Use and effectiveness of a two-level initiation strategy for fixed-dose prothrombin complex concentrate according to the initial international normalized ratio in an emergency department in Japan

Kei Suzuki,1,2 Kaoru Ikejiri,2 Ken Ishikura,2 and Hiroshi Imai2

1Department of Hematology and Oncology, Mie University Graduate School of Medicine, and 2Emergency and Critical Care Center, Mie University Hospital, Mie, Japan

Aim: Prothrombin complex concentrate (PCC) was recently approved for patients on warfarin therapy with international normalized ratios (INRs) exceeding 2 in Japan. However, rapid normalization of INR is necessary even in patients who do not meet the aforementioned criteria. We previously found that a fixed PCC dose of 500 IU is insufficient in some patients with INR elevation but is effective in patients with INR less than 2.5. On the basis of the results, we revised the protocol to administer a PCC dose of 500 IU to patients with INR less than 2.5 or 1,000 IU to patients with higher INRs. This study aimed to validate this revised protocol at an emergency department (ED) in Japan.

Methods: We retrospectively collected data for all patients who received PCC in accordance with the revised protocol at our ED between October 2014 and December 2017 (period B) and compared the findings with those in the previous period (January 2013 to September 2014, period A).

Results: In total, 15 and 11 patients received PCC without complications during periods A and B, respectively. All but one patient obeyed the protocol during period B. The average INRs at baseline and within 120 min after PCC infusion were 2.58 and 1.39, respectively, in period A (n = 9), versus 2.54 and 1.28, respectively, in period B (n = 8). Significantly more patients exhibited optimal responses (INR < 1.35) during period B (7/8) than during period A (3/9, P = 0.049).

Conclusion: Our revised protocol effectively normalized INR.

Key words: Critical bleeding, hemostatic management, Japanese, prothrombin complex concentrate (PCC), warfarin

INTRODUCTION

Warfarin has a narrow therapeutic window, and it can cause a variety of hemorrhages. The annual incidence of major bleeding, which can be potentially life-threatening, ranges from 1.1% to 1.5%.1-3 Because this risk of hemorrhage increases in parallel with increases in the international normalized ratio (INR), rapid reversal of long-term oral anticoagulant therapy (OAT) is crucial in cases of acute major bleeding or emergency invasive intervention in patients with elevated INRs.4

In recent clinical guidelines, including those published in Japan,5 prothrombin complex concentrate (PCC) has been recommended for the rapid reversal of OAT.6-13 Two types of PCCs are currently available in Japan: PPSB-HT Nichiyaku (Nihon Pharmaceutical, Tokyo, Japan) and Kcentra (CLS Behring, Tokyo, Japan); however, only Kcentra has been approved for the reversal of OAT. In addition, its use is limited to patients with INR over 2. However, rapid normalization of INR during hemostatic management is necessary even in patients with critical bleeding who do not meet the treatment criterion.14,15 Although PCC has emerged as the preferred option in emergency settings, the optimal dosing strategy, especially in Japanese patients, remains unknown. We reported 15 cases of PCC treatment in the emergency department (ED) in 2015 and found that a fixed PCC dose of 500 IU is insufficient in some patients with INR elevation.14 Conversely, this dose was effective in patients with INR less than 2.5.14 On the basis of these findings, in October 2014, our institution implemented a two-
fixed-dose initiation strategy for PCC featuring an initial dose of 500 or 1,000 IU according to the initial INR (Fig. 1).

The present study aimed to validate this revised protocol of PCC administration for rapidly normalizing INR and achieving control of hemorrhage at an ED in Japan.

**METHODS**

This was a retrospective, single-center study of consecutive patients who received OAT and/or exhibited INR elevation. Because of the hospital’s policy for off-label use, the patients who received PPSB-HT were specified by the attending physician. Hence, we selected all patients who received PPSB-HT in the ED and completed a chart review study. Eligible patients were those admitted to our ED who required acute reversal of INR elevation using PCC from April 2012 to December 2017. Patients were eligible for study entry if they (i) required INR normalization as a result of acute bleeding or (ii) underwent an emergency surgical or urgent invasive diagnostic intervention. We divided these patients into two groups according to the use of a single fixed dose of PCC (period A, from January 2013 to September 2014) or a two-level fixed dose (period B, from October 2014 to December 2017). The results evaluated in period A were reported in our previous study, and this study was performed using the same data.

