Clinical Experience With Three-Factor Prothrombin Complex Concentrate to Reverse Warfarin Anticoagulation in Intracranial Hemorrhage

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Background and Purpose—The effectiveness of prothrombin complex concentrate (PCC) products available in the United States that contain low levels of factor VII (3-factor PCC) has not been tested. The purpose of this study was to review our experience with 3-factor PCC (Profilnine) in the setting of warfarin-associated intracranial hemorrhage (wICH).

Methods—In November 2007, we implemented a protocol for reversal of anticoagulation in wICH using Profilnine. Additional treatment with fresh-frozen plasma was at the discretion of the treating physician. Medical records of all patients receiving PCC for wICH between November 1, 2007, and December 7, 2011 were reviewed. Correction of the international normalized rate (INR) was defined as an INR <1.4.

Results—Seventy wICH patients were treated with Profilnine, including 46 (66%) with intraparenchymal hemorrhage, 22 (31%) with subdural hemorrhage, and 2 (3%) with subarachnoid hemorrhage. Mean INR was reduced from 3.36 to 1.96, and in 44 (62.9%) patients the INR corrected to <1.4. Baseline INR ≥3.0 decreased the likelihood of INR correction. Concomitant administration of fresh-frozen plasma (mean, 2.6 U) did not increase the likelihood of INR correction. Seven (10%) patients had serious adverse events during their hospital course, including 2 sudden deaths from suspected pulmonary embolism.

Conclusions—Reversal of coagulopathy in wICH with Profilnine was incomplete and associated with serious adverse events. In the absence of available 4-factor PCC, options for urgent reversal of anticoagulation in wICH remain limited. (Stroke. 2012;43:00-00.)

Key Words: acute intracranial hemorrhage warfarin

Warfarin-associated intracranial hemorrhage (wICH) is the most feared complication of oral anticoagulation with warfarin and poses a frequent clinical challenge.1,2 Prothrombin complex concentrates (PCC) have been advocated as an alternative to fresh-frozen plasma (FFP) for reversal of anticoagulation. However, PCC products available in the United States (3-factor PCC) contain low levels of factor VII.3,4 Further, there is a lack of safety data for the use of 3-factor PCC for wICH. We reviewed our experience of anticoagulation reversal with 3-factor PCC (Profilnine) in wICH.

Materials and Methods

We reviewed the medical records of all patients receiving PCC admitted to Georgia Health Sciences University hospital between November 1, 2007, and December 7, 2011. Inclusion criteria were: acute intracranial hemorrhage confirmed by head computed tomography, warfarin-associated coagulopathy; and treatment with PCC. The study protocol is described in the Online Data Supplement. Our Institutional Review Board approved this study.

Statistical analyses were performed using SAS 9.3. Correction of international normalized ratio (INR) was defined as an INR <1.4. The χ² test examined INR correction between those receiving and those not receiving FFP. The Kaplan-Meier survival analysis examined time to INR correction after the first and second doses of PCC. Patients were stratified by baseline INR into 3 groups (<3.0, 3.0–4.9, and >4.9). The log rank test examined time to INR correction between those receiving and those not receiving FFP.

Results

Seventy patients were included (Supplementary Table I). The mean pre-PCC INR was 3.36 (±2.42; range, 1.5–13.7). Using our weight-based protocol, the mean initial dose of PCC was 3914 IU (47.0 IU/kg). After the first PCC dose, the mean INR was reduced to 1.96 (±1.64), and in 44 (62.9%) patients it

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corrected (<1.4). Eighteen patients (25.7%) received a second PCC dose with a mean of 2651 IU (31.9 IU/kg); the mean INR was further reduced to 1.57 (±0.59), and 11 (61.1%) of the 18 patients had a corrected INR. Additionally, 21 (30%) patients received FFP (mean, 2.6 U) before or concomitant with the initial PCC dose, and 18 patients received FFP after PCC, for a total of 39 (55.7%) patients and a mean of 4.9 U. Lower initial INR were more likely correct (P<0.001; Supplementary Table II). Higher initial INR took longer to correct (P=0.04; Figure 1). FFP infusion concomitant with or before PCC dose did not impact the likelihood of INR reversal or the time to reversal (Supplementary Table II and Figure 2).

