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Clinical effectiveness and safety outcomes associated with prothrombin complex concentrates

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Abstract Prothrombin complex concentrates (PCCs) are indicated for urgent reversal of warfarin and used for reversal of novel oral anticoagulants, in patients with acute major bleeding or need for an urgent procedure. The research goal was to evaluate effectiveness and safety outcomes with PCC usage at our institution. A retrospective review of electronic medical records identified patients that received a PCC commercially available in the United States (KCentra® or Profilnine®) at twelve hospitals in a tertiary care health system from July 1, 2013 to April 30, 2014. A total of 193 patients received PCC, of which 184 patients received four-factor PCC. The patient population was 48 % male and 75 % Caucasian, with a mean age of 73 years old. Clinical outcomes of interest included time to achieve a target INR ≤1.3, time to Hgb >7 g/dL, and incidence of thromboembolism. A total of 143 patients were on warfarin (74.1 %) at baseline, whereas 18 patients (9.3 %) were taking a novel anticoagulant. Target INR of ≤1.3 was achieved in 125 patients (65.8 %), within a median time of 8.03 h (IQR 3.38–34.07). Among patients with a baseline Hgb <7 g/L ($n = 13$), the median time to Hgb >7 g/dL was 8.48 h (IQR 6.95–13.00). Eight patients (4.1 %) developed an acute venous thromboembolism following PCC administration. INR reversal was achieved in approximately two-thirds of patients, with a low incidence of venous thromboembolism. Four-factor PCC is a viable alternative to plasma.

Keywords Prothrombin complex concentrates · Hemorrhage · Hemostasis · Warfarin

Introduction

Hemorrhagic complications are a significant side effect of oral anticoagulants, with gastrointestinal and intracranial bleeding as the most life-threatening [1]. Prothrombin complex concentrates (PCCs) have been approved as an alternative to fresh frozen plasma when urgent reversal of anticoagulation is needed, such as in the setting of a life-threatening bleed or need for urgent surgery [1–8]. Both four-factor (KCentra®) and three-factor (Profilnine®) PCC products were approved for use in our health system in July 2013. Therefore, we reviewed the effectiveness and safety of PCC at our institution in the context of the current literature [8–13].

Methods

A retrospective review of electronic medical records was conducted to identify adult patients documented as having received either KCentra® or Profilnine® at twelve hospitals within a health system, which included both community hospitals and academic tertiary care centers. Patients were included in this review if they received at least one dose of

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KCentra® or Profilnine® from July 1, 2013 to April 30, 2014. Patients were identified through an electronic medical record data repository that contains full-text medical records and integrates information from central transcription, laboratory, pharmacy, finance, administrative, and other departmental databases [14]. To maintain patient confidentiality, all data were de-identified through the use of an honest broker system. Criteria were met for exemption from informed consent by the university's Institutional Review Board.

All labs were collected to evaluate time to international normalized ratio (INR) and hemoglobin (Hgb) correction. Pre-defined targets included an INR of ≤1.3 and a Hgb >7 g/dL. Baseline lab values were defined as the last reported result prior to PCC administration. The incidence of venous thromboembolism (VTE) during hospitalization was identified as a safety outcome. Incidence of acute VTE was identified through hospital discharge summaries. All inpatient progress notes were then evaluated to confirm documentation of VTE and to identify only those events that occurred following PCC administration. Additional information was captured to summarize the patient population, including demographics, indication for PCC administration, type of oral anticoagulation, average dose of PCC product administered, and patient disposition. Descriptive statistics were reported for all endpoints.

Table 1 Patient population (n = 193)

Male sex, *n* (%)	92 (48 %)
Age, mean (SD; range)	73 (15; 20–98)
Age group, *n* (%)	
<65	43 (22 %)
≥65 and <75	37 (19 %)
≥75	93 (49 %)
Unknown	20 (10 %)
Race, *n* (%)	
Caucasian	145 (75 %)
Non-caucasian	28 (15 %)
Unknown	20 (10 %)
Co-morbidities, *n* (%)	
Hypertension	104 (54 %)
Atrial fibrillation	104 (54 %)
Anemia	88 (46 %)
Chronic heart failure	84 (44 %)
Coronary artery disease	73 (38 %)
Chronic kidney disease	30 (16 %)
Chronic liver disease	24 (12 %)
History of Venous Thromboembolism	15 (8 %)
Home anticoagulation, *n* (%)	
Warfarin	143 (74.0 %)
Rivaroxaban	14 (7.3 %)
Dabigatran	3 (1.6 %)
Apixaban	1 (0.5 %)
Unknown	32 (16.6 %)

Results and discussion

One hundred and ninety three patients were identified (Table 1), and 184 patients received four-factor PCC while nine patients received three-factor PCC. Patients had a mean length of stay of 9.7 days (SD 10.2). A total of 161 patients (83.4 %) were found to be on anticoagulation at home, with warfarin being the most common oral anticoagulant (74.0 %). An institutional protocol to guide PCC administration was developed, however, this did not become available to physicians until January 2014 (Fig. 1). Any patient with an INR >2 could receive PCC for warfarin reversal at the treating physician's discretion at our institution, leading to PCC usage in a broad context. Nevertheless, neurovascular indications were the most common reason documented for PCC administration (Table 2), accounting for 80 patients (41.4 %).