As previously described, we used a commercially available four-factor PCC formulation (PPSB-HT). For each patient, the decision to administer PCC with vitamin K and/or fresh frozen plasma, as well as the decision regarding the administered dose, was made by the attending physician. INR and blood samples were examined for all patients on admission, and INR after PCC administration was measured within 120 min if possible. We used Wilcoxon’s signed-rank test for analysis using STATISTICA software (StatSoft, Tulsa, OK, USA). A P-value less than 0.05 was considered significant. The primary study endpoint was normalization of INR within 120 min after the end of the PCC infusion. Although the optimal target of INR was defined by each study, we defined INR normalization as a value of less than 1.35, in accordance with the Japanese Guidelines for the Management of Stroke (2015). In addition, hemostatic efficacy, outcomes, and thrombotic events were evaluated as described in our previous study. According to a previous report, the attending physician’s rating categories for clinical hemostatic efficacy were as follows: 1 = very good (prompt cessation of existing bleeding and/or a rapid decline in INR), 2 = satisfactory (>1–2-h delay in bleeding cessation and a decrease in INR), 3 = questionable (>2-h delay in the cessation of bleeding and a decrease in INR or the efficacy of PCC could not be determined), and 4 = none (no effect on bleeding and INR). The corresponding definitions among patients undergoing invasive interventional procedures were as follows: 1 = very good (normal hemostasis during the

---

**Fig. 1.** Two-level fixed-dose initiation strategy for PCC in our institution. PCC is used at an initial dose of 500 or 1,000 IU in accordance with the initial INR in patients requiring rapid OAT reversal. INR, international normalized ratio; PCC, prothrombin complex concentrate; OAT, oral anticoagulant therapy.
procedure), 2 = satisfactory (mildly abnormal intraprocedural hemostasis as judged by the quantity or quality of blood loss), 3 = questionable (moderate abnormality), and 4 = none (severe hemostatic abnormality).

RESULTS

Clinical characteristics

The baseline clinical characteristics of the patients are presented in Table 1. A total of 26 patients (period A, 15; period B, 11), all of whom were Japanese, met the inclusion criteria. The male-to-female ratios in periods A and B were 7:8 and 6:5, respectively, and the average patient ages in these periods were 71.4 and 66.8 years, respectively. The average body weights in periods A and B were 58.0 and 52.0 kg, respectively. Body weight was less than 70 kg in all but one patient. The baseline average INRs in periods A and B were 2.20 (range, 1.04–4.14; median, 1.95) and 2.41 (range, 0.94–6.98; median 1.94), respectively. Sex, age, body weight, and baseline INR did not significantly differ between the periods.

Indications for prothrombin complex concentrate administration

Details regarding the indications for PCC administration are listed in Table 2. Almost all patients (period A, 93.3%; period B, 81.8%) were administered PCC for acute bleeding. As noted in our previous report, there were more indications for trauma and iatrogenic events (period A, 66.7%; period B, 54.5%) than for endogenous bleeding.

Clinical course and outcomes

A summary of patient outcomes is presented in Table 3. The average doses per kilogram of body weight in periods A and B were 8.98 (range, 6.3–13.1; median, 8.77) and 10.8 IU (range, 7.6–18.9; median, 10.0), respectively. In total, 10/15 (66.7%) patients received concomitant agents in period A, and all but one patient in period B (90.9%) received concomitant agents. Overall, INR uniformly declined from 2.20 to 1.26 in period A and from 2.41 to 1.26 in period B after PCC administration. However, the timing of follow-up blood sampling varied. Approximately 75% of the patients who received PCC achieved relatively good (very good and satisfactory) hemostatic efficacy in each period. The in-hospital mortality rates in periods A and B were 13.3 and 9%, respectively. None of the patients had viral transmission or acute thromboembolic complications.

