

Emergency reversal of anticoagulation with a three-factor prothrombin complex concentrate in patients with intracranial haemorrhage

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Background. Intracranial haemorrhage is a serious and potentially fatal complication of oral anticoagulant therapy. Prothrombin complex concentrates can substantially shorten the time needed to reverse the effects of oral anticoagulants. The aim of this study was to determine the efficacy and safety of a prothrombin complex concentrate for rapid reversal of oral anticoagulant therapy in patients with intracranial haemorrhage.

Methods. Patients receiving oral anticoagulant therapy and suffering from acute intracranial haemorrhage were eligible for this prospective cohort study if their International Normalised Ratio (INR) was higher than or equal to 2.0. The prothrombin complex concentrate was infused at doses of 35-50 IU/kg, stratified according to the initial INR.

Results. Forty-six patients (25 males; mean age: 75 years; range 38-92 years) were enrolled. The median INR at presentation was 3.5 (range, 2-9). At 30 minutes after administration of the prothrombin complex concentrate, the median INR was 1.3 (range, 0.9-3), and the INR then declined to less than or equal to 1.5 in 75% of patients. The benefit of the prothrombin complex concentrate was maintained for a long time, since the median INR remained lower than or equal to 1.5 (median, 1.16; range, 0.9-2.2) at 96% of all post-infusion time-points up to 96 hours. No thrombotic complications or significant adverse events were observed during hospitalisation; six patients (13%) died, but none of these deaths was judged to be related to administration of the prothrombin complex concentrate.

Conclusions. Prothrombin complex concentrates are an effective, rapid and safe treatment for the urgent reversal of oral anticoagulation in patients with intracranial haemorrhage. Broader use of prothrombin complex concentrates in this clinical setting appears to be appropriate.

Keywords: intracranial haemorrhage, oral anticoagulants, prothrombin complex concentrates.

Introduction

Oral anticoagulant therapy (OAT) is an effective and commonly used treatment for long-term primary and secondary prophylaxis of arterial thrombosis (e.g. for patients with atrial fibrillation or mechanical heart valves) and venous thrombosis (e.g. for patients with deep vein thrombosis or pulmonary embolism)¹.

Despite meticulous surveillance of the treatment by regular monitoring of the International Normalised Ratio (INR), bleeding is frequent in patients receiving OAT, and intracranial haemorrhage remains the most serious and potentially fatal complication of such therapy²⁻⁶. Intracranial haemorrhages account for about 20-30% of the major bleeding complications

reported in large scale epidemiological studies involving patients receiving OAT, in whom the annual incidence of fatal or life-threatening bleeding complications was reported to be between 1 and 3%^{2,7}. Moreover, the mortality rate in patients with OAT-associated intracranial haemorrhage is very high, ranging from 50 to 60%^{8,9}.

Patients on OAT who suffer from intracranial haemorrhage require timely and complete reversal of anticoagulation and immediate replacement of functional coagulation factors is, therefore, indicated. Fresh-frozen plasma (FFP) is a possible option, even if the time to prepare and infuse it can cause clinically relevant delays. Moreover, the effect may be inadequate, especially in patients with exceedingly high INR values¹⁰ and volume overload is a frequent complication observed following rapid transfusion of large volumes of FFP^{10,11}.

All the prothrombin complex concentrates (PCCs) are derived from human plasma and contain the vitamin K-dependent coagulation factors II, IX and X (with or without variable amounts of factor VII) in a concentrated form and in well-standardised amounts. PCCs produce a rapid and adequate action and substantially shorten the time needed to reverse the effects of OAT¹²⁻¹⁵. Moreover, these products are virally inactivated and they can be administered very rapidly without the need for either blood group matching or thawing¹⁶. In addition, a number of studies enrolling small numbers of patients have suggested that PCC are able to correct warfarin-related coagulopathy more quickly and completely than FFP can^{10,11,17-19} and to reduce the risk of expansion of haematoma²⁰. For these reasons, several clinical guidelines recommend that PPCs should be infused instead of FFP for urgent reversal of anticoagulation in patients with life-threatening bleeding^{1,21-23}.

