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ORIGINAL ARTICLE

Evaluation of a Fixed, Weight-Based Dose of 3-Factor Prothrombin Complex Concentrate Without Adjunctive Plasma Following Warfarin-Associated Intracranial Hemorrhage

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Abstract
Introduction Data regarding use of prothrombin complex concentrate (PCC) for international normalization ratio (INR) reversal in warfarin-associated intracranial hemorrhage (wICH) is variable with regards to dosages, adjunctive agents, and product choice. In 2012, we implemented a fixed, weight-based [30 IU/kg] dosing protocol of 3-factor PCC (3PCC) utilizing a rapid infusion rate and no requirement for fresh frozen plasma (FFP) following factor product administration. We aimed to evaluate the impact of this protocol on immediate and delayed INR reversal in patients admitted with wICH in the absence of FFP co-administration.
Methods We conducted a retrospective review of patients receiving 3PCC following wICH between January 1, 2012 and December 10, 2013. The primary objective was to determine the percentage of patients achieving goal INR ($\leq$1.4) following 3PCC administration. Patients were excluded if their bleed was not intracranial in origin, received a dose outside of the specified protocol, or were given FFP as an adjunctive agent.
Results We included 35 patients with a mean presenting INR of 3.2 $\pm$ 1.3. Thirty patients (85.7 %) achieved goal INR ($\leq$1.4) following one dose of 3PCC. The mean INR after infusion of 3PCC was 1.3 $\pm$ 0.2. The median duration between 3PCC infusion and subsequent INR was 48.0 min (30–70.1 min). Vitamin K was utilized in 33 (94.3 %) patients. No patient experienced a thromboembolic event within 7 days of 3PCC administration.
Conclusions Fixed, weight-based dosing of 3PCC without adjunctive FFP resulted in high rates of complete INR reversal without significant adverse events.

Keywords Intracranial hemorrhage · Prothrombin complex concentrate · Warfarin · Fresh frozen plasma · Anticoagulation

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Introduction

Anticoagulation with warfarin is associated with numerous complications, the most significant being intracranial hemorrhage (wICH). Prothrombin complex concentrate (PCC) is recommended for rapid international normalization ratio (INR) reversal; however data are variable