Table 1. The baseline characteristics of 26 patients

| Characteristic | Period A | Period B | P |
|---------------|----------|----------|---|
| Gender, n (%) |          |          |   |
| Male          | 7 (47)   | 6 (55)   | 0.69 |
| Female        | 8 (53)   | 5 (45)   |   |
| Age (years), median (years) | 71.4 (71) | 66.4 (68) | 0.27 |
| Age, years, n (%) |          |          |   |
| <60           | 1 (7)    | 3 (27)   |   |
| 60–69         | 4 (27)   | 3 (27)   |   |
| 70–79         | 7 (47)   | 3 (27)   |   |
| 80–89         | 3 (20)   | 2 (18)   |   |
| Body weight (kg), median (kg) | 58 (57) | 52 (53) | 0.12 |
| Body weight (kg), n (%) |          |          |   |
| <50           | 2 (13)   | 3 (27)   |   |
| 50–59         | 7 (47)   | 5 (45)   |   |
| 60–69         | 5 (33)   | 3 (27)   |   |
| ≥70           | 1 (7)    | 0 (0)    |   |
| INR, median   | 2.2 (1.95) | 2.41 (1.94) | 0.52 |
| INR, n (%)    |          |          |   |
| <2            | 8 (53)   | 6 (55)   |   |
| 2–3           | 4 (27)   | 3 (27)   |   |
| 3–4           | 2 (13)   | 1 (9)    |   |
| ≥4            | 1 (7)    | 1 (9)    |   |
| Indication for OAT†, n (%) |          |          |   |
| Atrial fibrillation | 11 (79) | 6 (55) |   |
| Heart valve replacement | 2 (14) | 4 (36) |   |
| Deep venous thrombosis | 1 (7) | 0 (0) |   |
| Without OAT†, n (%) |          |          |   |
| Warfarin      | 13 (93)  | 10 (90)  |   |
| Apixaban (Eliquis) | 1 (7) | 0 (0) |   |

INR, international normalized ratio; OAT, oral anticoagulant therapy.
*All patients were Japanese.
†Total number of patients receiving OAT: 14.
‡Four patients also received concomitant antiplatelet agent therapy.

International normalized ratio values

As expected, INR dramatically declined after PCC administration (INR decreased on average from 2.29 to 1.26). However, these values varied with the timing of follow-up blood sampling. Therefore, to simply focus on the efficacy of PCC, we examined patients who underwent follow-up INR measurements within 120 min of infusion and excluded patients with protocol violations. Accordingly, six and two patients were excluded in periods A and B, respectively. One patient in period B was additionally excluded because the initial PCC dose was insufficient for the initial INR. In
this subgroup analysis (period A, nine patients; period B, eight patients), the follow-up INR decreased on average from 2.58 to 1.39 in period A and from 2.47 to 1.26 in period B. In addition, the proportion of patients who achieved INR less than 1.35 was significantly higher in period B than in period A (33% [3/9] versus 88% [7/8], P = 0.049; Table 4).

**DISCUSSION**

This RETROSPECTIVE STUDY illustrated that (i) even among patients with INR less than 2.0, rapid OAT reversal is sometimes required, especially in the ED, and (ii) the potential effectiveness of our revised two-level initiation strategy of fixed-dose PCC based on the individual INR was supported. Currently, PCC (Kcentra) is commercially available for the rapid reversal of OAT in Japan. According to the product labeling, the PCC dose should be individualized on the basis of the patients’ baseline INR and body weight; however, PCC was approved only for patients with INR over 2.0.16 In other words, PCC must be used off-label in patients with INR 2.0 or less. Our study revealed that PCC administration for trauma as well as iatrogenic events resulted in satisfactory efficacy in clinical practice. In patients without hypofibrinogenemia (e.g., intracranial hemorrhage, cardiac tamponade, soft tissue injury) in whom mechanical hemostasis cannot be achieved, PCC may be effective even when INR is not elevated.14,15 In fact, the joint commission stated that for hemorrhagic stroke in the setting of warfarin-induced coagulopathy, reversal should be initiated for patients with INR over 1.417 or 1.35, favoring PCC for reversal, but guidance on dosing for PCC is lacking.

