Prothrombin Complex Concentrate Accelerates International Normalized Ratio Reversal and Diminishes the Extension of Intracranial Hemorrhage in Geriatric Trauma Patients

MATHEW EDAVETTAL, M.D., PH.D., AMELIA ROGERS, B.S., FREDERICK ROGERS, M.D., MICHAEL HORST, PH.D., WICHITAH LENG, PHARM.D

From Lancaster General Health, Lancaster, Pennsylvania

Warfarin therapy increases the incidence intracranial hemorrhage (ICH), especially in the geriatric population. Timely reversal of international normalized ratio (INR) is integral in the management of these patients for whom fresh frozen plasma (FFP) with vitamin K is the standard of treatment. We hypothesized that implementing a protocol that used prothrombin complex concentrate (PCC) would reverse INR values more swiftly and decrease the amount of FFP administered. In November 2011, a protocol was implemented for administering PCC to the geriatric population on warfarin admitted for life-threatening bleeds. These patients received 25 IU/kg ideal body weight of a three-factor PCC (Profilnine SD) if their INR was over 1.5 or greater. FFP was given if follow-up INR revealed an INR of 1.5 or greater. Retrospectively the data from 29 patients who received PCC were compared with a historical control group of 34 patients. Protocol use resulted in a significantly faster INR reversal (PCC: 151.6 ± 84.3 minutes vs control: 485.0 ± 321 minutes; \( P < 0.001 \)), time to achieve an INR less than 1.5 (PCC: 484 ± 242 minutes vs control: 971 ± 1208 minutes; \( P = 0.036 \)), and less FFP administered (PCC: 1.3 ± 1.0 vs control:3.3 ± 1.5; \( P < 0.001 \)). PCC patients had a decreased incidence of progression of their ICH (PCC: 17.2% vs control: 44.2%; \( P = 0.031 \)). Rapid reversal of coagulopathy in geriatric patients on warfarin is vital to limit the extent of ICH. PCC allows a much more rapid reversal than standard treatment with only FFP and vitamin K. Adopting such a protocol is associated not only with a more rapid reversal and less FFP use, but also less patients went on to extend their head bleeds.

The geriatric population represents one of the fastest growing segments of our society. The 2010 U.S. Census data note that adults older than 65 years now comprise 13 per cent of U.S. residents. Many of these patients represent a significant healthcare burden when they get injured because of comorbid conditions. A significant proportion of these patients are on oral anticoagulant therapy (OAT) such as warfarin because of comorbidities such as atrial fibrillation, history of deep vein thrombosis, pulmonary embolism, or prophylaxis after prosthetic valve replacement. When these patients are injured, they can be vexing management problems for trauma surgeons because of their tendency to bleed, especially if they sustain head injuries. There are numerous studies that attest to the fact that preinjury OAT worsens outcome after head injury.\(^2\)\(^7\) Furthermore, it has been shown that the rapidity of reversal of OAT can improve mortality.\(^7\)\(^9\) The mainstay of OAT reversal involves vitamin K and/or fresh-frozen plasma (FFP). Although vitamin K is highly efficacious in reversing warfarin induced coagulopathy, peak effect may take up to 24 hours.\(^10\)\(^11\) FFP can work faster, but still requires time for type and cross, thawing, and administration.\(^12\)\(^13\) Both FFP and vitamin K are time-dependent reversal agents in which one is dealing with a threatening intracranial bleed.

Prothrombin complex concentrate (PCC) is a concentrate vitamin K-dependent coagulation factor that was first used to treat hemophilia.\(^14\) PCC confers an advantage over vitamin K and FFP in the reversal of OAT in that it does not require type and cross and thawing. Most of the research that has been done on reversal of OAT has been conducted in Europe and has used four factor PCC.\(^15\)\(^18\) In the United States,
there had only been three-factor PCC (Profilnine SD and Bebulin VH) available until May 2013 when four-factor PCC became available. Presently, very little research has been published pertaining to the efficacy of three-factor PCC. Chong et al.\(^1\) concluded that three-factor PCC prevented intracranial hematoma (ICH) expansion and was able to quicken neurosurgical intervention in patients of all ages. Cabral et al.\(^2\) showed rapid reversal of elevated international normalized ratio (INR) in patients with ICH, but their median initial INR was 2.3. Switzer et al.\(^3\) showed partial efficacy of high-dose, three-factor PCC in reversing an increased INR in patients with ICH; however, this study had a high complication rate, including pulmonary embolism, ischemic strokes, and venous thrombosis. None of the studies included a control group or examined primarily geriatric patients.\(^1\)–\(^3\)