There were 7 (10%) major adverse events possibly related to PCC. This included 3 definite venous thrombotic or thromboembolic events; 1 of which occurred in a patient with multiple myeloma. Two of these patients received a single dose of PCC, whereas the third patient received a second dose. Two patients had ischemic strokes after PCC treatment. One of these patients received a second dose of 26 IU/kg Profilnine because of incomplete reversal. Two patients had sudden death from pulseless electric activity within 120 minutes of the initial PCC infusion. One of these presented with a small (<5 mL) thalamic hemorrhage with intraventricular extension, and the other presented with nonaneurysmal subarachnoid hemorrhage. In both cases of sudden death the presumed diagnosis was a venous thromboembolic event; however, imaging was not obtained before death and autopsy was declined.

### Discussion

PCC has been advocated as first-line therapy for reversal of coagulopathy in wICH. PCC products, however, vary in factor VII content, and the efficacy of 3-factor PCC available...
in the United States has not been rigorously tested in wICH. Our experience suggests incomplete efficacy of the 3-factor PCC Profilnine for INR correction and a worrisome serious complication rate.

Our results should be interpreted in the context of previous studies. First, consistent with previous observations, when administered alone, the 3-factor PCC formulation Profilnine did not completely reverse anticoagulation.5-7 Holland et al8 described 23 patients treated with low-dose (25 IU/kg) and 17 patients treated with high-dose (50 IU/kg) Profilnine, all without wICH. The mean INR was reduced from 9.0 to 4.6 and from 8.6 to 4.7, respectively, and only half the patients achieved INR <3.0, regardless of dose. Similarly, Baggs et al9 detailed the use of Profilnine for reversal of coagulopathy in 50 patients, and only 58% achieved a target INR of ≤1.5. Second, in our study, the median time to correction was prolonged and the likelihood of INR correction diminished in patients with higher baseline INR. Baggs et al9 also showed that a higher baseline INR was a significant predictor of lack of INR reversal with Profilnine. Third, in our study, higher doses of Profilnine did not increase the likelihood of INR correction. Using a mean initial dose of 47.0 IU/kg, only 62.9% of patients experienced correction. Of the 18 patients who received an additional dose of PCC (31.9 IU/kg), 7 (39%) did not correct. Holland et al8 used a similar initial dose (50 IU/kg) with a posttreatment INR of 4.7. Therefore, for many patients Profilnine doses of ≥50 IU/kg appear inadequate for complete INR reversal.

Sudden cessation of anticoagulation may present a significant risk for thrombotic events. Nevertheless, a concerning number of serious complications were identified in our patients. Two of the events were sudden deaths attributable to presumed venous thromboembolic events in patients with an initially reasonably good prognosis. Of further concern is that almost half of the recipients died or went to hospice within the first few days after admission, potentially obscuring detection of additional thrombotic complications. Because each unit per kilogram of Profilnine increases plasma factor IX concentration by 1%, higher doses of Profilnine may increase the likelihood of thrombotic complications. However, most of the thrombotic complications occurred after a single dose (47 IU/kg). There are limited data in the literature on the safety of 3-factor PCC in the setting of wICH. Chong et al10 reported 1 case of pulmonary embolus 3 days after a relatively low dose of 14.9 IU/kg Profilnine in 1 of 7 patients. No thrombotic events were reported in studies of other 3-factor PCC products, such as Prothrombinex VF or Uman Complex DL, within 1 month of treatment.7,8 Thrombotic complications were uncommon in 2 large series of patients treated with 4-factor PCC.8,10

This study has several limitations. First, our study is retrospective and thus limited to the data available in medical records. Second, patients were not treated in a consistent manner. FFP was administered at the discretion of treating physicians, which was potentially biased. Third, the timing of INR testing after PCC was inconsistent, limiting the determination of time to reversal. Fourth, without a control arm, we are unable to directly compare our results with other reversal strategies, such as using FFP alone, 4-factor PCC, or recombinant factor VIIa. Finally, the significance of INR correction in terms of improving clinical outcome is not established. In fact, recent evidence suggests that rapid INR correction alone may not improve outcome in wICH.9

Conclusion

The 3-factor PCC Profilnine was incompletely effective in reversing anticoagulation in the setting of wICH and significant complications occurred. In the United States, where 4-factor PCC is unavailable and options for urgent reversal of anticoagulation remain limited, caution should be applied when using Profilnine in wICH. Prospective studies, such as the ongoing INCH trial, are needed to determine the safest and most efficient strategy for INR correction in wICH.11

Disclosures

None.