Meanwhile, the strategy for determining the optimal dose of PCC has not been reported. Although several studies attempted to determine the optimal dose of PCC using a variety of dosing regimens, no dosing strategy has proven superior.18 Because the recommended dose of PCC is 25–50 IU/kg, which was originally selected for the treatment of hemophilia, many previous reports used that dosing regimen.7,19 In fact, Kcentra adopted this dosing regimen (e.g., initial INR > 2–3.9, 25 IU/kg; INR = 4–6, 35 IU/kg, INR > 6, 50 IU/kg).16 Although the balance between therapeutic efficacy and safety is a critical component in evaluating the use of PCC, cost cannot be overlooked.20 As we previously demonstrated,14 an extremely low fixed dose of 500 IU is likely inadequate for successful OAT reversal in patients with moderate INR elevation (initial INR > 2.5); however, these doses (25–50 IU/kg) may be excessive in some patients, thereby increasing costs and the risk of thrombogenicity. Recent fixed-dose PCC protocols for OAT reversal that exhibited reasonable efficacy adopted a relatively higher dose (1,500–2,000 IU) than our institutional protocol.21–23 According to our previous results,14 the efficacy for normalization of INR using a fixed PCC dose of 500 IU could not be confirmed in Japanese patients. In this study, we used a fixed PCC dose of 1,000 IU in patients with initial INR over 2.5 and achieved good laboratory responses.

We experienced no complications related to PCC administration. Two major complications of PCC administration are viral transmission and thromboembolic complications. PCC use is associated with the emergence of serious thromboembolic events, especially at a high dose.6 Therefore, care must be exercised during PCC use, and excessive doses should be avoided if possible.

In this study, almost all patients weighed less than 70 kg. Because the response of PCC is related to the patient weight and initial INR, a higher dose (>1,000 IU/patient) should be considered in heavier patients (e.g., >80 kg) with an excessive INR, even among Japanese patients. Moreover, INR may not be the best surrogate marker for the reversal of anticoagulation at present because patients who did not display INR optimization had relatively good clinical hemostatic

| Table 2. Indication for prothrombin complex concentrate administration |
|---------------------------------------------------------------|
| **Indication, n (%)** | **Period A** | **Period B** |
|------------------------|-------------|-------------|
| **n = 15** | **n = 11** | **n = 11** |
| **Bleeding** | | |
| Trauma | 7 (47) | 3 (27) |
| Intracranial hemorrhage | 4 (27)* | 2 (18)^† |
| Soft tissue hemorrhage | 1 (7) | 1 (9) |
| Bleeding from multiple sites | 2 (13)^‡ | 0 (0) |
| **Endogenous** | | |
| Intracranial hemorrhage | 4 (27) | 3 (27) |
| Aortic rupture | 2 (13) | 0 (0) |
| Pulmonary hemorrhage | 1 (7) | 1 (9) |
| **Iatrogenic** | | |
| Cardiac tamponade, cardiac injury | 2 (13) | 2 (18) |
| Retroperitoneal bleeding | 1 (7) | 1 (9) |
| **Interventional procedure** | | |
| Abdominal surgery | 1 (7)^§ | 1 (9)^§ |
| **Prophylaxis** | | |
| 0 (0) | 1 (9) |

*One case each of traumatic subarachnoid hemorrhage and chronic subdural hemorrhage.
†One case each of traumatic subarachnoid hemorrhage and chronic subdural hemorrhage.
‡One case each of traumatic subarachnoid hemorrhage, soft tissue hemorrhage, hemothorax, retroperitoneal bleeding, intra-abdominal bleeding, and traumatic aortic dissection.
§Obstructive ileus.

© 2021 The Authors. *Acute Medicine & Surgery* published by John Wiley & Sons Australia, Ltd on behalf of Japanese Association for Acute Medicine
Table 3. Summary of 26 patients