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

Material and methods

Study population

Patients admitted to eight Italian centres with objectively diagnosed (by computed tomography scan or nuclear magnetic resonance imaging) acute

symptomatic intracranial haemorrhage during OAT and with an index INR ≥ 2.0 were eligible for inclusion. Other inclusion criteria were age ≥ 18 years and written informed consent. If a candidate was unable to sign informed consent, then the consent could be obtained from a legal representative or a family member of the patient. Exclusion criteria were a concomitant acute ischaemic cardiovascular disorder, disseminated intravascular coagulation, sepsis, pregnancy, breast feeding and mental retardation. Patients were recruited at any time of the day or night, 7 days a week.

Treatment

All included patients received 35 to 50 IU/kg body weight of Uman Complex DI 500 IU/20 mL (Kedrion S.p.A., Castelveccchio Pascoli, Italy). Uman Complex DI 500 IU/20 mL is a human PCC and nominally contains the following amounts of human coagulation factors: factor II (25 IU/mL), factor IX (25 IU/mL) and factor X (20 IU/mL). The product also contains the coagulation inhibitor protein C and its cofactor protein S (approximately 9 IU/mL). Uman Complex DI is manufactured by two ion-exchange chromatography steps with no albumin added as a stabiliser. The safety of the plasma used for manufacturing Uman Complex DI is ensured by a robust safety programme that includes two validated viral inactivation methods: solvent-detergent treatment (TnBP-TWEEN 80 to 25 °C-26 °C for not less than 8 hours) of the non-lyophilised preparation plus dry heat treatment (99.5 °C \pm 1 °C for 30 minutes) of the final lyophilised product.

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

Study outcomes

The primary end-point of the study was the percentage of INR values ≤ 1.5 at 30 minutes after the PCC infusion: pre-specified secondary end-points included the percentages of INR levels ≤ 1.5 at 6, 24, 48, 72 and 96 hours after infusion.

Clinical end-points included mortality, recurrence of intracranial haemorrhage, 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 the hospital stay and for 90 days of follow-up. End-points were adjudicated locally.

Laboratory and clinical assessments

Blood samples were collected for determination of INR prior to the infusion and at 0.5, 6, 24, 48, 72 and 96 hours afterwards. Prothrombin time, activated partial thromboplastin time, fibrinogen, haemoglobin, D-dimer concentrations and platelet count were determined at baseline and after 0.5, 6 and 24 hours. The INR and the haematological parameters were measured at the study centres' local laboratories.

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, recurrent intracranial haemorrhage and allergic reactions) and the need for urgent neurosurgery was monitored after 7, 30 and 90 days. Viral exposure was evaluated at baseline and 7, 30 and 90 days after infusion of PCC. The eventual resumption of OAT during follow-up was registered for all patients.

Sample size and statistical analysis

All statistical analyses were performed with SPSS software version 11.0. Continuous variables such as INR values were analysed using the ANOVA test for repeated measurements with Dunnett's multicomparison test. The 95% confidence intervals (95% CI) were also calculated for categorical variables expressed as percentages. All statistical tests were two-sided and p values < 0.05 were considered statistically significant. The following considerations were made when calculating the sample size. The primary efficacy end-point of this prospective cohort study was the

percentage of patients achieving an INR value ≤ 1.5 at least 30 min after the PCC infusion. We hypothesised that at least 90% of patients on OAT treated with PCC could achieve an INR ≤ 1.5 by 6 hours after the infusion of PCC. Therefore, with a sample of at least 90 patients, the 95% CI of a "success rate" of 90% is 83%-96% and with a hypothesised success rate of 90% in at least 90 subjects we could be confident that the PCC infusion would be successful in more than 80% of the study sample.