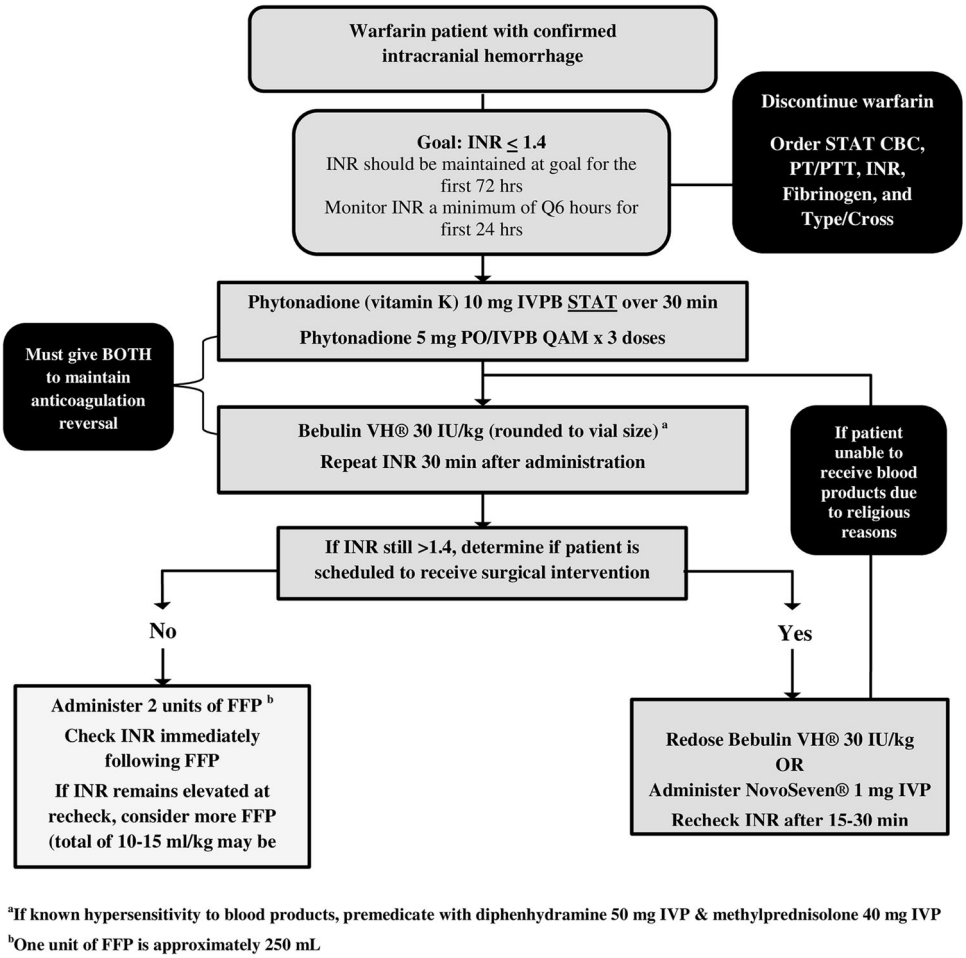

Fig. 1 Institution-specific protocol for use of Bebulin VH® in Warfarin-associated intracerebral hemorrhage

regarding product choice, dosing, and adjunctive agents [1–3]. Since hematoma volume and subsequent expansion have been shown to worsen patient outcomes, it is critical to achieve rapid INR reversal following diagnosis of wICH [4–6]. Unfortunately, safe and effective dosing of 3PCC remains controversial, with the majority of evidence utilizing varying dosing strategies [7–10]. In addition, some guidelines recommend adjunctive use of fresh frozen plasma (FFP) in order to effectively produce hemostasis when utilizing 3PCC [9]. The potential adverse effects of FFP administration are well-known and include pulmonary, hemodynamic, and infectious abnormalities [11]. In addition, new guidelines have begun to highlight the importance of euvolemia, which may be more difficult to achieve due to the large fluid volume associated with FFP administration [12, 13]. As a result of these recommendations there is little data addressing both the ideal dosing of 3PCC without adjunctive FFP administration as well as the impact of this treatment strategy on both emergent and sustained INR reversal.

In order to standardize treatment for wICH, our institution implemented a 3PCC protocol (Fig. 1) using a fixed, weight-based dosing strategy [30 IU/kg] with a rapid infusion rate (200 IU/min). In addition to 3PCC, our protocol recommends all patients receive 10 mg intravenous vitamin K upon initial presentation. We aimed to review our experience with a 3PCC protocol for reversal of wICH and examine its impact on INR reversal in the absence of FFP co-administration.

Methods

We evaluated all patients treated within our health system who were aged 18 years or older, discharged between January 1, 2012 and December 10, 2013, and received treatment with a 3PCC for wICH confirmed by computed tomography. Sample size was determined by evaluating all patients at our institution who reviewed 3PCC during the specified time period and no formal power analysis was conducted. The primary objective was to determine the percentage of patients achieving goal INR following 3PCC administration. Secondary objectives were to determine the safety of 3PCC administration and to evaluate the ability to

provide adequate INR reversal in patients with initial INR values greater than 4.5. Patients were excluded if their bleeding event was not intracranial in origin, were administered a dose outside of that recommended by our protocol, or received any amount of adjunctive FFP. Correction of INR was defined as an INR $\leq$ 1.4 per our institution-specific protocol. The presence of thromboembolic adverse events was defined as documentation or diagnosis of any arterial or venous thromboembolism within 7 days of 3PCC infusion. In subjects that expired prior to day seven, data was limited until time of death. The presence of an infusion reaction was defined as documentation of reaction in the medical record and/or any stoppage or delay during 3PCC infusion. Statistical analyses were performed using SPSS Version 21 (Chicago, IL). Descriptive statistics were used for initial evaluation, with parametric data presented as mean $\pm$ standard deviation and non-parametric data as median [25–75 % interquartile range]. After initial evaluation, patients were stratified into two groups based upon baseline INR result greater than 4.5, with Fisher's exact test used to compare rates of goal INR achievement between groups. This study was approved by the University of Tennessee institutional review board.

