45.3% of PCC reversals, 10.2% of FFP-only reversals ($p < 0.001$ vs. PCC), and 77.8% of rFVIIa/FFP reversals ($p=0.004$ vs. PCC). The median time to target INR for the PCC, FFP, and rFVIIa/FFP groups were 3.6h, 4.8h ($p=0.17$ vs. PCC), and 1.3h ($p=0.002$ vs. PCC), respectively.

Conclusions:
PCC use resulted in greater hemostasis compared to FFP alone. rFVIIa use resulted in the fastest and greatest proportion of INR reduction, though a larger sample size and adverse event data are needed to recommend its use.

Keywords: warfarin, reversal, hemostasis, recombinant factor VIIa, prothrombin complex concentrates

1. Background

Bleeding episodes associated with warfarin therapy can lead to significant morbidity and mortality, and a number of products are available for urgent warfarin reversal (e.g. in cases of active bleeding or need for immediate surgery). These include fresh frozen plasma (FFP), recombinant factor VIIa (rFVIIa), and prothrombin complex concentrates (3-factor (Profilnine®) and 4-factor (Kcentra®) PCCs), with 4-factor PCCs considered the preferred agent for warfarin reversal.[1,2] Since the addition of PCCs to our system formulary in July 2013, hundreds of patients have received these products. An evaluation was conducted in 2014 to characterize their first year of use.[3] However, no comparison has yet been made to evaluate differences in outcomes between PCCs and FFP or rFVIIa since the formulary change. Additionally, limited published data comparing rFVIIa and PCCs are available.

A number of studies have compared the efficacy and safety of PCCs to FFP and other reversal products. These have shown that the use of PCCs may produce more rapid INR reduction compared to FFP without an increase in thromboembolic events or bleeding events.[4-8] The few published comparisons of PCCs and rFVIIa have shown that rFVIIa may work as quickly as PCCs and may even allow for more rapid achievement of target INR.[8,9] By directly providing the coagulation factors that are inhibited by warfarin, we expect PCCs to achieve hemostasis rapidly compared to other reversal agents. In this study, INR reduction, hemoglobin stability, and frequency of blood transfusions were used to compare the effectiveness of 4-factor PCCs and FFP or rFVIIa.

2. Methods

A retrospective review of patient data was conducted using previously identified patient records.[3] These records were used to establish three patient cohorts for comparison, identified as two historical pre-PCC cohorts (warfarin reversals taking place prior to PCC formulary approval) and one contemporary PCC cohort (warfarin reversals taking place after PCC formulary approval). The two pre-PCC groups included administrations of only FFP for rapid reversal and reversals using both rFVIIa and FFP (designated as rFVIIa/FFP). The PCC group included administrations of only PCC for rapid reversal.

Inclusion criteria for the pre-PCC cohorts included admission to a tertiary care, academic medical center between October 19, 2010 through September 30, 2012 with an International Classification of Diseases, Ninth Revision, Clinical Modification (ICD9-CM) bleeding diagnosis code, documentation of inpatient charge codes for either FFP or rFVIIa, and documentation of warfarin as a home medication per the initial electronic health record note. Inclusion criteria for the PCC cohort included admission to any of 12 hospitals within the health system between July 1, 2013 through April 30, 2014, documentation of inpatient charge codes for Kcentra®, and documentation of warfarin use prior to admission. Because many patients received more than one dose of a particular reversal agent, each cohort included individual instances of administration rather

than individual patient encounters. To maintain patient confidentiality, all data were de-identified through an honest broker. The research was conducted in compliance with the university Institutional Review Board for an exempt study.

The primary outcome was the proportion of each group that reached an INR ≤1.3 within 8 hours of reversal agent administration. This time frame was selected based on the median time to the target INR as determined by Hedges et al.[3] Secondary outcomes included the proportion of each group with stable hemoglobin, defined as a post-reversal hemoglobin that remained within 1 gm/dL of the pre-reversal value; the median difference in INR reduction at 8 hours post-reversal; the proportion of each group that required blood transfusions within 24 hours of reversal; the median number of packed red blood cell (PRBC) units transfused among those that required transfusions; and the median time required to achieve INR ≤1.3. Proportional outcomes were compared using Chi-square. Numerical data were evaluated using the Mann-Whitney U test. This research was conducted with approval from the University's Institutional Review Board.