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

Results

Between October 2005 and September 2007, 46 patients were enrolled; 26 patients were admitted in emergency departments, 6 in neurosurgical departments, 12 in internal medicine departments and 2 in stroke units. The baseline characteristics of the patients are reported in Table I and the indications for OAT use are summarised in Table II.

Table I - The patients' baseline demographic and clinical data.

| Characteristics | Descriptive statistics |
|----------------------------|------------------------|
| Mean age (range), years | 75 (38-92) |
| Sex, males/females, n. | 25/21 |
| Body weight (kg), mean SD | 72.5 (19.1) |
| INR n. (%) | |
| 2-3.9 | 37 (79) |
| 4-6 | 6 (14) |
| >6 | 3 (7) |
| Oral anticoagulant, n. (%) | |
| Warfarin | 37 (80) |
| Acenocoumarol | 9 (20) |

Table II - Indications for OAT use.

| Indication | Number of patients (%) |
|-------------------------|------------------------|
| Atrial fibrillation | 26 (56) |
| Mechanical heart valves | 10 (22) |
| Venous thromboembolism | 9 (19) |
| Severe cardiomyopathy | 1 (3) |

Intracranial haemorrhage was spontaneous in 25 patients (54%) and post-traumatic in the remaining 21 patients (46%). Thirty-two patients (70%) presented with intracerebral haemorrhage, 9 (19%) with subdural haemorrhage and 5 (11%) with subarachnoid haemorrhage. Twenty-two patients (52%) underwent urgent craniotomy for evacuation of the haemorrhage.

According to the baseline INR levels (Table I), a single PCC dose of 35-39, 40-45 or 46-50 IU/kg body weight was infused to 37, 6 and 3 patients, respectively²⁵⁻²⁷. The mean dose of PCC was 2,412 IU per patient (SD: ± 732 UI) (range, 500-4,000 IU) over a mean infusion period of 30 minutes (SD=0.8) (range, 15-60 minutes). All patients received concomitant vitamin K (10 mg intravenously).

The median INR at presentation was 3.5 (range, 2-9). At 30 minutes after PCC administration the median INR was significantly reduced to 1.3 (range, 0.9-3) ($p < 0.0001$), and declined to ≤ 1.5 in 75% of the patients. In detail, the percentages of patients with an INR ≤ 1.5 by 30 minutes after the PCC infusion were 89% in the group with a baseline INR of 2.0-3.9, 33% in the group with a baseline INR of 4-6, and 0% in the group with a baseline INR > 6 . Only two patients (4.3%), with an INR exceeding 2.0 after the first administration of PCC, received a second infusion of the concentrate.

The benefit of PCC was maintained for a long time, since the median INR remained ≤ 1.5 (median, 1.18; range, 0.9-2.3) in 96% of all time-points up to 96 hours post-infusion (Figure 1). In detail, the median INR values at pre-treatment, 30 minutes and 6, 24, 48, 72 and 96 hours post-treatment were 3.5, 1.3, 1.2, 1.1, 1.1 and 1.0, respectively.

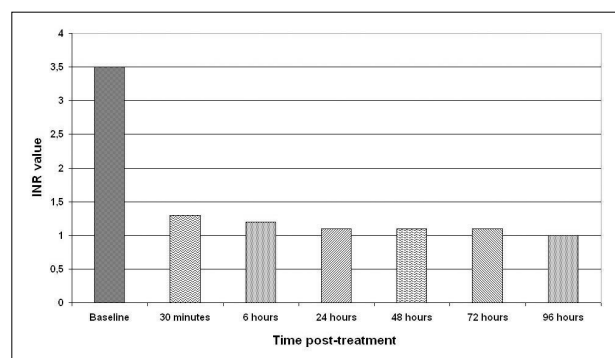


Figure 1 - INR values before and after PCC infusion.

No thrombotic complications or significant adverse events were observed during hospitalisation; only one patient suffered from a non-fatal recurrence of intracranial haemorrhage with an INR at the time of the recurrence of 1.4. There were no cases of excessive peri-operative bleeding in patients undergoing surgery and none of the operated patients required a repeated intervention.

