Prothrombin Complex Concentrates for Urgent Anticoagulation Reversal in Patients with Intracranial Haemorrhage

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Key Words

Intracranial haemorrhage • Oral anticoagulants • Prothrombin complex concentrates

Abstract

Background: Intracranial haemorrhage (ICH) is a serious and potentially fatal complication of oral anticoagulant therapy (OAT). Prothrombin complex concentrates (PCCs) produce a rapid and effective reversal of OAT effects, but little evidence exists on their efficacy and safety in the management of ICH in patients on OAT. **Aim:** To evaluate the efficacy and safety of PCCs for the rapid reversal of OAT in patients with ICH. **Methods:** Patients suffering from acute ICH while receiving OAT were eligible for this prospective cohort study if their international normalized ratio (INR) was ≥ 2.0 . Stratified 35–50 IU kg⁻¹ PCC doses were infused based on initial INR. **Results:** A total of 92 patients (50 males; mean age 74 years, range 34–92 years) were included. The median INR at presentation was 3.3 (range 2–9). At 30 min after PCC administration the median INR was 1.4 (range 0.9–3.1), declining to ≤ 1.5 in 75% of patients. The benefit of PCC was maintained for a long time, since in 98% of all post-infusion time points through 96 h the median INR remained ≤ 1.5 (median 1.19; range 0.9–2.3). During hospitalization neither thrombotic

complications nor significant adverse events were observed and 11 patients died (11.9%). None of the deaths was judged to be related to PCC administration. **Conclusions:** PCC administration is an effective, rapid and safe treatment for the urgent reversal of OAT in patients with ICH. Broader use of PCC in this clinical setting appears to be appropriate.

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Introduction

Oral anticoagulant therapy (OAT) is an effective and commonly used treatment for long-term primary and secondary prophylaxis of arterial (including atrial fibrillation, mechanical heart valves) and venous thrombosis (such as deep vein thrombosis and pulmonary embolism) [1]. Despite meticulous surveillance of the treatment by regular international normalized ratio (INR) monitoring, bleeding events are frequent, and intracranial haemorrhage (ICH) remains the most serious and potentially fatal complication of OAT [2–6]. ICHs account for about 20–30% of the major bleeding complications reported in large-scale epidemiological studies involving patients receiving OAT, in which the annual incidence of fatal or life-threatening bleeding complications was reported be-

tween 1 and 3% [2, 7]. Moreover, in patients with OAT-associated ICH, mortality is very high, ranging from 50 to 60% [8, 9].

Timely and complete reversal of OAT is required in patients suffering from ICH in whom immediate replacement of functional coagulation factors is indicated. Fresh frozen plasma (FFP) is a possible option, even if the time to prepare and infuse it could be associated with a clinically important delay of effective administration. Moreover, the effect may be inadequate especially in patients with exceedingly high INR values [10], and volume overload is a frequent complication observed following rapid transfusion of large volumes of FFP [10, 11].

Prothrombin complex concentrate (PCC) is human plasma-derived and contains vitamin K-dependent coagulation factors II, IX, X and VII (the latter not in preparations licensed in Italy) in a concentrated form and in a well-standardized amount. PCCs produce a rapid and adequate action and substantially shorten the time needed to reverse OAT effects [12–15]. Moreover, these products are virally inactivated and can be administered very rapidly without the need for matching the blood group or thawing the product [16]. In addition, a number of studies enrolling small numbers of patients have suggested that PCCs are able to correct more quickly and completely warfarin-related coagulopathy than FFP [10, 11, 17–19] and to reduce the risk of haematoma growth [20]. For these considerations, several clinical guidelines recommend that PCC infusion should be administered instead of FFP for urgent reversal of anticoagulation in patients with life-threatening bleeding [1, 21–23]. However, there are currently no clinical studies that have adequately assessed the efficacy and safety of PCCs in a sufficiently large group of patients with the most threatening complication of OAT, that is, ICH.

The aim of this prospective, multicenter cohort study was therefore to evaluate the efficacy and safety of PCC infusion for rapid reversal of OAT and bleeding control in patients with acute ICH.