Results

During the specified time frame, 46 patients received 3PCC for warfarin-associated major bleeding. We excluded two patients due to receipt of much lower doses than recommended by our protocol (<10 IU/kg) and four patients whose bleeding event was not intracranial. Five intracranial hemorrhage patients were excluded from our analysis due to the receipt of FFP. A total of 35 patients were included in our analysis. Baseline characteristics are presented in Table 1. The most common location of wICH was intraparenchymal (26 patients) followed by subdural and subarachnoid occurring in only six and three patients, respectively. On admission, the baseline INR was 3.2 ($\pm$1.3; range 1.8–7.3) and 33 (94.3 %) patients were administered adjunctive vitamin K per our protocol. After rounding of all doses to the nearest vial size, the mean dose administered was 29 IU/kg $\pm$ 5.0 infused at a median rate of 193.1 IU/min [163.1–200.7] (Table 2). Overall, 30 (85.7 %) of patients achieved goal INR ($\leq$1.4) following a single dose of 3PCC. The median duration from 3PCC administration to follow up INR was 48 min [30–70.1 min], with mean INR reduced to 1.3 ($\pm$0.2; range 1.1–1.8; Table 2). The mean INR remained below goal at 1.2 ($\pm$0.1; range, 1.1–1.8) 24 h after 3PCC administration. Amongst all patients, the median time from 3PCC infusion to goal INR was 50.5 min [30.0–116.8]. Of the 35 patients evaluated, 7 (20.0 %) presented with a baseline INR > 4.5, of which six achieved goal INR following a single dose of 3PCC per our protocol. Compared to those with a lower presenting INR, a higher baseline INR did not influence the likelihood of achieving goal INR ($p > 0.99$). Patients who did not achieve adequate reversal with a single dose of 3PCC are presented in Table 3. The mean INR following 3PCC administration was 1.6 in those who did not achieve adequate reversal, with only one patient noted to have an INR sustained above 1.4 at 24 h.

We found no documentation of any infusion reactions despite utilization of a rapid 200 IU/min infusion rate. One patient did receive premedication with corticosteroids and antihistamines prior to initiation of 3PCC, which is included as a treatment option in our institutional protocol. Furthermore, there were no documented thromboembolic

Table 1 Baseline characteristics ($n = 35$)

Characteristic	Result
Age (years)	69.5 $\pm$ 16.1
Weight (kg)	104.7 $\pm$ 25.6
Height (in.)	67.0 $\pm$ 5.2
Male, *n* (%)	19 (54.3)
African American, *n* (%)	13 (37.1)
Location of bleed	
Intraparenchymal, *n* (%)	26 (74.3)
Subdural, *n* (%)	6 (17.1)
Subarachnoid, *n* (%)	3 (8.6)
Vitamin K administration, *n* (%)	33 (94.3)
Milligrams	10 $\pm$ 1

Data presented as mean $\pm$ SD unless otherwise noted

Table 2 3PCC administration information

Variable	Result
3PCC dosing	
Total (IU)	2,706 $\pm$ 776
Weight-based (IU/kg)	29.0 $\pm$ 5.0
Infusion duration (min)[a]	15.0 [12.0–17.0]
Time from end of 3PCC infusion to first INR drawn (min)[a]	48.0 [30.0–70.1]
INR measurements	
Baseline	3.2 $\pm$ 1.3
Post-3PCC administration	1.3 $\pm$ 0.2
24 h	1.2 $\pm$ 0.1
Efficacy	
INR $\leq$ 1.4 following PCC, *n* (%)	30 (85.7)
INR $\leq$ 1.4 at 24 h, *n* (%)	34 (97.1)
Time to INR $\leq$ 1.4 (min)[a]	50.5 [30.0–116.8]

Data presented as mean $\pm$ SD unless otherwise noted

[a] Data presented as median [25–75 % interquartile range]

INR international normalization ratio, *PCC* prothrombin complex concentrate

Table 3 Patients not achieving adequate INR reversal

Patient	Baseline INR	INR following 3PCC	Received repeat 3PCC dose	INR at 24 h	Outcome
1	5.0	1.7	Yes	1.4	Expired <48 h
2	3.0	1.5	No	1.2	Expired >48 h
3	3.6	1.5	Yes	1.1	Expired <48 h
4	2.1	1.8	No	1.8	Expired <48 h
5	2.6	1.7	Yes	1.4	Survived

INR International normalization ratio

events reported within 7 days of 3PCC administration. However, 18 patients expired prior to day seven and adverse event reporting was therefore limited.

Discussion

Based on our experience, a fixed, weight-based dose of 3PCC without additional FFP led to high rates of complete INR reversal following wICH. Use of our institution-specific protocol resulted in over 85 % of patients achieving goal INR after administration of 3PCC regardless of baseline INR. In our study cohort, we also observed rapid and complete reversal for the entire 24 h period following admission despite only one dose of 3PCC without the use of supplemental FFP.

With numerous international societies and guidelines recommending the use of PCC for immediate reversal of warfarin-induced major bleeding, the choice of product, adjunctive agents, and dosing strategy has become crucially important [1–3, 9, 14, 15]. Current available literature presents a wide array of reports examining the role of 3PCC for INR reversal, the vast majority of these in conjunction with FFP. As a result, some international guidelines have recommended adjunctive use of FFP for significant life-threatening bleeding due to warfarin therapy [9]. Despite these recommendations, there are several reports in the literature describing the use of 3PCC without FFP for INR reversal that achieved success rates similar to that observed in our cohort [16, 17].

