Real world usage of PCC to "rapidly" correct warfarin induced coagulopathy

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Background. Life threatening bleeding and emergency procedures in patients on vitamin K antagonists are indications for urgent reversal with prothrombin complex concentrate and vitamin K. Rapid reversal in these situations is emphasized in the literature and guidelines, but only very limited information is available on its real life use, especially on the timing of treatment in relation to presentation.

Materials and methods. We retrospectively audited emergency warfarin reversal in 131 consecutive patients. We studied the indication, use of vitamin K, time between presentation and administration of vitamin K and PCC, effectiveness in INR reduction and clinical outcome.

Results. The median PCC dose was 26.8 IU/kg. The median INR was reduced from 3.1 to 1.2. Vitamin K (5 mg) was given in 91.6% of evaluable patients. We found significant delays in administration of PCC and vitamin K. The median time between presentation and administration of vitamin K/PCC was 3.6 and 5.2 hours respectively. The times in intracranial haemorrhage were 2.7 and 3.0 hours and in emergency procedures 17.4 and 15.9 hours respectively. Mortality related to bleeding was 7.6% overall but in patients with intracranial haemorrhage 22.8%. The thrombotic rate within 7 days of reversal was 1.5%.

Discussion. The local protocol for reversal with PCC and vitamin K was adhered to well but the delay in pre-procedural patients, suggests that intravenous vitamin K alone may be sufficient in many cases and PCC administration can be avoided by better planning. Intracranial haemorrhage in warfarinised patients carries a high mortality. Treatment delays should be avoided by making PCC stocks available within emergency departments, simple dosing structures independent of INR and administering PCC without waiting for INR and CT scan results in those with strong suspicion of intracranial haemorrhage and clear trauma. Future reports and studies should always include the time from presentation to PCC treatment.

Keywords: prothrombin complex concentrate, vitamin K antagonist, reversal, warfarin, haemorrhage.

Introduction

Increasing age and emphasis on stroke prevention has led to an increasing use of vitamin K antagonists (VKA) in developed countries. A longitudinal population-based study from Finland showed an increase in the number of patients taking warfarin from 0.68% in 1993 to 2.28% in 2008[1].The main concern with the use of VKA, however, is haemorrhage. A recent meta-analysis of 23,518 patients on warfarin for different indications showed an annual risk of major bleeding of 0.6-3.3%. The incidence of intracranial haemorrhage (ICH) in patients on VKA therapy for currently accepted indications was 0.17%-0.45% and carried a mortality rate of 44%[2]. Of the extracranial bleeds, 4% were fatal[2]. Furthermore, the case fatality of ICH for patients on warfarin is approximately twice of that for patients with ICH not on warfarin[1,3,4] and warfarin was an independent predictor for 2 and 28 day mortality[1].

Patients on VKA treatment have reduced levels of functional coagulation factors II, VII, IX and X. In case of life or limb-threatening bleeding or prior to urgent invasive procedures, rapid and complete reversal of VKA anticoagulation is essential. Accepted methods to reverse VKA include vitamin K, prothrombin complex concentrate (PCC) and fresh frozen plasma (FFP). Vitamin K given intravenously significantly corrects the INR after 6- 8 hours of administration[5] but if more rapid reversal is required it should be given together with PCC or FFP. The preferred option for rapid VKA reversal is PCC as FFP administration is time consuming and usually only partially corrects the INR unless given in impractically large volumes. FFP has a risk

of fluid overload, is blood group specific, has a risk of anaphylactoid reactions and transfusion related lung injury and in most cases is not virally inactivated. PCC in contrast contains factors II, IX, X and a variable amount of factor VII in a small volume, is virally inactivated, not group specific and corrects VKA induced coagulopathy within 10 minutes of administration. Overall, PCC containing FVII (four factor concentrate) is favoured over PCC containing little or no FVII (three factor concentrate) as the latter produce poor correction of the INR but this is subject of continuing debate[6]. In the UK Beriplex® (CSL Behring, Haywards Heath, United Kingdom) and Octaplex® (Octapharma Limited, Manchester, United Kingdom), both four factor concentrates, are licensed for the emergency reversal of warfarin and the British Committee on Standards in Haematology (BCSH) recommends their use in combination with 5mg intravenous vitamin K over FFP[7]. Methods for elective and emergency reversal of warfarin were recently reviewed[8].