3. Results

The two pre-PCC cohorts, FFP-only and rFVIIa/FFP, consisted of 394 and 27 reversals, respectively. The PCC cohort consisted of 64 reversals. Patients' baseline characteristics are presented in Table 1. The majority of patients were Caucasian males, with a median age of approximately 80 years. No statistically significant differences in baseline characteristics were found for any of the patient groups, except in the incidence of atrial fibrillation, which was present in a larger proportion of patients in the pre-PCC cohorts compared to the PCC cohort. A similar proportion of instances in each group received vitamin K as an adjunct reversal agent. The median pre-reversal INRs for the FFP-only, rFVIIa/FFP, and PCC groups were 2.4, 2.3, and 2.8, respectively (Table 1).

The target INR was reached less frequently in the FFP-only group compared with the PCC group (10.15% vs. 45.31%, P <0.001) (Table 2). The target INR was reached more frequently in the rFVIIa/FFP group compared with the PCC group (77.78% vs. 45.31%, P=0.004). The median time to reach the target INR was similar between the PCC and FFP-only cohorts. The shortest time to reach the target INR was associated with the use of rFVIIa/FFP and was significantly shorter than the median time observed for the PCC cohort (1.3h vs. 3.6h, P=0.002). The FFP-only group achieved a smaller median difference in pre- and post-reversal INRs compared to the PCC cohort (-0.6 vs. -1.3, P <0.001). The rFVIIa/FFP group reduced the INR to a similar degree compared to the PCC group. A significantly greater proportion of the FFP-only group also received blood transfusions within the first 24 hours of reversal compared to the PCC group (44.9% vs. 21.9%, P=0.001). Among those instances of reversal that required blood transfusions, the FFP-only group also received more units of PRBCs compared to the PCC group (2 units vs. 1.5 units, P=0.008). No differences in blood transfusions were observed between the rFVIIa/FFP group and the PCC group.

Table 1. Baseline characteristics of treatment groups.

Characteristic	FFP-only (n=394)	rFVIIa/FFP (n=27)	PCC (n=64)
Median age, yr (IQR)	80.5 (69.6, 87.5)	78.7 (70.7, 85.4)	82.3 (74.5, 88.8)
Male, n (%)	185 (53.2)	17 (48)	36 (57.4)
Caucasian, n (%)	252 (72.6)	29 (84)	52 (83.3)
African-American, n (%) Comorbidities, n (%)	39 (11.3)	2 (4)	5 (7.5)
Coronary artery disease	140 (40.3)	22 (64)	33 (53.6)
Atrial fibrillation[a]	347 (100)	35 (100)	36 (75.8)
Valvular disease	56 (16.1)	3 (8)	7 (10.7)
Congestive heart failure	129 (37.1)	13 (36)	31 (49.3)
History of venous thromboembolism	0 (0)	0 (0)	1 (1.6)
Hypertension	213 (61.3)	27 (76)	35 (57.1)
Diabetes	123 (35.5)	18 (52)	24 (38.3)
Chronic kidney disease	61 (17.7)	3 (8)	13 (21.3)
Chronic liver disease	15 (4.3)	0 (0)	1 (1.6)
Received vitamin K (%)	79.7	74.1	76.6
Median pre-reversal INR, g/dL (IQR)[b]	2.4 (1.9-3.4)	2.3 (1.8-2.9)	2.8 (2.3-3.6)
Median pre-reversal Hgb, g/dL (IQR)[c]	9.9 (8.3-12.0)	10.4 (8.0-11.6)	11.1 (9.6-13.2)

FFP: fresh frozen plasma; Hgb: hemoglobin; INR: international normalized ratio; IQR: interquartile range; PCC: prothrombin complex concentrate; rFVIIa: recombinant factor VIIa

[a] Significant difference with FFP-only and rFVIIa/FFP compared to PCC ($p < 0.001$ for both comparisons)

[b] Significant difference with FFP-only compared to PCC ($p=0.02$) and rFVIIa/FFP compared to PCC ($p= 0.009$)

[c] Significant difference with FFP-only compared to PCC ($p=0.007$)

Table 2. Results from comparison of the pre-PCC cohorts (FFP-only and rVIIa/FFP) to the PCC cohort.