| Case | Age (sex) | OAT | Indication | PCC dose (IU) | BW (kg) | IU/kg Concurrent medication | FFP (unit) | PC (unit) | Cryo (unit) | Pre-INR | Post-INR | Elapsed time | INR next day | Hemostatic efficacy | Treatment | Outcome | ICU stay (days) |
|------|-----------|-----|------------|--------------|---------|----------------------------|------------|-----------|------------|--------|---------|--------------|-------------|-------------------|-----------|---------|---------------|
| 1    | 71 (M)    | WF  | AEDH       | 500          | 52.2    | 9.6 VK                      | —          | —         | —          | 2.01   | 1.45    | 90 min        | 1.21        | Very good         | Conservative | Survived | 1              |
| 2    | 76 (M)    | WF  | AEDH       | 500          | 64      | 7.8 VK                      | —          | —         | —          | 1.71   | 1.14    | 100 min       | 1.08        | Very good         | Conservative | Survived | 12             |
| 3    | 72 (F)    | WF  | ASDH       | 500          | 40      | 12.5 VK, FFP                | 2          | —         | —          | 4.14   | 1.59    | 35 min        | 1.28        | Questionable     | Operation | Survived | 6              |
| 4    | 67 (M)    | WF  | CSDH       | 500          | 80      | 6.3 VK                      | —          | —         | —          | 1.46   | 1.17    | 24 h          | 1.17        | Satisfactory      | Operation | Survived | 8              |
| 5    | 67 (F)    | WF  | Soft tissue hemorrhage | 500 | 52 | 9.6 & VK, FFP | — | — | — | 3.29 | 1.4 | 120 min | 2.04 | Very good | Conservative | Survived | 4              |
| 6    | 76 (M)    | WF  | Multiple hemorrhage | 500 | 60 | 8.3 VK, PC | 10 | — | — | 6.39 | 1.41 | 120 min | 1.04 | Satisfactory | IVR | Survived | 4              |
| 7    | 69 (M)    | —   | Multiple hemorrhage | 500 | 65 | 7.7 VK, FFP, PC, Cryo | 40 | 20 | 20 | 1.94 | 0.75 | 5.5 h | 1.06 | None | IVR | Died | 6              |
| 8    | 75 (M)    | WF  | ICH         | 500          | 57      | 8.8 VK                      | —          | —         | —          | 2.11   | 1.23    | 30 min        | 0.98        | Very good         | Conservative | Survived | 4              |
| 9    | 80 (F)    | WF  | Aortic rupture | 500          | 52      | 9.6 VK                      | —          | —         | —          | 1.52   | 1.15    | 15 h          | 2.05        | Questionable     | Operation | Survived | 60             |
| 10   | 84 (M)    | WF  | Aortic rupture | 500          | 58      | 8.6 VK                      | —          | —         | —          | 1.95   | 1.21    | 10 h          | 1.21        | Questionable     | Operation | Survived | 29             |
| 11   | 71 (F)    | WF  | Pulmonary hemorrhage | 500          | 57      | 8.8 VK                      | —          | —         | —          | 1.88   | 1.11    | 7 h           | 1.28        | Satisfactory      | Conservative | Died | 43             |
| 12   | 77 (F)    | WF  | Cardiac tamponade | 500 | 66 | 7.6 FFP, PC | 2 | — | — | 2.37 | 1.41 | 35 min | 1.41 | Satisfactory | Drainage | Survived | 15             |
| 13   | 70 (M)    | EL  | Cardiac tamponade | 500 | 66 | 7.6 & VK, FFP | 2 | — | — | 5.04 | 1.99 | 12 h | 1.04 | Satisfactory | Drainage | Survived | 14             |
| 14   | 84 (F)    | WF  | Retropertitoneal bleeding | 500 | 38 | 13.1 & VK, FFP, PC | 40 | 20 | 20 | 1.94 | 1.14 | 120 min | 1.35 | Satisfactory | IVR | Survived | 2              |
| 15   | 41 (F)    | WF  | Abdominal surgery | 500          | 57      | 8.8 VK                      | —          | —         | —          | 2.84   | 1.71    | 20 min        | 1.11        | Very good         | Operation | Survived | 7              |
| 16   | 87 (M)    | WF  | Soft tissue hemorrhage | 500          | 56      | 8.9 VK                      | —          | —         | —          | 0.97   | 0.87    | 18 h          | 0.87        | Very good         | IVR | Survived | 3              |
| 17   | 73 (F)    | WF  | Cardiac injury | 500          | 34      | 14.7 VK                      | —          | —         | —          | 1.41   | 1.22    | 120 min       | 1.19        | Very good         | Operation | Survived | 8              |
| 18   | 62 (F)    | WF  | CSDH        | 500          | 50      | 10 & VK                      | —          | —         | —          | 1.71   | 1.14    | 90 min        | 1.26        | Very good         | Operation | Survived | 14             |
| 19   | 56 (F)    | WF  | ICH         | 500          | 56      | 8.9 VK                      | —          | —         | —          | 1.52   | 1.19    | 20 min        | 1.51        | Very good         | Conservative | Survived | 24             |
| 20   | 77 (M)    | WF  | ASDH        | 500          | 63      | 7.9 VK                      | —          | —         | —          | 2.1    | 1.3     | 120 min       | 1.19        | Satisfactory      | Operation | Survived | 53             |
| 21   | 73 (F)    | WF  | Abdominal surgery | 500          | 40      | 12.5 VK                      | —          | —         | —          | 1.94   | 1.41    | 30 min        | 1.55        | Satisfactory      | Operation | Survived | 30             |
| 22   | 43 (M)    | WF  | Retropertitoneal bleeding | 1,000 | 66 | 7.6 FFP, PC, Cryo | 6 | 10 | 16 | 2.71 | 1.34 | 110 min | 1.41 | Satisfactory | Conservative | Survived | 3              |
| 23   | 68 (M)    | WF  | ICH         | 500          | 60      | 8.3 VK                      | —          | —         | —          | 3.14   | 1.49    | 120 min       | 1.49        | Questionable     | Operation | Died | 2              |
| 24   | 68 (M)    | WF  | Prophylaxis | 1,000        | 53      | 18.86 VK, FFP              | 2          | —         | —          | 6.98   | 1.34    | 120 min       | 1.18        | NA                | Conservative | Survived | 42             |
| 25   | 90 (M)    | WF  | Cardiac     | 500          | 44      | 11.36 VK, FFP              | 6          | —         | —          | 2.62   | 1.3     | 12 h          | 1.3         | Very good         | Drainage | Survived | 90             |
| 26   | 33 (F)    | —   | Pulmonary hemorrhage | 500 | 50 | 10 VK, FFP, PC, Cryo | 10 | 10 | 12 | 1.41 | 1.28 | 120 min | 1.31 | Questionable | Operation | Survived | 90             |