References


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Supplemental Methods

In 2007, we implemented a protocol for reversal of anticoagulation in wICH using 3-factor PCC (Profilnine). All patients with a wICH received 10 mg IV vitamin K. Unless the treating physician deems clinical futility, 50 IU/kg of PCC were administered intravenously (slight adjustments were made in dose by the pharmacy to use complete vials of Profilnine). We planned to check the INR thirty minutes after PCC administration, however, this aspect of the protocol was not well adhered to and post-PCC INR was collected at a mean of 1.9 (± 2.89) hours post-PCC. If the INR remained ≥1.4, a second dose of PCC of 25 IU/kg was infused. The protocol also advised repeating the INR every six hours for 24 hours; however, the timing of subsequent INR collection was also inconsistent. Adjunctive administration of FFP was at the discretion of the treating physician.
Table 1. Demographic and clinical characteristics in 70 patients.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Descriptive Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years; mean (SD)</td>
<td>70.5 (11.7)</td>
</tr>
<tr>
<td>Weight, kgs; mean (SD)</td>
<td>83.2 (20.2)</td>
</tr>
<tr>
<td>Men; number (%)</td>
<td>40 (57.1)</td>
</tr>
<tr>
<td>Race; number (%)</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>47 (68.1)</td>
</tr>
<tr>
<td>African-American</td>
<td>20 (30.0)</td>
</tr>
<tr>
<td>Other</td>
<td>2 (2.9)</td>
</tr>
<tr>
<td>Intracranial Hemorrhage subtype; number, (%)</td>
<td></td>
</tr>
<tr>
<td>IPH</td>
<td>46 (65.7)</td>
</tr>
<tr>
<td>SDH</td>
<td>22 (31.4)</td>
</tr>
<tr>
<td>SAH</td>
<td>2 (2.9)</td>
</tr>
<tr>
<td>Hemorrhage Growth; ≥12.5 mL or ≥33%, (%)</td>
<td>3 (9.7)*</td>
</tr>
<tr>
<td>Discharge Disposition (%)</td>
<td></td>
</tr>
<tr>
<td>Hospice or Death</td>
<td>32 (46.9)</td>
</tr>
<tr>
<td>Skilled Nursing Facility</td>
<td>13 (18.8)</td>
</tr>
<tr>
<td>Inpatient Rehabilitation</td>
<td>12 (17.4)</td>
</tr>
<tr>
<td>Home</td>
<td>12 (17.4)</td>
</tr>
</tbody>
</table>

* Of the 70 subjects, 39 did not have a baseline scan (due to transfer from outside facility) or follow-up scan (due to sudden death or withdrawal of care) for comparison, or underwent surgery prior to follow-up scan, leaving 31 for analysis.

IPH = intraparenchymal hemorrhage, SDH = subdural hemorrhage, SAH = subarachnoid hemorrhage
Table 2: INR Correction by FFP use and by INR level with single dose of PCC.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Use or level</th>
<th>INR Corrected</th>
<th>N</th>
<th>%</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FFP use</td>
<td>No (N=49)</td>
<td></td>
<td>32</td>
<td>65.3</td>
<td>0.52</td>
</tr>
<tr>
<td></td>
<td>Yes (N=21)</td>
<td></td>
<td>12</td>
<td>57.1</td>
<td></td>
</tr>
<tr>
<td>INR before 1st PCC dose</td>
<td>&lt;3.0 (N=44)</td>
<td></td>
<td>35</td>
<td>79.6</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3.0 – 4.9 (N=15)</td>
<td></td>
<td>5</td>
<td>33.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>&gt;4.9 (N=9)</td>
<td></td>
<td>3</td>
<td>33.3</td>
<td></td>
</tr>
</tbody>
</table>