Patients and Methods

Study Population

Patients admitted to 10 Italian centers with objectively diagnosed (computed tomography or nuclear magnetic resonance scan) acute symptomatic ICH during OAT and with an INR ≥ 2.0 were eligible for inclusion. Other inclusion criteria were age ≥ 18 years and the obtainment of written informed consent. If a candidate was unable to sign informed consent, consent could be obtained from a legal representative or a family member of the pa-

tient. Exclusion criteria were concomitant acute ischemic cardiovascular disorder, disseminated intravascular coagulation, sepsis, pregnancy, breast feeding and mental retardation. Patients were recruited 24 h a day and 7 days a week.

Treatment

All included patients received 35–50 IU kg⁻¹ body weight of Protromplex (Baxter, Milan, Italy). Protromplex is a biochemically well-balanced PCC derived from plasma prepared using pasteurization and nanofiltration and contains the following coagulation factors: factor II (35.5 IU/ml), factor IX (31.8 IU/ml) and factor X (28.6 IU/ml). Protromplex is manufactured from plasma which is subjected to a robust safety program including plasma/donor selection, extended virus screening, non-returning donor rejection, >3 months inventory hold, look-back and IQ-PCR testing for all plasma pools (HIV, HBV, HCV). Protromplex undergoes a virus inactivation process through a 2-step steam treatment (10 h at 60°C plus 1 h at 80°C) and several virus-partitioning steps [24].

PCCs were administered within 6 h from ICH diagnosis at different doses depending on baseline INR levels: 35–39 IU kg⁻¹, 40–45 IU kg⁻¹ or 46–50 IU kg⁻¹ body weight doses were infused to patients with baseline INRs of 2.0–3.9, 4.0–6.0 or >6.0 , respectively. Prior to PCC infusion, all patients were also treated with intravenous infusion of 10 mg of vitamin K. Concomitant therapy with whole blood, plasma or plasma fraction was not allowed within the first 30 min after PCC infusion, unless urgently required as judged by the attending clinician. Conversely, an additional infusion of PCCs was allowed at intervals of 6 h after the administration of the first dose, depending on the INR level reached.

Study Outcomes

The primary end-point of the study was the rate of INR values of ≤ 1.5 after 30 min from the infusion of PCCs; prespecified secondary end-points included the rate of INR levels ≤ 1.5 at 6, 24, 48, 72 and 96 h after infusion. Clinical end-points included mortality, ICH recurrences, thromboembolic complications, viral infections, adverse events, need for neurosurgical drainage of the haematoma and time to resumption of OAT. The occurrence of clinical end-points was monitored throughout hospital stay and within 90 days of follow-up. The adjudication of the end-points was done locally.

Laboratory and Clinical Assessment

Blood samples were collected for determination of INR prior to infusion and at intervals of 0.5, 6, 24, 48, 72 and 96 h afterward. Prothrombin time, activated partial thromboplastin time, fibrinogen, haemoglobin, platelet count and D-dimer were determined at baseline and after 0.5, 6 and 24 h. The INR and the haematology parameters were measured at the local laboratories of the study centres. At enrolment, all patients underwent a complete clinical assessment that included medical history, physical examination and determination of vital signs. The occurrence of any adverse events (including death, thromboembolic complications, ICH recurrences and allergic reactions) was monitored after 7, 30 and 90 days, as well as the need for urgent neurosurgery. Viral exposure was evaluated at baseline and 7, 30 and 90 days after infusion of PCCs. In all patients, the eventual resumption of OAT during follow-up was registered.

Sample Size and Statistical Analysis

All statistical analyses were performed with the use of SPSS software version 11.0. Continuous variables such as INR values were analysed using ANOVA test for repeated measurements with the Dunnett multicomparison test. The 95% confidence intervals (CI) were also calculated for categorical variables expressed as percentages. All statistical tests were two-sided and $p < 0.05$ was considered statistically significant. For sample size calculation, the following considerations were performed. The primary efficacy end-point of this prospective cohort study was considered the percentage of patients achieving an INR value <1.5 after at least 30 min following the PCC infusion. We hypothesized that at least 90% of OAT patients treated with PCC could achieve an INR value <1.5 six hours after the infusion of PCC. Therefore, with a sample size population of at least 90 patients, a percentage of 90% of 'successes' has a 95% CI of 83–96%. Thus, with a success rate of 90% and a sample size of at least 90 subjects we could be confident that PCC infusion could achieve a percentage of successes above 80%.