The BCSH guidelines also recommend that patients on warfarin who have a strong suspicion of intracranial bleeding after a clear head injury should have immediate warfarin reversal before computed tomography (CT) and INR results are available. The rationale for this is to prevent further haematoma expansion even though the dynamics of expansion in warfarinised patients remain unclear[9] and there is only very limited evidence for the impact on mortality. A recent retrospective study however showed that reversal of INR was associated with a significant reduction in mortality in patients with ICH but not in other patient groups with major haemorrhage[10]. Given the need for rapid reversal of the VKA induced coagulopathy and the availability of an effective agent to achieve this, it is surprising that very little information on the day to day use of PCC is available in the literature. This is particularly true on information on the timely administration of PCC in a routine clinical setting outside controlled studies. Safaoui *et al.* recently reported on its use in patients with intracranial haemorrhage and described delays in PCC administration[11]. Barillari *et al.* described the use of a three factor PCC in 47 patients in a routine clinical setting in Italy[12]. Guidelines were not always followed and only a quarter of all patients received vitamin K. The timing of PCC administration was not specifically discussed but it was acknowledged that there may have been a delay in some patients in receiving PCC due to variable uptake of reversal protocols on different hospital wards[12]. Another study reporting on real life experience with PCC showed its efficacy in reducing the INR in 1152 Portuguese patients but little other information on its use was reported[13]. Bobbitt *et al.* reported on the routine experience in New Zealand and Australia but focused on the potential thrombotic risk associated with PCC[14].

Given the lack of data on the timely use of PCC in the routine clinical setting, but it's clinical importance, we audited the use of Beriplex® in our institution over a one year period with respect not only to the indication for reversal, dose, efficacy in terms of INR reduction and the concurrent use of vitamin K but specifically also studied the time lapse between presentation, the time to booking of an INR sample into the laboratory and the time to administration of vitamin K and PCC.

Materials and methods

The study was registered as an audit as required locally to assess compliance with BCSH guidelines and the effectiveness of the management of these patients.

This was a single centre, retrospective, observational audit between November 2010 and November 2011. Our local protocol suggests Beriplex® at a dose of 30 units/kg (maximum dose 3,000 units) to be given intravenously over 5-10 minutes in combination with 5mg intravenous vitamin K (Konakion MM®, Roche, Welwyn Garden City, United Kingdom). Haematology advice is often obtained but is not required prior to its administration.

We studied the indication for warfarin reversal with PCC, the concomitant use of vitamin K, the time lapse between presentation and the administration of vitamin K and PCC, the effectiveness of PCC to reverse the INR and clinical outcome including thrombotic rate and mortality during hospital stay. The thrombotic rate was assessed by electronic checks for re-admissions and investigations for thromboembolic disease for the 60 days after initial presentation. PCC is stored in blood bank and records including dose and indication for its use are kept on all patients. Patients were therefore identified through blood bank records and additional information was obtained through examination of the medical notes and drug prescription charts to obtain information on the time lapse between presentation and vitamin K/PCC administration. The presentation time was the time logged electronically when a patient presented to the A&E department or the time was documented in the medical notes when a patient was first seen with complaints leading to warfarin reversal on the ward. The time of receipt of a sample in the laboratory is logged in the laboratory results system and this was used to calculate the time between presentation and INR analysis. This system was also used to calculate the time lapse for INR measurements after PCC administration. During this period 131 consecutive patients requiring emergency reversal of warfarin anticoagulation were identified and included in the audit. Full case note review was possible in 107 out of 131 cases (82%). On the remaining patients only partial information from accident and emergency department notes, blood bank records and the laboratory results system were available.

Results

Baseline characteristics

There were more male (79 patients, mean age 69.5 years, range 26-90 years) than female patients (52 patients, mean age 73.8 years, range 47-97 years). All patients were on warfarin, none were on other VKA. One received Octaplex® whilst all others received Beriplex®. PCC was administered in 62 cases (47.3%) in the accident and emergency department, in 37 cases (28.2%) on medical wards, in 27 (20.6%) cases on surgical wards and in 5 cases (3.8%) on high dependency or intensive care wards. INR measurements before PCC was given were available in 128/131 (97.7%) patients with a median INR of 3.1 (range 1.5-20). The majority had an INR below 5 (103/128 [80.5%]), 25/128 (19.5%) had an INR greater than 5 of which 13 (10.2%) had an INR greater than 8.

Vitamin K and PCC administration

Whether vitamin was given or not could only be assessed through review of the full notes and prescription charts. These were available in 108 patients. Of those 99 (91.6%) received vitamin K at a median dose of 5mg.

The median PCC dose given was 2,000 units overall (131 patients) equivalent to a median of 26.8 units/kg for those in whom there was a recorded weight (81 patients). The indications for warfarin are summarised in Table I and reversal indications in Table II. Of the 35 intracranial bleeds, 2 were extradural, 11 subdural, 2 subarachnoid, 2 intraventricular and 18 intraparenchymal.

Table I - Indications for warfarin at presentation.