After discharge, two patients (4.3%; 95% CI, 0.9-9%) suffered from thromboembolic complications. One 56-year old man died from an ischaemic stroke that occurred 37 days after PCC infusion; he had restarted anticoagulant treatment 5 days after the intracranial haemorrhage. 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 admitted to hospital because of an acute myocardial infarction 47 days after PCC infusion, while taking antiplatelet drugs; her history included arterial embolism and severe cardiomyopathy.

Overall, nine patients (20%; 95% CI, 12-26%) died: six patients died during their stay in hospital and three died after discharge. The causes of the death were as follows: heart failure (3 cases), pneumonia (2 cases), renal failure (1 case), sepsis (1 case), ischaemic stroke (1 case) and cancer (1 case). None of the deaths was judged to be related to the PCC administration.

Of note, during the study period OAT was not resumed in eight patients, since it was judged to be either unnecessary or associated with an excessive risk of recurrent bleeding.

At the end of the follow-up there was no evidence of viral transmission or other adverse events in any of the patients. No patients had a diagnosis of fluid overload associated with the process of reversing anticoagulation.

Discussion

Bleeding is the most frequent complication of OAT¹, but only a few studies have focused on treatment options available for the acute reversal of anticoagulation in the case of intracranial haemorrhage. The results of our study suggest that PCC infusion produces effective and long-lasting reversal of OAT by rapidly normalising the INR in nearly all cases. In our cohort of patients, we did not observe either thrombotic complications or significant

adverse events in the immediate post-infusion period and there were no cases of excessive peri-operative bleeding in patients undergoing surgery. The long-term safety of our management strategy was also supported by the low rate of adverse events at a 3-month follow-up.

Our experience compares favourably with previously published series describing the use of PCC for urgent reversal of the effects of warfarin in patients with major bleeding, including intracranial haemorrhages²⁴⁻³⁰. Lankiewicz *et al.*³⁰ retrospectively investigated the feasibility, efficacy and safety of administering PCC to urgently reverse the anticoagulant effect of warfarin in 58 patients enrolled in a single centre; 36 of these patients (62%) presented with intracranial haemorrhage. The doses of PCC were determined according to baseline INR levels and ranged between 25 and 50 IU/kg. The administration of PCC was very effective, since immediately after the infusion 76% of the patients had INR levels lower than 1.5 and 96.5% had INR levels lower than 2.0. Pabinger *et al.*³¹ prospectively evaluated whether balanced PCC allow INR normalisation (defined as INR ≤ 1.3) in 43 anticoagulated patients requiring either emergency surgery or an urgent invasive diagnostic intervention or who were suffering from acute major bleeding. The study demonstrated that PCC treatment was an effective and rapid resource for controlling haemorrhage in the setting of emergency reversal of anticoagulation, since 30 minutes after infusion of the PCC the INR decreased to ≤ 1.3 in 93% of the treated patients. Yasaka *et al.* enrolled 42 anticoagulated patients admitted to an emergency department for major haemorrhagic complications, which involved the central nervous system in 35 cases¹⁷; their trial showed the efficacy of PCC with regards to rapid normalisation of the INR in almost all cases. Finally, Vigu   *et al.* investigated the efficacy and safety of PCC for ultra-rapid INR normalisation in 18 anticoagulated patients with intracranial haemorrhage requiring urgent surgery: it was demonstrated that a bolus infusion of PCC (administered over 1 minute) was able to completely reverse anticoagulation within 3 minutes in all the patients³². Other studies have also demonstrated the utility of PCC infusion for rapid and complete reversal of anticoagulation^{10,13,14,27,28}.

In our study the overall mortality during

hospitalisation and within the first 90 days of follow-up was 20%; this figure is much lower than that in historical series in untreated patients, in whom the reported mortality rate was about 50-60%^{8,9}. Of interest, the mortality rate in our trial was similar to that in a small study of anticoagulated patients treated with PCC for acute intracranial haemorrhage, in which 22% of the cases died within 6 months of follow-up³².