The study was performed in accordance with the International Conference on Harmonization Good Clinical Practice guidelines and the 1996 Declaration of Helsinki. Moreover, the study protocol was approved by the local ethic committees of the participating centres.

Results

Between October 2005 and December 2007, 92 patients were enrolled; 52 patients were admitted in emergency departments, 23 in neurosurgical departments, 12 in internal medicine departments and 5 in stroke units. One patient was excluded from the analysis of the results because he was treated before the INR was available and his pre-treatment baseline INR turned out to be 1.7. Baseline characteristics of the patients are reported in table 1 and indications for OAT use are summarized in table 2.

ICH was spontaneous in 52 patients (56%) and post-traumatic in the remaining 40 patients (44%). 74 patients (80%) presented with intracerebral haemorrhage, 12 (13%) with subdural haemorrhage and 6 (7%) with subarachnoidal haemorrhage. 42 patients (45%) underwent urgent craniotomy for evacuation of the haemorrhage.

According to the baseline INR levels (table 1), a single PCC dose of 35–39, 40–45 and 46–50 IU kg⁻¹ body weight was infused in 73, 13 and 6 patients, respectively [24, 25]. The mean rate of PCC administration was 2,386 IU per patient (SD 728 IU, range 500–4,000 IU), over a mean infusion time of 30 min (SD 0.7 min, range 15–60 min). All patients received concomitant vitamin K (10 mg intravenously); 1 patient also received FFP as part of his anticoagulation reversal.

The median INR at presentation was 3.3 (range 2–9). At 30 min after PCC administration the median INR was

Fig. 1. INR values before and after PCC infusion.

Table 1. Demographic and clinical baseline patient data

	Descriptive statistics
Mean age, years	74 (34–92)
Sex, males/females	50/42
Body weight, kg	70.3 ± 18.5
INR	
2–3.9	73 (79%)
4–6	13 (14%)
>6	6 (7%)
Oral anticoagulant	
Warfarin	72 (78%)
Acenocumarol	20 (22%)

Table 2. Indications for OAT use

	Patients
Atrial fibrillation	50 (54%)
Mechanical heart valves	22 (24%)
Venous thromboembolism	18 (16%)
Severe cardiomyopathy	2 (6%)

significantly reduced to 1.4 (range 0.9–3.1; $p < 0.0001$), declining to ≤ 1.5 in 75% of patients. Only 5 patients (5.4%) with an INR exceeding 2.0 after first administration of PCC received a second infusion of the concentrates.

The benefit of PCC was maintained for a long time, since in 98% of all post-infusion time points through 96 h the median INR remained ≤ 1.5 (median 1.19, range 0.9–2.3; fig. 1). In detail, the median INR values at pre-treatment, 30 min, 6, 24, 48, 72 and 96 h after treatment were 3.3, 1.4, 1.2, 1.2, 1.2, 1.2 and 1.1, respectively.

During hospitalization only one patient suffered from non-fatal ICH recurrence, while neither thrombotic complications nor significant adverse events were observed. No case of excessive perioperative bleeding in patients undergoing surgery occurred and in none of them a re-intervention was necessary.