Indication for warfarin	Number of patients (%)
Atrial fibrillation	57/131 (43.5%)
Venous Thromboembolism	32/131 (24.4%)
Prosthetic heart valve	22/131 (16.8%)
Ischemic stroke	2/131 (1.5%)
Cardiomyopathy	1/131 (0.8%)
Thromboprophylaxis	1/131 (0.8%)
Unknown	16/131 (12.2%)

Table II - Indications for PCC administration. ICH: intracranial haemorrhage.

Indication for PCC	Number of patients (%)
Emergency surgery	39/131 (29.8%)
GI haemorrhage	36/131 (27.5%)
ICH	35/131 (26.7%)
Large haematoma*	9/131 (6.9%)
Pulmonary haemorrhage	5/131 (3.8%)
Aortic rupture/dissection	4/131 (3%)
Other	3/131 (2.3%)

Legend *Includes large muscle and other soft tissue bleeds and intra-abdominal/pelvic bleeds.

Time to vitamin K and PCC administration

The time intervals between presentation, arrival of the INR sample in the laboratory, administration of vitamin K and administration of PCC are summarised in Table III. The calculation of these intervals is dependent on the clinician recording the time of presentation (for patients on the ward) and administration of vitamin K and PCC. As these were not always available the calculations were made on the subgroup of patients for which these were available. The numbers of patients in each group are given in Table III. For all patient groups requiring reversal taken together, there was a median time interval of 2 hours before an INR sample was received in the laboratory, a further 1.6 hours before vitamin K was administered and finally an interval of 1.6 hours between vitamin K administration and administration of PCC. These intervals were shorter for patients presenting with ICH (median time interval from presentation to INR sample being received in the laboratory 1.3 hours, a further 1.4 hours to vitamin K administration and 0.3 hours to administer PCC) but considerably longer in patients requiring emergency surgery (median time to INR sample booking into the laboratory from presentation 3.1 hours, time to PCC administration after the sample was booked into the laboratory of 12.8 hours whereas vitamin K was given 1.5 hours after PCC administration). In gastrointestinal (GI) haemorrhage the median time for booking into the laboratory was 1.6 hours, vitamin K was given 1.9 hours after this and PCC was administered 3.8 hours after vitamin K administration.

Outcome (effect of PCC on INR, mortality and thrombotic events)

The INR after PCC administration was available in 112/131 patients and checked at a median of 3.4 hours after its administration. The INR was less than 1.5 in 96/112 (85.7%) patients, 1.5-2.0 in 14/112 (12.5%) and greater than 2.0 in 2/112 (1.8%). The median INR overall was 1.2 after PCC administration and was the same in the 25 patients with an initial INR greater than 5 and in the subgroup of 13 patients with an INR greater than 8. Of the patients that did not reach an INR of less than 1.5, 6 had no or insufficient vitamin K (and had INR measurements 12-15 hours after PCC administration), 5 had lower doses of PCC than recommended (15-17 units/kg) and the remainder had other reasons for continuing coagulopathy including liver disease and severe sepsis) whilst on 2 patients no information was available.

The overall mortality was 25.2% (33/131) and mortality related to haemorrhage was 7.6% (10/131). Of the 10 patients that died related to haemorrhage, 9 did so within 24 hours of admission. The cause of death was ICH in 8, inferior vena cava rupture in 1 and a ruptured

Table III - Time intervals between presentation, time for INR sample received in the laboratory, time to vitamin K administration and time to PCC administration.

	All patients		ICH		GI haemorrhage		Emergency procedures	
	Median time (mean)	Number of patients	Median time (mean)	Number of patients	Median time (mean)	Number of patients	Median time (mean)	Number of patients
Presentation to INR	2 hours (4 hours)	88	1.3 hours (1.9 hours)	25	1.6 hours (3.8 hours)	26	3.1 hours (5.7 hours)	23
Presentation to vitamin K	3.6 hours (8.9 hours)	82	2.7 hours (3.0 hours)	24	3.5 hours (7.1 hours)	22	17.4 hours (22 hours)	18
Presentation to PCC	5.2 hours (11.5 hours)	85	3.0 hours (3.9 hours)	24	7.3 hours (11.8 hours)	28	15.9 hours (20.6 hours)	21

aortic aneurysm in 1.Within the deaths related to ICH 2 had subdural haemorrhage, 4 had a parenchymal bleed, 1 a subarachnoid haemorrhage and 1 an intraventricular bleed. The median INR in these patients was 2.7 prior to reversal. There were no deaths due to thromboembolic events but three patients had a pulmonary embolus (PE, day 4, 13 and 60 after PCC administration), one had a deep vein thrombosis (DVT, day 21 after PCC administration) and one had an ischemic stroke (6 hours after PCC administration). The overall thrombotic rate was 3.8% within 60 days and 1.5% for events within the first week after reversal.