The mean baseline INR was 3.1 (SD 1.9) and Hgb was 10.7 (SD 2.8). The average net dose of PCC administered was 3792 international units. A total of 125 patients (65.8 %) achieved an INR reduction ≤1.3, and the median time to achieve this INR was 8.03 h (IQR 3.38–34.07). A sub-analysis of only patients that received four-factor PCC indicated similar results; a total of 123 of 184 patients (66.8 %) achieved an INR reduction ≤1.3, and the median time to achieve this INR was 7.92 h (IQR 3.34–34.07). A total of 162 patients (83.9 %) had a baseline Hgb >7 g/dL and 18 (9.3 %) patients had incomplete labs; thus, they were excluded from analysis. Among the patients that had a baseline Hgb <7 g/dL ($n = 13$), the median time to Hgb >7 g/dL was 8.48 h (IQR 6.95–13.00). Of note, all patients with a baseline Hgb <7 g/dL received four-factor PCC.

There were a total of 8 of 193 patients (4.1 %) that developed an acute venous thromboembolism during their hospital stay following PCC administration, including two patients that developed an acute pulmonary embolism. Five of the patients that developed a VTE were on warfarin at baseline, while it was unknown what anticoagulation three patients were receiving prior to PCC administration. Additionally, five of these patients received PCC product to reverse INR prior to surgery. Only one patient that developed venous thromboembolism was known to have a history of VTE on admission, and none of the patients that developed a VTE received three-factor PCC. A total of 50 patients (25.9 %) either died or were discharged to hospice care following PCC administration. Additionally, 56 patients (29.0 %) transferred to a skilled nursing or long-

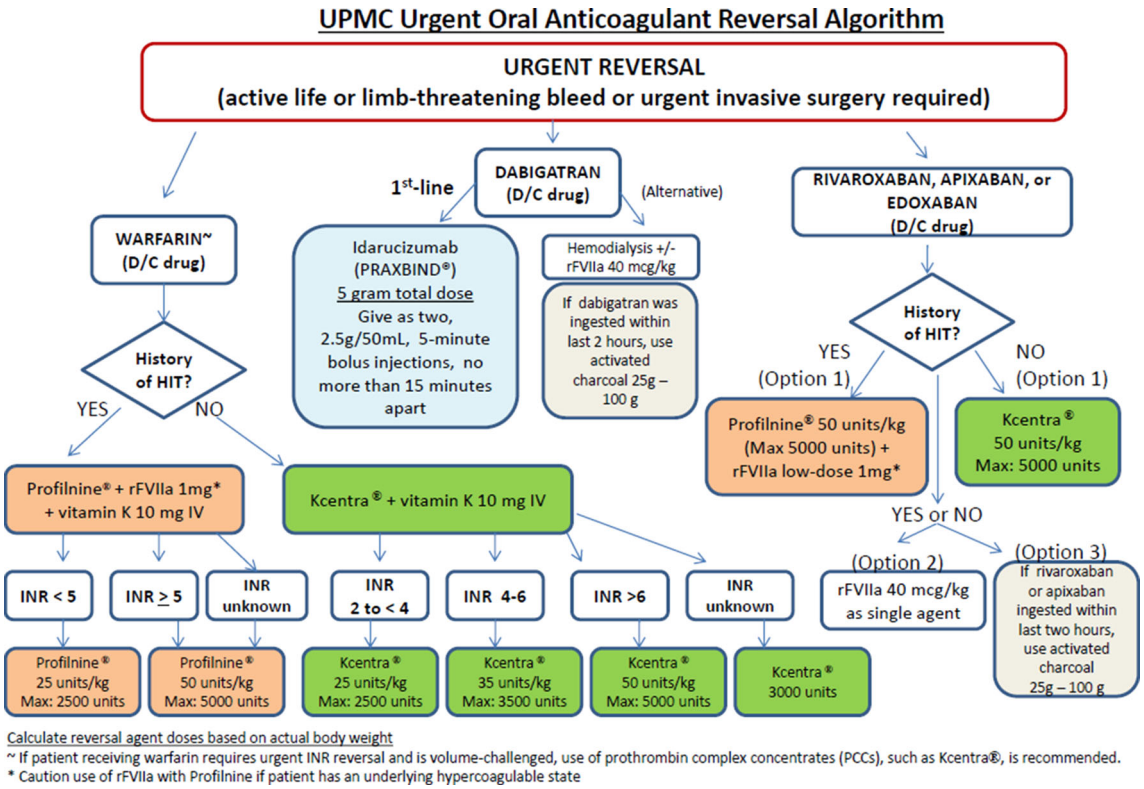

Fig. 1 UPMC algorithm for PCC usage in the setting of oral anticoagulant reversal