After discharge, 5 patients (5.4%, 95% CI 0.8–10%) suffered from thromboembolic complications. One 56-year-old man died because of the occurrence of an ischaemic stroke 37 days after PCC infusion; he had restarted anticoagulant treatment 5 days after ICH. The patient was at increased risk of thrombosis because of the concomitant presence of a prosthetic mechanical mitral valve and atrial fibrillation. One 79-year-old female was hospitalized for an acute myocardial infarction 47 days after PCC infusion, while taking antiplatelet drugs; her history included arterial embolism and severe cardiomyopathy. Three patients suddenly developed symptoms suggestive for acute deep vein thrombosis of the lower limbs, at 70, 85 and 87 days after PCC therapy; their history included previous deep vein thrombosis (2 patients) and pulmonary embolism (1 patient). In all of them, OAT had not been resumed and a prophylactic dose of low-molecular-weight heparin had been started. Color duplex sonography revealed acute thrombosis of the right popliteal vein (2 patients) and of the left femoro-popliteal vein (1 patient). Overall, 18 patients (19%, 95% CI 11–27%) died, 11 patients during hospitalization and 7 after discharge. None of the deaths was judged to be related to PCC administration. Of note, during the study period, OAT therapy was not resumed in 15 patients, since it was judged to be either unnecessary or associated with an excessive risk of recurrence of bleeding.

In no patients was there evidence of viral transmission or other adverse events at the end of follow-up. No patient had a diagnosis of fluid overload associated with the reversal process.

Discussion

Bleeding is the most frequent complication of OAT [1], but only few studies have focused on treatment options available for the acute reversal of anticoagulation in case of ICH. To our knowledge, this is the largest study that has specifically evaluated the efficacy and safety of PCCs for the management of ICH in OAT patients. The results of our study suggest that PCC infusion produces an effective and long-lasting reversal of OAT by rapidly nor-

malizing INR levels in nearly all cases. In our cohort of patients, we neither observed thrombotic complications nor significant adverse events in the immediate post-infusion period; no case of excessive perioperative bleeding in patients undergoing surgery occurred. The long-term safety of our management strategy was also supported by the low rate of adverse events at 3-month follow-up.

Our experience compares favourably with previously published series describing the use of PCCs for urgent reversal of warfarin in patients with major bleedings, including ICH [25–30]. Lankiewicz et al. [29] retrospectively investigated the feasibility, efficacy and safety of administering PCCs to urgently reverse the anticoagulant effect of warfarin in 58 patients enrolled in a single center; 36 of them (62%) presented with ICH. PCC doses were determined according to baseline INR levels, ranging between 25 and 50 IU kg⁻¹. PCC administration was very effective, since immediately after infusion 76% of the patients had INR levels <1.5 and 96.5% had INR levels <2.0. Pabinger et al. [30] prospectively evaluated whether balanced PCCs allow INR normalization (defined as INR levels of ≤1.3) in 43 anticoagulated patients requiring either an emergency surgical or urgent invasive diagnostic intervention or suffering from an acute major bleeding. The study demonstrated that PCC treatment was an effective rapid hemorrhage control resource in the emergency anticoagulant reversal setting, since 30 min after treatment infusion the INR levels declined to ≤1.3 in 93% of the treated patients. Yasaka et al. [17] enrolled 42 anticoagulated patients admitted to an emergency department for major haemorrhagic complications, 35 of whom involved the central nervous system; this trial showed the efficacy of PCCs to rapidly normalize the INR values in almost all cases. Finally, Vigù et al. [31] investigated efficacy and safety of PCC for ultra-rapid INR normalization in 18 anticoagulated patients with ICH requiring urgent surgery. This study demonstrated that a bolus infusion of PCC (1 min) was able to completely reverse anticoagulation within 3 min in all patients. Other studies have also demonstrated the utility of PCC infusion for rapid and complete reversal of anticoagulation [10, 13, 14].

In our study, the overall mortality during hospitalization and within 90 days of follow-up was 19%; this figure is much lower than that shown in historical series in untreated patients, in whom the reported mortality rate was about 50–60% [8, 9]. Of interest, the mortality rate observed in our trial was similar to that shown in a small study of anticoagulated patients treated with PCC for an

acute ICH, in which 22% of the cases died within 6 months of follow-up [31].

In our study, we have used a 3-factor PCC, which contains only factors II, IX and X in approximately equal quantities, with no detectable factor VII activity; currently, in Italy only 3-factor PCCs are available. Moreover, administration of PCCs with significant factor VII content does not seem to be essential, or any more effective, than PCCs with low (or absent) factor VII activity to reverse warfarin-induced bleeding complications [32]; however, until now no head-to-head PCC comparative studies have been conducted to explore this issue.