AEDH, acute epidural hemorrhage; ASDH, acute subdural hemorrhage; BW, body weight; Cryo, cryoprecipitate; CSDH, chronic subdural hemorrhage; EL, Apixaban (Eliquis); FFP, fresh frozen plasma; ICH, intracranial hemorrhage; ICU, intensive care unit; INR, international normalized ratio; IVR, interventional radiology; NA, not available; OAT, oral anticoagulation therapy; PC, platelet concentration; PCC, prothrombin complex concentrate (PPSB-HT); VK, vitamin K; WF, warfarin.
ef
cacy. We should validate ef
cacy using both laboratory
values and thromboelastogram in future studies.14

This study had several limitations. First, and most impor-
tantly, this study was retrospectively performed in a single
institution with a small number of patients, and the
findings of this study cannot be generalized. The treatment policy was
selected by individual physicians; therefore, potential biases
cannot be eliminated. The majority of patients received other
reversal agents, particularly fresh frozen plasma. Therefore, it
is difficult to conclude whether the revised two-level initia-
tion strategy itself is effective. Second, the patients examined
in this study were relatively old with a low body weight, and
these results may not be adequate for heavier patients.
Finally, the complexity of the disease varied in our study,
especially among patients with trauma-related bleeding, and
optimal target of INR was not generalized. Prospective trials
involving large numbers of patients who require urgent nor-
malization of INR are required to overcome these limitations
and clarify the remaining unsolved issues.

In conclusion, a two-level fixed dose of PCC according to
the initial INR is a potentially reasonable strategy for nor-
malizing INR in a Japanese ED. However, patients with
supratherapeutic initial INR and/or higher weight may
require a higher or supplemental dose. Additional studies
with hemostatic outcome measures are needed to further elu-
cidate the efficacy of a relatively low fixed-dose PCC regi-
men in Japan.