Dosing of PCC products can be a challenging and arduous task depending on the strategy and method used. Numerous approaches have been described in the literature and include standardized, non-weight based doses, as well as doses depending on patient weight or initial INR [16–21]. In an effort to standardize treatment of our patients and facilitate rapid ordering and administration, we chose to utilize a fixed, weight-based dosing strategy of 30 IU/kg regardless of initial INR. At our institution, once 3PCC is ordered, a pharmacist automatically calculates the dose based upon the patient's actual body weight and rounds the dose depending on the available vial size. The dose selected represents a moderate dose previously shown to effectively and emergently reverse an elevated INR. The dose was also chosen in an attempt to attenuate probable dose-dependent thrombotic risks seen with factor products, particularly recombinant factor VII. In this study, our weight-based dose provided adequate reversal of INR without the need for additional doses and resulted in no documented thromboembolic complications. While we observed no adverse events from 3PCC administration, only 48.6 % of patients survived a full 7 days.

Currently, a wide variety of literature in the United States related to 3PCC utilizes Profilnine SD® (0.35 units of factor VII per unit of factor IX). While some studies have shown successful results, others have suggested that using this 3PCC product alone or in combination may be unable to reduce INR adequately [20–25]. In our study, the 3PCC product utilized is Bebulin VH® (0.05–0.2 units of factor VII per unit of factor IX) [6] and our results demonstrated a sustained, 24-h INR reversal after a single dose was combined with intravenous vitamin K. This sustained reversal was seen regardless of the initial INR, although only a small percentage of our patients presented with a baseline INR > 4.5. Cases of rebound elevations in INR have also been reported in the literature following administration of factor products [25, 26]. This phenomenon may be more associated with recombinant factor VII due to its short half life in relation to other vitamin K dependent clotting factors [26]. In a recently published report, recombinant factor VII was associated with a 50 % rate of rebound INR when administered to 8 patients [25]. While we did not observe any increase in INR following 3PCC administration, the lower average baseline INR of patients in our study may indicate that there was adequate endogenous factor VII to allow for complete reversal utilizing a 3PCC only [27]. Some authors have proposed that as INR increases above 4.5, endogenous factor VII is depleted so much so that 3PCC may not be an effective method of reversal [27]. While they are frequently considered to be equally efficacious, direct comparisons between 3PCC products may be needed to fully elucidate the role of each in the management of wICH.

It is important to note that this study has several limitations. Most importantly, this study is retrospective in

nature thus impairing any potential examination of causality. Our small population limits the overall ability to generalize our conclusions over a large patient population, particularly those with an extremely elevated INR. In addition, many of the previous studies on this subject employed a different goal than our institution. To examine the possibility that this may have impacted our results, we also determined the percentage of patient achieving a goal INR $\leq$ 1.3. Utilizing this new endpoint, 20 patients (57.1 %) achieved an INR of $\leq$1.3, a similar percentage as seen in a recent randomized, controlled trial [28].

Our study does have several important strengths in relation to published reports. Since our institution uses a predefined protocol, all patients received the same weight-based dose and infusion rate of 3PCC. This is in contrast to many other reports which utilized varying dosages and infusion rates of 3PCC making extrapolation to clinical practice difficult. Moreover, the timing of our repeat INR measurements was very reliable and therefore reflective of 3PCC therapy only. In contrast to our study, previous reports are highly variable and report initial repeat INR results as far as 12 h following PCC administration, compared to the median time of 48 min in our cohort [20, 25]. As evidenced by the majority of previous literature, obtaining reliable repeat INR results following PCC administration seems to be a difficult task particularly outside of a randomized trial environment. It is our belief that creation of a fixed, weight-based dosing protocol may have increased clinician awareness of the urgent nature of wICH, allowing more prompt and reliable laboratory measurements.

Conclusions

A fixed, weight-based 3PCC dosing protocol without adjunctive FFP is safe and resulted in high rates of INR reversal following wICH. Baseline INR results did not influence the rate of INR reversal as those presenting with an INR $>$ 4.5 showed comparable reversal rates as those with a lower baseline INR. The inclusion of FFP with 3PCC in warfarin reversal protocols may be unnecessary and should be evaluated further.

Conflict of interest Kerry M. Mohrien, Andrew B. Boucher, Lucas Elijovich, and G. Morgan Jones have no conflicts of interest to disclose.

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