We had noted at our Level II trauma center that several patients had progression of their intracranial bleeds with deleterious outcomes while undergoing OAT reversal with FFP and vitamin K. We petitioned our Pharmacy and Therapeutics Committee to place PCC on formulary for the rapid reversal of OAT in patients with an intracranial bleed using a strict protocol and assiduous performance improvement. We hypothesized that a PCC protocol would decrease the time for OAT reversal, decrease the use of FFP, and halt the extension of ICHs of elderly patients on OAT after head injury.

**Methods**

The trauma service at Lancaster General Hospital is a mature, Level II trauma center verified by the Pennsylvania Trauma Systems Foundation since 1986. Approval by the Institutional Review Board of Lancaster General Health has been received for this study. In November 2011, our institution implemented a policy for administering PCC in the geriatric population (age 65 years or older) sustaining life-threatening bleeding for the reversal of warfarin-induced coagulopathy (Fig. 1). Coagulopathy was defined as an INR of 1.5 or greater. Profilnine SD (Grifols Biologicals Inc., Los Angeles, CA), a three-factor PCC obtained from pooled human plasma; viral inactivation is conducted by solvent detergent.\(^4\) The factor composition is 100 to 150 IU/mL factor IX, 1.5 IU or less factor II per 1 IU factor IX, 1 IU or less factor X per 1 IU factor IX, and 0.35 IU or less factor VII per 1 IU Factor IX.\(^5\) Profilnine SD does not contain any heparin.\(^4\) If the initial INR is 1.5 or greater, then patients were given 25 IU/kg PCC (Profilnine SD) of ideal body weight along with 10 mg vitamin K intravenously over 30 minutes. A half hour after PCC administration, patients had a follow-up INR check. If the repeat INR was not 1.5 or less, then patients were given FFP.

We retrospectively examined patients who received PCC and compared them with a historical control group of patients (control) obtained from our trauma registry (“Collector”; Digital Innovations, Forest Hills, No. 4 PCC VS. FFP IN ICH FOR WARFARIN REVERSAL  ·  Edavettal et al. 373

**Fig. 1.** Post-PCC implementation: anticoagulant reversal management guideline.
The control group consisted of all patients admitted to the trauma service from November 2010 into November 2011 who were 65 years of age or older on prehospital warfarin with a head injury of Abbreviated Injury Score (AIS) 2 or greater and reversed with only vitamin K and FFP (Fig. 2). Patients included in the PCC group were 65 years of age or older, on prehospital warfarin, with a head injury of AIS 2 or greater and reversed with PCC and vitamin K. Patients were excluded from either group if they were given factor VII, had an initial INR 1.0 or less, or had a pre-existing thrombus, for which PCC was contraindicated.

We collected age, gender, trauma activation level, initial INR, follow-up INR, time for INR to decrease to less than 1.5, amount of FFP given, time in minutes between the first head computed tomography (CT) scan and when PCC or FFP was first given, time in minutes between the first INR and second INR, admission Glasgow Coma Scale (GCS), discharge GCS, if neurosurgical intervention occurred, intensive care unit days, hospital length of stay, Injury Severity Score (ISS), AIS for the head, if the bleed increased on follow-up head CT scan, and mortality during hospital admission (Table 1). A bleed was considered to be extended based on the radiologist’s impression of the follow-up head CT scan. The PCC group was compared with the FFP group using Student’s t-test for continuous variables and Fisher’s exact test for discontinuous variables. A P value < 0.05 was considered significant.