In our study we used a "three-factor" PCC containing only factors II, IX and X in approximately equal quantities, with no detectable factor VII activity. The administration of a PCC with significant factor VII content does not seem to be essential or any more effective than PCC with low (or no) factor VII activity to reverse warfarin-induced bleeding complications, although PCC with a significant factor VII content may be more efficient in correcting remarkably increased INR³³. It is, therefore, possible that the good results obtained in our study with a PCC not containing factor VII may have been favoured by the relatively low baseline INR levels of our patients. No head-to-head comparative PCC studies have been conducted so far to explore this issue.

Although PCC are currently considered the optimal therapeutic option for acute reversal of OAT in patients with intracranial haemorrhage^{21,22}, there is a paucity of studies comparing the efficacy of these products with that of other available haemostatic interventions, such as FFP and recombinant activated factor VII (rVIIa). In the studies that have compared PCC with FFP, the PCC had a substantially faster and more stable effect than that of FFP^{10,11,18,20}. rVIIa has shown promising results in this setting³⁴⁻³⁶, but no randomised clinical trials have yet compared its efficacy and safety against PCC or FFP. In an animal model of sustained anticoagulation designed to simulate standard long-term oral coumarin therapy in patients, PCC was shown to be more effective than rVIIa in restoring haemostatic function³⁷. Moreover, in *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 generation³⁸. The very short half-life of rVIIa can be a serious drawback to the treatment of bleeding in anticoagulated patients, with the risk of exposing patients to a potentially dangerous time window of a persistent anticoagulant effect¹⁶.

The results of our trial add important information

on the use of PCC for the urgent reversal of warfarin in patients with intracranial haemorrhage. First, our population was quite homogenous when compared to those enrolled in other similar trials. In fact, we included only patients requiring reversal of warfarin because of an acute intracranial haemorrhage, while all the other published trials recruited patients requiring urgent reversal of anticoagulation for surgical or invasive diagnostic interventions³² or normalisation of the INR because of acute bleeding in different sites^{31,32,38}. Second, in most previous studies the INR values were recorded for a short period, usually not exceeding 24 hours after the PCC infusion^{31,38}. In our study we evaluated the long-term course of changes in INR, showing that the benefit of the PCC was maintained for a long time; in fact, the median INR remained ≤ 1.5 in 96% of all the checks up to 96 hours post-infusion. Finally, we collected data about the rate of reintroduction of anticoagulant therapy. In our study at the end the follow-up (90 days after intracranial haemorrhage) 38 patients had restarted anticoagulant treatment without recurrent bleeding; in detail, the median time after which anticoagulation was restarted was 15 days (range, 4-48 days).

Other clinical observations also support the efficacy of PCC: excessive perioperative bleeding complications did not occur in the group of patients undergoing surgery and none needed a repeated intervention.

A potential complication of the administration of PCC is venous and/or arterial thromboembolism^{12,13,30,31}. In our series, no cases of thrombosis occurred during the initial hospitalisation, while two late thromboembolic events were recorded during the follow-up period. Given the long period between PCC administration and the occurrence of the thrombotic events, it is unlikely that all the observed events can be related to the use of PCC. Finally, no cases of viral transmission had occurred by the end of the follow-up.

Our study does have 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 PCC 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 have been representative of the overall population and, therefore, definitive conclusions cannot be drawn from our data. Nevertheless, the practical difficulties associated with obtaining suitable patients in this clinical setting make our results of interest, despite these limitations. 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, which was reduction of INR levels³⁸. However, the association between INR levels and the risk of bleeding complications is well established.

In conclusion, administration of a PCC is an effective, rapid and safe treatment for the urgent reversal of OAT in patients with intracranial haemorrhage³⁹; unfortunately, this important resource seems to be still underused in daily clinical practice for the treatment of this potentially life-threatening complication^{4,5,40}. A broader use of PCC in this clinical setting should be encouraged.

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