PROTHROMBIN COMPLEX CONCENTRATE FOR RAPID REVERSAL OF WARFARIN-INDUCED ANTICOAGULATION AND INTRACEREBRAL HEMORRHAGE IN PATIENTS SUPPORTED BY A LEFT VENTRICULAR ASSIST DEVICE

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SUMMARY

Background: Intracerebral hemorrhage (ICH) is one of the most serious complications in patients supported by a left ventricular assist device (LVAD). We evaluate the efficacy of prothrombin complex concentrate (PCC) for rapid reversal of warfarin-induced anticoagulation in this population.

Methods: A total of 38 consecutive ICH events in patients supported by an LVAD between 1996 and 2007 were retrospectively reviewed. Fourteen ICH events were treated with fresh frozen plasma (FFP) (Group FFP) and 24 ICH events were treated with PCC (Group PCC). The efficacy and outcome of PCC administration versus FFP were evaluated.

Results: The proportion of patients surviving after an ICH event was significantly smaller in Group FFP than Group PCC (35.7% vs. 75.0%, p < 0.05). None of the patients in Group FFP were able to undergo heart transplantation, whereas 21.4% patients in Group PCC successfully underwent heart transplantation.

Conclusion: Patients on LVAD are in need for intensified anticoagulation and are at high risk of ICH; therefore, adequate use of PCC in the event of ICH could be of importance for survival and allow subsequent heart transplantation. [International Journal of Gerontology 2010; 4(3): 143–147]

Key Words: anticoagulants, cerebral hemorrhage, heart-assist devices, heart transplantation, prothrombin complex concentrate

Introduction

Heart transplantation (HTx) has provided a great survival benefit for patients with end-stage heart failure; however, the majority of patients on the HTx waiting list require long-term use of a left ventricular assist device (LVAD) because of donor shortages1. Development of intracerebral hemorrhage (ICH) is one of the most serious complications in patients supported by LVADs, who require extensive oral anticoagulant therapy2. ICH associated with anticoagulation has a high mortality, and more than 50% of patients die within 30 days3. Thus, warfarin-related ICH is considered a medical emergency especially in patients supported by LVADs. Nevertheless, there are no guidelines for reversal of...
anticoagulation in such patients. Reversing warfarin-induced anticoagulation by vitamin K is time consuming\(^4\). The administration of fresh frozen plasma (FFP) requires substantial intravenous volume\(^5\), which is not appropriate in patients with heart failure. Prothrombin complex concentrate (PCC), which contains a high concentration of the vitamin K-dependent coagulation factors II, VII, IX and X, has been reported to be effective for rapid reversal of warfarin-induced anticoagulation\(^6,7\). PCC has been reported to reduce the prothrombin time–international normalized ratio (PT-INR) faster than FFP or vitamin K\(^7,8\). The PCC product (PPSB-HT; Nihon Pharmaceuticals, Tokyo, Japan) became available at our institution in 2001, and it has been used for emergency reversal of warfarin-induced anticoagulant effects, such as ICH, intraabdominal hemorrhage and cardiac tamponade.

In this study we investigated the effects of PCC for rapid reversal of warfarin-induced anticoagulation in patients supported by LVADs and who developed ICH.

### Materials and Methods

**Patients and study design**

Thirty-eight consecutive ICH events, which occurred in patients supported by LVADs as a bridge to HTx between April 1996 and March 2007 at our institution, were retrospectively reviewed. All patients received warfarin with targeted value of PT-INR between 3 and 4. Rapid reversal of warfarin-induced anticoagulation was attempted for all cases. Fourteen ICH events treated by FFP were classified as Group FFP, and 24 ICH events treated by PCC were classified as Group PCC. Vitamin K was never used for patients in Group FFP nor Group PCC. The coagulation status before and after ICH events and the clinical outcomes were compared between the groups. Patients who survived more than 1 month after an ICH event were defined as “patients survived through ICH events.” Patients who recovered from ICH events with only limited neurological after effects were defined as “patients survived and back on the waiting list.”

FFP and PCC administrations are accepted and financially covered by the National Health Insurance System of Japan, and studied patients provided written informed consent for drug administration. The present study was approved by the Institutional Review Board and Institutional Ethical Committee for Human Research of the National Cardiovascular Center, and was executed according to the Declaration of Helsinki.