Results

There were 29 patients in the PCC group and 34 patients in the historical control group; two patients were dropped from the control group for incomplete data. Care was withdrawn within the first hour of arriving at the hospital on one patient, who was subsequently removed from the PCC group. The PCC group is comparable to the control group in their mean initial INRs (PCC 3.9 ± 1.6 vs control 3.4 ± 2.1; P = 0.972; Table 1), mean ISS (PCC 16 ± 8.0 vs control 18.4 ± 7.4; P = 0.217), mean AIS head score (PCC 3.6 ± 1.2 vs control 3.9 ± 0.95; P = 0.192) as well as the mean second INR (PCC 1.66 ± 0.26 vs control 1.70 ± 0.63; P = 0.772). However, there was a significant decrease in the time between initial INR and second INR in the PCC group compared with the control group (PCC 164 ± 90.7 minutes vs control 412 ± 381 minutes; P = 0.001; Table 1). Also, the amount of time in minutes to achieve an INR of less than 1.5 was significantly lower in the PCC group (PCC 164 ± 90.7 minutes vs control 412 ± 381 minutes; P = 0.001; Table 1). There was a significant decrease in the mean amount of FFP given the PCC group (PCC 0.86 ± 1.1 units vs control 3.32 ± 1.5 units; P < 0.001). In addition, the PCC group saw a significant decrease in the number of patients who had an extension of their ICH as seen on repeat CT scan (17.2% PCC vs 44.2% control; P = 0.031; Table 1). We also observed a decrease in the rate of mortality (6.9% PCC vs 14.7% control) and need for
neurosurgical intervention (10.3% PCC vs 25.5% control), although they did not reach statistical significance.

Discussion

In this study we have demonstrated that the use of PCC in a protocolized format is efficacious in decreasing the time for reversal of OAT in head-injured patients, decreasing the amount of FFP needed to reverse OAT, and decreasing the amount of patients that increased the size of their intracranial hemorrhage.

There are two types of PCC available for commercial use: three-factor PCC vs four-factor PCC. In the United States, there are currently only two brands of PCCs commercially available (Profilnine SD and Bebulin VH) both of which are three-factor PCC. In Europe, Japan, and Australia commonly use four-factor PCC, which contains significant amounts of anticoagulation factors such as antithrombin, protein C, protein S, and protein Z. Heparin may also be added as well to inhibit activated factors. PCC has been shown to be efficacious in swiftly reversing vitamin K-dependent coagulopathy, whether in the setting of ICH, gastrointestinal bleeding, or to perform an invasive procedure or surgery. It may also be used to reverse the anticoagulant effect of the oral factor Xa inhibitor rivaroxaban (Xalreto). PCC has also been used in reversing the bleeding associated with cardiac surgery or other invasive procedures. Others have demonstrated that PCC is effective in the correction of traumatic coagulopathy and dilutional coagulopathy. Kalina et al. showed that a discretionary PCC protocol to treat patients on warfarin sustaining ICH did decrease the time for normalization of INR and time to operative intervention compared to FFP administration but did not show any difference between groups with respect to intensive care unit days, hospital days, or mortality. The PCC that was used in this study (Proplex T) is no longer available in the United States.

There are limitations to this study. The sample sizes are small and its retrospective format restricts the interpretation of the data. There was a decrease in the rate intensive care unit length of stay, ventilator use, and total ventilator days, but they did not reach significance, which may be the result of the study being underpowered and therefore represents a Type II error. Further investigation in the differences in neurologic function and outcome between different treatment modalities is crucial.

We have shown that PCC is efficacious in rapidly reversing the INR of patients on OAT. It also decreases the amount of FFP used in reversal and therefore may decrease the incidence of transfusion-related acute lung injury and transfusion-associated circulatory overload secondary to FFP. However, FFP may be needed to supplement three-factor PCC, especially for extremely elevated INRs. In addition, patients who received PCC were significantly less likely to experience an increase in the size of the ICH. We believe an urgent protocolized approach to OAT in using PCC has the potential to improve outcome in our geriatric head-injured patient population.