ACKNOWLEDGEMENTS

This study was funded in part by a grant under the
category ‘JSPS KAKENHI Grant Number 19K18349’
to K. Suzuki. We thank all colleagues in the Emergency
and Critical Center, Mie University Hospital (Drs K. Sasaki,
F. Okuno, R. Esumi, A. Ito, Y. Akama, T. Shinkai, Y. Senga,
G. Miyamura, D. Niimi, Y. Ieki, E. Kawamoto, K.
Yokoyama, T. Kaneko, and T. Takeda), Department of
Hematology and Oncology, Mie University Hospital (Dr. T.
Yamaguchi, A. Nakamura, T. Matsumoto, I. Tawara, and
N. Katayama), and Department of Internal Medicine, Yoshida
Clinic (Dr. M. Fujioka) for their assistance. We thank Joe
Barber Jr, PhD, from Edanz Group (https://en-author-service
s.edanz.com/ac) for editing a draft of this manuscript.

DISCLOSURE

Approval of the Research Protocol: This study was per-
formed in accordance with the International Conference on
Harmonization Good Clinical Practice Guidelines and the
1996 Declaration of Helsinki. The study protocol including
the administration of PCC was approved by the ethics com-
mittees of our institution (approved number H2020-189).
Informed Consent: We posted information about this study
on the hospital website and gave participants the opportunity
to opt out, and those who did not opt out were considered to
have provided tacit consent for study participation.
Registry and the Registration No. of the study/Trial: N/A.
Animal Studies: N/A.
Conflict of Interest: None declared.

REFERENCES

1 Palareti G, Leali N, Coccheri S et al. Bleeding complication of
oral anticoagulant treatment: an inception-cohort, prospective
collaborative study (ISCOAT). Italian Study on Complications of Oral Anticoagulant Therapy. Lancet. 1996; 348: 423–8.
2 Go AS, Hylek EM, Chang Y et al. Anticoagulation therapy
for stroke prevention in atrial fibrillation: how well do

Table 4. Comparison of patient characteristics and INR
changes (evaluated within 120 min)

| Characteristic* | Period A | Period B | P |
|-----------------|---------|---------|---|
| Gender, n (%)   |         |         |   |
| Male            | 3 (33)  | 3 (38)  | 0.4 |
| Female          | 6 (67)  | 5 (63)  |    |
| Age (years), median (years) | 70 (72) | 60.1 (62) | 0.25 |
| Age, years, n [%] |         |         |   |
| <60             | 1 (11)  | 3 (38)  |    |
| 60–69           | 2 (22)  | 2 (25)  |    |
| 70–79           | 5 (56)  | 3 (38)  |    |
| ≥80             | 1 (11)  |         |    |
| Body weight (kg), median (kg) | 54.6 (57) | 58 (51.5) | 0.58 |
| Body weight (kg), n (%) |        |         |   |
| <50             | 2 (22)  | 1 (13)  |    |
| 50–59           | 4 (44)  | 4 (50)  |    |
| 60–69           | 3 (33)  | 2 (25)  |    |
| ≥70             | 0 (0)   |         |    |
| PCC dose (IU/kg), median (IU/kg) | 9.46 (8.77) | 11.3 (10.0) | 0.2 |
| Baseline INR, median | 2.58 (2.37) | 2.47 (1.83) | 0.17 |
| Post-treatment INR, median | 1.39 (1.41) | 1.28 (1.28) | 0.19 |
| Achieved INR < 1.35, n (%) |         |         |   |
| Yes             | 3 (33)  | 7 (88)  | 0.049 |
| No              | 6 (67)  | 1 (13)  |    |