**Protocol for FFP and PCC administration**

None of the ICH events were treated with vitamin K. In Group FFP, the FFP was initially administered after the ICH event at the dosage of body weight (kg) \(* 0.08 \times (100\text{-hematocrit}/100) \times 0.3 \times 0.2 \times 1000 \text{ mL}\). If the PT-INR was still greater than 2 after the initial FFP administration, additional FFP was administered. In Group PCC, the initial dosage of 500–1000 units was administered for 30–60 minutes, and if the INR was greater than 2 after the initial PCC administration, additional PCC was given.

**Statistical analysis**

Data are presented as mean±standard deviation. Normality was evaluated for each variable based on normal distribution plots and histograms and by the Kolmogorov-Smirnov test. Clinical characteristics, coagulation status after anticoagulation reversal, and clinical outcome were compared between groups by a Student unpaired two-tailed \(t\) test or \(\chi^2\) analysis. Mortality after ICH events was compared by Kaplan-Meier analysis and the log rank test. All statistical analyses were performed using JMP7.0 software (SAS Institute, Cary, NC, USA).

**Results**

The demographic and clinical data of the patients are summarized in Table 1. The anticoagulant status before and after the ICH event and the outcome in both groups are shown in Table 2. The INR values before and on the day of the ICH event were not different between the groups; however, the INR values after treatment were markedly reduced in Group PCC. The proportion of patients who survived an ICH event was significantly greater in Group PCC than Group FFP, although the proportion of patients requiring subsequent neurosurgery was not significantly different between the groups. The proportion of patients who returned to the HTx waiting list tended to be greater in Group PCC than Group FFP. None of the patients in Group FFP underwent HTx compared with 21.4% of patients in Group PCC (Table 2).

Representative computed tomography scans from the two groups are shown in Figure.
Discussion

Although this is a single center retrospective analysis, the present study is the first head-to-head comparison of PCC versus FFP as a treatment for reversal of warfarin-induced anticoagulation in a clinical setting in the light of prognosis after treatment. The present study demonstrated that (1) immediate PCC administration after an ICH event in patients supported by LVADs was effective in the prompt reversal of warfarin-induced anticoagulation; and (2) the patients supported by LVADs who had an ICH were able to have HTx only when they were treated by PCC, not by FFP.

The majority of patients on the HTx waiting list require long-term use of an LVAD because of donor shortages. In the REMATCH study, sepsis was the

Table 1. Demographic and clinical data from patients

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group FFP (n=14)</th>
<th>Group PCC (n=24)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at LVAD implantation (yr)</td>
<td>33.1±13.4</td>
<td>39.1±5.9</td>
<td>0.064</td>
</tr>
<tr>
<td>Age at ICH events (yr)</td>
<td>33.6±13.4</td>
<td>39.9±6.3</td>
<td>0.056</td>
</tr>
<tr>
<td>Male</td>
<td>11 (78.6%)</td>
<td>3 (12.5%)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Blood pressure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic (mmHg)</td>
<td>102±12.9</td>
<td>92±15.9</td>
<td>0.053</td>
</tr>
<tr>
<td>Diastolic (mmHg)</td>
<td>61±9.9</td>
<td>59±10.9</td>
<td>0.576</td>
</tr>
<tr>
<td>Disease for LVAD implantation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonischemic cardiomyopathy</td>
<td>14 (100.0%)</td>
<td>24 (100.0%)</td>
<td>–</td>
</tr>
<tr>
<td>Ischemic cardiomyopathy</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>–</td>
</tr>
<tr>
<td>Type of LVAD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Toyobo</td>
<td>14 (100.0%)</td>
<td>23 (95.8%)</td>
<td>0.782</td>
</tr>
<tr>
<td>EVAHEART</td>
<td>0 (0.0%)</td>
<td>1 (4.2%)</td>
<td>0.782</td>
</tr>
<tr>
<td>Drugs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Warfarin</td>
<td>14 (100.0%)</td>
<td>24 (100.0%)</td>
<td>–</td>
</tr>
<tr>
<td>Aspirin</td>
<td>12 (85.7%)</td>
<td>21 (87.5%)</td>
<td>0.734</td>
</tr>
<tr>
<td>β-blockers</td>
<td>12 (85.7%)</td>
<td>20 (83.3%)</td>
<td>0.833</td>
</tr>
<tr>
<td>ACE inhibitors or A-II antagonists</td>
<td>9 (64.2%)</td>
<td>16 (66.7%)</td>
<td>0.837</td>
</tr>
<tr>
<td>Intravenous inotropic agents</td>
<td>4 (28.5%)</td>
<td>4 (16.7%)</td>
<td>0.648</td>
</tr>
</tbody>
</table>

*pData presented as mean±standard deviation or n (%). FFP=fresh frozen plasma; PCC=prothrombin complex concentrate; LVAD=left ventricular assist device; ICH=intracerebral hemorrhage; Toyobo=Toyobo-type extracorporeal LVAD (Toyobo Corp. Ltd., Tokyo, Japan); EVAHEART=implantable rotary blood pump LVAD (Sun Medical Technology Research Corp. Ltd., Nagano, Japan); ACE=angiotensin converting enzyme; A-II=angiotensin II.