Even if PCCs are actually considered the optimal therapeutic option for the acute reversal of OAT in patients with ICH [21, 22], there is a paucity of studies comparing their efficacy with other available haemostatic interventions, such as FFP and recombinant activated factor VII (rVIIa). In the studies that compared PCCs with FFP, PCCs showed a substantially more rapid and stable effect than FFP [10, 11, 18, 20]. rVIIa has shown promising results in this setting [33–35], but no randomized clinical trials have yet compared its efficacy and safety against PCCs or FFP. In a sustained anticoagulation animal model designed to simulate standard long-term oral coumarin therapy in patients, PCC was shown to be more effective than rVIIa in restoring haemostatic function [36]. Moreover, in an experimental study using *in vivo* rat and *in vitro* human models of anticoagulation, both PCC and rVIIa were associated with a reversal of prothrombin time, but only PCC restored overall thrombin generation [37]. The very short half-life of rVIIa can be a serious drawback for the treatment of bleeding in anticoagulated patients, with the risk of exposing the patients to a potentially dangerous time window of persistent anticoagulant effect [16].

The results of our trial add important information on the use of PCCs for the urgent reversal of warfarin in patients with ICH. Firstly, our population was quite homogeneous when compared to those enrolled in other similar trials. In fact, we have included only patients requiring reversal of warfarin because of an acute ICH, while all other published trials have recruited anticoagulated patients requiring urgent reversal for surgical or invasive diagnostic interventions [30] or INR normalization because of acute bleeding in different sites [29, 30, 36]. Second, in most previous studies the INR values were followed for a short time, usually not exceeding 24 h after infusion [29, 36]. In our study we evaluated the long-term time course of change in INR, showing that the benefit of

PCCs was maintained for a long time; in fact, in 98% of all post-infusion time points through 96 h, median INR remained ≤ 1.5 . Finally, we have data about the rate of re-introduction of anticoagulant therapy; in our study at the end of the follow-up (90 days after ICH), 59 patients had restarted anticoagulant treatment without recurrent bleeding.

Other clinical observations also support the efficacy of this approach. In fact, in the group undergoing surgery we observed neither perioperative excessive bleeding complications nor the need for re-intervention. Moreover, in our series the overall mortality was 19.6%, a rate which is lower than that reported in other previous studies [3, 29].

A potential complication of PCC administration is the occurrence of venous and arterial thromboembolism [12, 13, 29, 30]. In our series, no case of thrombosis occurred during the initial hospitalization, while we observed five late thromboembolic events during the follow-up period. Given the broad time frame between PCC administration and the occurrence of thrombotic events, it is unlikely that all observed events can be related to the use of PCCs. Finally, no case of viral transmission was registered at the end of the follow-up.

This study has some limitations. First, we did not include a control group. The use of an untreated control group was obviously not ethical; moreover, since several European clinical guidelines recommend PPC infusion as the treatment of choice for the urgent reversal of anticoagulation in patients with life-threatening bleeding [21, 22], a comparison with other haemostatic agents (such as FFP or rVIIa) was unfeasible. Second, because of the relatively small sample size, the patients included in this study may not be representative of the overall population and, therefore, definitive conclusions cannot be drawn from these data. However, this is, to our knowledge, the largest study ever published on emergency anticoagulation reversal in patients with ICH; moreover, the practical difficulties associated with obtaining suitable patients in this clinical setting make our results, albeit limited, of interest. Finally, the clinical significance of our findings could be considered questionable, since the primary end-point of the study was based on a surrogate marker of efficacy, that is reduction of INR levels [38]. However, the association between INR levels and the risk of bleeding complications is well established.

In conclusion, PCC administration is an effective, rapid and safe treatment for the urgent reversal of OAT in patients with ICH; unfortunately, this important resource

still seems to be underused in daily clinical practice for the treatment of this potentially life-threatening complication [4, 5, 37]. A broader use of PCCs in this clinical setting should be encouraged.

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