### Table 1. Differences in Outcomes of PCC versus FFP Groups

<table>
<thead>
<tr>
<th>Case: PCC + FFP</th>
<th>Control: FFP Only</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. 29 (46.03%)</td>
<td>34 (53.97%)</td>
<td>0.803</td>
</tr>
<tr>
<td>Female 44.1%</td>
<td>48.3%</td>
<td></td>
</tr>
<tr>
<td>Mean age (SD)</td>
<td>83.55 (8.88)</td>
<td>77.21 (12.76)</td>
</tr>
<tr>
<td>Mean ISs</td>
<td>16 (8.02)</td>
<td>18.44 (7.40)</td>
</tr>
<tr>
<td>Mean AIS of the head</td>
<td>3.59 (1.15)</td>
<td>3.94 (0.95)</td>
</tr>
<tr>
<td>Mean hospital LOS (SD)</td>
<td>5.03 (6.69)</td>
<td>5.12 (3.69)</td>
</tr>
<tr>
<td>Mean ICU LOS (SD)</td>
<td>2.17 (1.67)</td>
<td>3.09 (2.60)</td>
</tr>
<tr>
<td>Mean ventilator days (SD)</td>
<td>0.14 (0.74)</td>
<td>0.82 (2.46)</td>
</tr>
<tr>
<td>Ventilator required 1 (3.5%)</td>
<td>7 (20.6%)</td>
<td>0.060</td>
</tr>
<tr>
<td>Mean initial INR (SD)</td>
<td>3.39 (1.63)</td>
<td>3.41 (2.05)</td>
</tr>
<tr>
<td>Mean minutes Δ INR&lt;sub&gt;Initial to INR&lt;sub&gt;2nd&lt;/sub&gt; (SD)</td>
<td>164.3 (90.7)</td>
<td>412 (381)</td>
</tr>
<tr>
<td>Mean minutes Δ INR&lt;sub&gt;Initial to INR&lt;sub&gt;ICU&lt;/sub&gt; (SD)</td>
<td>489 (294)</td>
<td>959 (1192)</td>
</tr>
<tr>
<td>Mean Units FFP&lt;sub&gt;given&lt;/sub&gt; (SD)</td>
<td>0.86 (1.09)</td>
<td>3.32 (1.49)</td>
</tr>
<tr>
<td>Mean minutes PCC&lt;sub&gt;ordered&lt;/sub&gt; to PCC&lt;sub&gt;given&lt;/sub&gt; (SD)</td>
<td>20.66 (36.11)</td>
<td>—</td>
</tr>
<tr>
<td>Mean GCS&lt;sub&gt;Admit&lt;/sub&gt; (SD)</td>
<td>14.4 (0.95)</td>
<td>14.3 (2.20)</td>
</tr>
<tr>
<td>Mean GCS&lt;sub&gt;Discharge&lt;/sub&gt; (SD)</td>
<td>13.4 (3.31)</td>
<td>12.4 (4.48)</td>
</tr>
<tr>
<td>Mean GCS (SD)</td>
<td>−0.96 (2.94)</td>
<td>−1.91 (3.88)</td>
</tr>
<tr>
<td>Neurosurgical intervention</td>
<td>3 (10.3%)</td>
<td>8 (25.5%)</td>
</tr>
<tr>
<td>Mortality</td>
<td>2 (6.9%)</td>
<td>5 (14.7%)</td>
</tr>
<tr>
<td>Extension of intracranial hemorrhage</td>
<td>5 (17.2%)</td>
<td>15 (44.1%)</td>
</tr>
</tbody>
</table>

PCC, prothrombin complex concentrate; FFP, fresh-frozen plasma; SD, standard deviation; ISS, Injury Severity Score; AIS, Abbreviated Injury Score; LOS, length of stay; ICU, intensive care unit; INR, international normalized ratio; GCS, Glasgow Coma Scale.
REFERENCES