Table 2. Anticoagulant status pre- and post-intracerebral hemorrhage events (ICH) and outcome after ICH events

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group FFP (n=14)</th>
<th>Group PCC (n=24)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticoagulant status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline INR at stable situation</td>
<td>3.4±1.3</td>
<td>3.1±1.0</td>
<td>0.224</td>
</tr>
<tr>
<td>INR on the day of ICH event</td>
<td>3.6±2.0</td>
<td>3.0±1.2</td>
<td>0.175</td>
</tr>
<tr>
<td>INR after administration of initial dose of FFP or PCC</td>
<td>2.1±1.1</td>
<td>1.2±0.3</td>
<td>0.004</td>
</tr>
<tr>
<td>Time required for INR reduction (min)</td>
<td>906.7±437.8</td>
<td>135.4±66.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Outcome after ICH event (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients requiring subsequent neurosurgery</td>
<td>42.9</td>
<td>33.3</td>
<td>0.570</td>
</tr>
<tr>
<td>Patients survived through ICH events</td>
<td>35.7</td>
<td>75.0</td>
<td>0.016</td>
</tr>
<tr>
<td>Patients survived and back on the waiting list</td>
<td>18.2</td>
<td>57.1</td>
<td>0.051</td>
</tr>
<tr>
<td>Patients survived to heart transplantation</td>
<td>0.0</td>
<td>21.4</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*INR=international normalized ratio; FCC=fresh frozen plasma; PCC=prothrombin complex concentrate.
leading cause of death (29.5%) and stroke was the third most frequent cause of death (9.0%) after LVAD implantation. Development of ICH is one of the most serious complications in patients supported by LVADs who require extensive oral anticoagulant therapy.

Therefore, rapid reversal of warfarin-induced anticoagulation to prevent hematoma progression and to facilitate hematoma evacuation has a decisive impact on prognosis in such patients.

The anticoagulatory effect of warfarin is related to its ability to inhibit synthesis of the vitamin K-dependent clotting factors II, VII, IX and X. The appropriate way to reverse the anticoagulation effect of warfarin depends on the clinical situation. Minor or asymptomatic bleeding requires less aggressive reversal, whereas serious bleeding requires rapid reversal to avoid a subsequent fatal event, regardless of the reason for anticoagulation. For major bleeding, guidelines recommend the administration of vitamin K (5 mg intravenous or oral), and/or PCC (50 U/kg), and/or FFP (15 mL/kg).

PCC contains a high level of the vitamin K-dependent coagulation factors II, VII, IX and X. PCC promotes a much more rapid reduction of INR than FFP and/or vitamin K, which is explained by its higher concentration of coagulation factors than FFP. A large volume of FFP is required to achieve adequate INR reduction, because vitamin K-dependent coagulation factors vary considerably in FFP, and is not appropriate for patients with heart failure. Reversing anticoagulation with vitamin K requires 4–24 hours, which might result in a fatal outcome after an ICH event; also its persistent effect may promote clot formation. Thus, vitamin K administration is not a satisfactory treatment for LVAD-supported patients with ICH.

PCC has been available at our institution since 2001; therefore, patients in Group FFP consisted of patients of an earlier era in our LVAD program than those in Group PCC. The percentage of male patients was greater in Group FFP because larger body mass index was required for LVAD surgery at the earlier time.

Several studies have demonstrated the effect of recombinant activated factor VII on warfarin reversal and reported successful results in treating ICH events. Although recombinant activated factor VII does reduce the INR, it does not lead to complete reversal of all aspects of warfarin-associated coagulopathy. Further research is needed to understand the long-term effects of this treatment on LVAD-supported patients.
studies are required to establish the differences among PCCs, and the differences between PCCs and recombinant activated factor VII on warfarin reversal to establish the optimal treatment strategy for emergency INR reduction.

In conclusion, administration of PCC can result in a prompt reversal of warfarin-induced anticoagulation and could be of importance for the survival of patients supported by LVADs, who require intensified anticoagulation therapy and who are at high risk of ICH.

Acknowledgments

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References