INR, international normalized ratio.
*All patients were Japanese.
†Excluded for protocol violation.
randomized trials translate into clinical practice? JAMA 2003; 290: 2685–92.
3 Guerrouij M, Uppal CS, Alklabi A, Douketis JD. The clinical impact of bleeding during oral anticoagulant therapy: assessment of morbidity, mortality and post-bleed anticoagulant management. J. Thomb. Thrombolysis. 2011; 31: 419–23.
4 Hanley JP. Warfarin reversal. J. Clin. Pathol. 2004; 57: 1132–9.
5 The Joint Committee on Guidelines for the Management of Stroke. Japanese Guidelines for the Management of Stroke 2015 (in Japanase). Tokyo: Kyowa Kikaku, 2015.
6 Pabinger I, Brenner B, Kalina U, Knaub S, Nagy A, Ostermann H. Prothrombin complex concentrate (Beriplex P/N) for emergency anticoagulation reversal: a prospective multinational clinical trial. J. Thromb. Haemost. 2008; 6: 622–31.
7 Hirsh J, Fuster V, Ansell J, Halperin JL. American Heart Association/American College of Cardiology Foundation guide to warfarin therapy. Circulation 2003; 107: 1692–711.
8 Executive Committee and Scientific Advisory Committee of the Federal Physicians Chamber. Prothrombin complex concentrate. Guidelines for Therapy with Blood Components and Plasma Derivatives, 2nd edn. Köln: Deutscher Ärzte-Verlag GmbH, 2002; 95–111.
9 Ansell J, Hirsh J, Poller L, Bussey H, Jacobson A, Hylek E. The pharmacology and management of the vitamin K antagonists. Chest. 2004; 126: 204S–33S.
10 Baker RI, Coughlin PB, Gallus AS, Harper PL, Salem HH, Wood EM. Warfarin reversal: consensus guidelines, on behalf of the Australasian Society of Thrombosis and Haemostasis. Med. J. Aust. 2004; 181: 492–7.
11 O’Shaughnessy DF, Atterbury C, Bolton Maggs P et al. Guidelines for the use of fresh-frozen plasma, cryoprecipitate and cryosupernatant. Br. J. Haematol. 2004; 126: 11–28.
12 Baglin TP, Keeling DM, Watson HG. Guidelines on oral anticoagulation (warfarin): third edition - 2005 update. Br. J. Haematol. 2006; 132: 277–85.
13 Murasaki K. Guidelines for management of anticoagulant and antiplatelet therapy in cardiovascular disease (JCS 2009). Nihon Rinsho. 2011; 69: 567–71.
14 Suzuki K, Iwashita Y, Enokiya T et al. Use and effectiveness of prothrombin complex concentrate in an emergency department: a review of 15 cases. Acute Med. Surg. 2015; 3: 94–100.
15 Fujioka M, Suzuki K, Fujii E, Katayama N, Ito M, Imai H. Usefulness of prothrombin complex concentrate for cardiac injury in patients receiving oral anticoagulant therapy. Acute Med. Surg. 2015; 3: 210–1.
16 Kcentra [package insert]. Kankakee, IL: CLS Behring LLC, 2018.
17 The Joint Commission. Specifications Manual for Joint Commission National Quality Measures: Version 2017B2. Oak Brook, IL: Joint Commission Resources, 2017.
18 Schwebach AA, Waybright RA, Johnson TJ. Fixed-dose four-factor prothrombin complex concentrate for vitamin K antagonist reversal: Dose one dose fit all? Pharmacotherapy 2019; 39: 599–608.
19 Leissinger CA, Blatt PM, Hoots WK, Ewenstein B. Role of prothrombin complex concentrates in reversing warfarin anticoagulation: a review of the literature. Am. J. Hematol. 2008; 83: 137–43.
20 Kuwashiro T, Yasaka M, Itabashi R et al. Effect of prothrombin complex concentrate on hematoma enlargement and clinical outcome in patients with anticoagulant-associated intracerebral hemorrhage. Cerebrovasc. Dis. 2011; 31: 170–6.
21 Fuh L, Goldstein JN, Hayes BD. Initiation of a fixed-dose four-factor prothrombin complex concentrate protocol. J. Thromb. Thrombolysis. 2020; 50: 217–20.
22 Kim C, Cottingham L, Eberwein K, Komyathy K, Ratliff PD. Comparison of hemostatic outcomes in patient receiving fixed-dose vs. weight-based 4-factor prothrombin complex concentrate. J. Emerg. Med. 2020; 59: 25–32.
23 Bioni MT, Rumbarger RL, Absher RK, Curran LM. Prospective evaluation of a fixed-dose 4-factor prothrombin complex concentrate protocol for urgent vitamin K antagonist reversal. J. Emerg. Med. 2020; 58: 324–9.

© 2021 The Authors. *Acute Medicine & Surgery* published by John Wiley & Sons Australia, Ltd on behalf of Japanese Association for Acute Medicine