	FFP-only (n=394)	rVIIa/FFP (n=27)	PCC (n=64)	p-value – FFP-only vs. PCC	p-value – rFVIIa/FFP vs. PCC
INR ≤1.3 within 8h (%)Secondary outcomes	10.15	77.78	45.31	<0.001*	0.004*
Median time to target INR, hr (IQR)	4.8 (2.6-6.9)	1.3 (0.9-4.0)	3.6 (2.7-4.9)	0.169	0.002*
Median difference in INR (IQR)	-0.6 (-0.3 to -1.5)	-1.15 (-0.9 to -1.6)	-1.3 (-0.9 to -2.0)	<0.001*	0.493
% stable hemoglobin (IQR)	57.4	51.9	57.8	0.946	0.603
% receiving PRBCs (IQR)	44.9	29.6	21.9	0.001*	0.433
Median units PRBCs	2 (2.0-4.0)	1.5 (0.0-4.3)	1.5 (1.0-2.3)	0.008*	0.705

FFP: fresh frozen plasma; INR: international normalized ratio; IQR: interquartile range; PCC: prothrombin complex concentrate; PRBCs: packed red blood cells; rFVIIa: recombinant factor VIIa

*Statistically significant

4. Discussion

To our knowledge, this was the first evaluation of a four-factor PCC compared with either FFP or rFVIIa in a patient cohort of this size. The findings in this study suggest that the use of PCCs was more effective than FFP for warfarin reversal. Previous studies evaluating the use of 4-factor PCCs and FFP for warfarin reversal in approximately 200 participants have found that 55-62% of patients receiving PCC for warfarin reversal achieved an INR of 1.3 or lower within 30 minutes of administration, with 9-10% of patients in the FFP reaching the target INR within the same time frame.[6,7] A prospective trial by Steiner et al also found that among a total of 50 participants requiring warfarin reversal for intracranial hemorrhage, 67% of those receiving 4-factor PCC achieved a target INR of 1.2 or lower within 3 hours, compared to 9% of those receiving FFP.[10] Our retrospective findings in a larger cohort largely confirmed these INR reduction results.

Additionally, rFVIIa in our study produced the most rapid INR reduction with the highest proportion of reversals reaching the target INR among all of the reversal strategies evaluated, though the sample size was small. The majority of published studies for rFVIIa are in the traumatic brain injury and intracerebral hemorrhage populations. These studies suggest that the use of this reversal agent, with or without the concomitant use of other reversal agents, is associated with significant reduction in INR and a high proportion of patients achieving the investigators' target INR, without an observed improvement in mortality.[9,11-15] Our findings were largely similar to these with respect to the effect of rFVIIa on INR reduction. We also found that many markers of hemostasis were improved even when compared to PCC use, though the degree of INR reduction was similar between these agents.

Many publications evaluating rFVIIa have reported a similar frequency of thromboembolic events when compared to other reversal agents, but most have included fewer than 100 patients in the overall comparison.[9,12-14] An analysis of approximately 200 patients with warfarin-associated hemorrhage found a 2-fold increase in thromboembolic events associated with the combination of 3-factor PCC and rFVIIa when compared to FFP.[11] However, thromboembolic event data specifically evaluating 4-factor PCCs compared to rFVIIa are lacking.

Limitations of the present study should be taken into consideration. First, the retrospective study design limited all data collection to the constraints of electronic health record documentation. Additionally, adverse events and cost-effectiveness were not evaluated, which precludes a more complete assessment of these reversal strategies. Finally, surrogate markers for hemostasis and patient outcomes were used, which do not always translate to clinical outcomes.

In conclusion, our findings show that the use of 4-factor PCC for urgent warfarin reversal resulted in faster and greater frequency of successful reversals compared with the use of FFP, while the use of rFVIIa in combination with FFP resulted in more successful reversals compared with the use of 4-factor PCC.

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