Table 2 PCC administration indications

	n (%)
Neurovascular indications	
Subdural hematoma	37 (19 %)
Intracranial bleed	30 (16 %)
Subarachnoid hemorrhage	13 (7 %)
Abdominal indications	
Gastrointestinal bleed	14 (7 %)
Retroperitoneal hematoma	10 (5 %)
Miscellaneous indications	
Prior to surgical intervention	31 (16 %)
Various other hematomas	9 (5 %)
Coagulopathy[a]	9 (5 %)
Other[b]	23 (12 %)
Unknown	17 (9 %)

[a] Noted as coagulopathy of unknown origin, or liver cirrhosis with secondary coagulopathy

[b] Examples of other indications include hypovolemic shock, stroke with hemorrhagic conversions, musculoskeletal bleeding secondary to a motor vehicle accident, etc.

term care facility, while 27 patients (14.0 %) were discharged to a rehabilitation center.

PCCs are recommended as an alternative to plasma when urgent reversal of anticoagulation is required. PCCs are thought to be advantageous in that they may achieve a more rapid reversal of oral anticoagulants than plasma, since they have small infusion volumes and can be quickly administered without time needed for thawing. [1–3] Our study extends the limited published clinical experience with PCC in the United States, particularly with the four-factor product.

Our study should be reviewed in the context of previous findings. Our study included a stringent INR target of $\leq$1.3. We found that 125 patients (65.8 %) achieved target INR reduction, which was similar to the results reported by Sarode et al. [8]. Studies that included a less stringent INR target of $\leq$1.4 or 1.5 had a greater number of patients (75–89 %) that achieved the target INR [9–13]. The time to target INR in our study was substantially longer (8 h) relative to other studies which reported 30 min [8, 10, 12]. Clinicians had preference over when to check another INR, which may have influenced our time to INR reduction. We also collected Hgb values to provide a separate objective measure of hemostasis. Since a hemoglobin of 7 g/dL is often used as a threshold for transfusion, we defined our target as time to Hgb >7 g/dL [15]. A majority of patients had a baseline Hgb >7 g/dL, so we were able to report time to hemoglobin resolution only in a few patients.

A known risk of PCCs is thromboembolism [1–3]. Our incidence of venous thromboembolism was found to be less

than other studies evaluating four-factor PCCs, but similar to rates reported among studies that evaluated three-factor PCCs [8–13]. We captured only VTEs that occurred during hospitalization. Notably, our incidence does not account for any events that occurred after discharge, and a large portion of our patient population transferred to other locations for further care. Our overall mortality rate of 50 patients (25.9 %) was lower than previously reported in studies that exclusively reviewed patients with intracranial bleeding, yet comparable to most other studies [9–13].

Our study was subject to several limitations. First, this study was retrospective; therefore, data were limited to documentation in the electronic medical record. Data for three-factor PCC usage was included in this study as it is our preferred reversal agent for patients with a known history of heparin-induced thrombocytopenia; however, ultimately few patients received three-factor PCC (only 4.7 % patients). Therefore, more research is needed to clarify if similar outcomes would be achieved with three-factor PCC administration alone. Additionally, PCC use was ultimately at the discretion of the treating physician. We did not capture plasma usage, which may have influenced our outcomes. Overall, our prevalence of novel oral anticoagulant usage was low; therefore, we were not able to make any separate assessments about patient outcomes related to type of oral anticoagulant.

Conclusion

Effectiveness of four-factor PCC was demonstrated as most patients achieved an acceptable INR resolution. four-factor PCC is a viable alternative to FFP, however, the time to reversal was longer than previously reported. Finally, four-factor PCC was associated with VTE, but the incidence was relatively low and comparable to other studies.

Authorship Contributions A Hedges and JC Coons contributed to the following: the concept and design, analysis and interpretation of data, critical writing of the intellectual content, and final approval of the version to be published. M Saul contributed to the following: review of the study design, extraction of data from the electronic medical records, and final approval of the manuscript to be published. RE Smith contributed to the following: the concept and design, interpretation of data, revising the intellectual content, and final approval of the version to be published.

Compliance with ethical standards

Conflict of interest None.

Ethical approval Our study was approved by our Institutional Review Board. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study formal consent is not required.

Informed consent Because of the retrospective nature of the study design, we did not require informed consent. All data was de-identified by a certified honest broker.

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