Discussion

In this paper we describe the routine use of PCC for emergency reversal of VKA in a large tertiary hospital setting over a 1 year period. Nearly half of all PCC was used in the emergency department and doses were in line with our local policy. Vitamin K was given in over 90% of evaluable patients. PCC was effective in reducing the INR to a median of 1.2 and below 1.5 in 85.7% of patients. This was independent of the pre-treatment INR and in keeping with previously published prospective studies using four factor concentrates[15,16]. Of the 16 patients who did not achieve a post-treatment INR of less than 1.5, the majority had insufficient or no vitamin K or lower doses of PCC than recommended. Overall, however, the local protocol for administration of PCC and vitamin K was adhered to well.

The main findings of our study, however, relate to the indications for warfarin reversal and the timing of PCC administration in relation to hospital admission. Overall there was a delay of two hours between presentation and INR sample arrival in the laboratory, a further 1.6 hours until vitamin K was given and a final 1.6 hours between vitamin K and PCC administration. Emergency procedures were the indication for reversal in 29.8% of patients (excluding neurosurgery for intracranial haemorrhage). In this group there was a delay of 17.1 hours between presentation, the decision for surgery being made and the administration of PCC whilst vitamin K in these patients was given simultaneously with PCC. Our results in this group therefore suggest that in the majority of patients, vitamin K given intravenously at presentation would likely have been sufficient in correcting the INR and that PCC administration may have been avoided by better pre-operative planning. Even though there are many studies available in the literature describing the use of PCC to enable procedures other than neurosurgery, there are to our knowledge no studies available that report on the time between presentation and PCC administration in this setting. The routine appropriate use therefore in this setting is unknown.

The BCSH guidelines suggest that PCC should be used in surgery that cannot be delayed for 6-12 hours[7] whereas in others vitamin K alone may be sufficient. The rationale for this recommendation is the uncertainty about the thrombogenic potential of PCC as well as the cost. A recent meta-analysis of 27 studies which included 1,032 patients found an overall thrombotic rate of 1.4%, all of which occurred within 4 days of PCC administration[17]. However, it remains unclear if this was a reflection of the underlying thrombotic tendency for which anticoagulation was given or if the PCC carried an additional risk. We found five thromboembolic events (3.8%), two of which occurred within 7 days after PCC administration (1.5%). One patient, on warfarin for atrial fibrillation, suffered an ischemic stroke within 6 hours of PCC administration for GI haemorrhage with an INR of 10.3 and haemodynamic instability and the other, on warfarin for venous thrombosis, developed a PE whilst on prophylactic low molecular weight heparin 4 days after reversal of warfarin prior to a procedure. The other patients developed thrombotic events on days 13, 21 and 60 respectively. One was on LMWH prophylaxis whilst warfarin was restarted (INR 1.9), whereas the others were not on anticoagulation. These later events were more likely to represent the underlying thrombotic tendency. The overall thrombotic complications identified were in keeping with the literature.

In patients presenting with major haemorrhage, including those requiring neurosurgery for ICH, vitamin K was given earlier but there was still a delay of 2.7 hours in

ICH and 3.5 hours in GI haemorrhage. PCC was given at approximately the same time as vitamin K (3.0 hours) in ICH but there was an additional delay of 3.8 hours in GI haemorrhage after the decision was taken to reverse warfarin (i.e. vitamin K administration). It is therefore likely that PCC administration may also have been avoided in some patients with GI haemorrhage. There are two studies available in the literature reporting on the time to treatment in patients with ICH. The time to treatment in our cohort of patients with ICH was similar to a retrospective study of 28 patients by Safaoui e*t al.* who reported a median time to treatment of 2.8 hours[11] and shorter than in a recent study by Dowlatshahi *et al*. The latter was an observational prospective multicentre study and reported a median time to treatment of 6.3 hours in 141 patients[18]. The overall mortality rate reported by Safaoui *et al.* was 35% and by Dowlatshahi *et al.* was 36.8% overall. In the Dowlatshahi study 42.3% of patients with intraparenchymal bleeds died. The mortality in our cohort of patients was relatively low (22.8%) and similar to mortality rates in patients with ICH not on VKA. The likely explanation is that we had less extensive bleeds than other studies as the mortality in all groups (including intraparenchymal bleeds) was similar. It is, however, interesting that the mortality in our study as well as in the studies by Safaoui and Dowlatshahi (all of which reported a relatively quick time to start of treatment) is lower than others where mortality rates of up to 67% are described and no information on treatment modalities and times are given[19,20]. The high mortality of ICH in patients on VKA compared to those not on anticoagulant treatment, is thought to be related to higher volumes of the initial haemorrhage, a higher risk of re-bleeding with subsequent expansion which may be delayed[3,19,21]. One study also found an independent association between time to neurological imaging and risk of expansion[19]. Given that time to treatment may be crucial in preventing expansion, particularly in patients who have small/moderate volume haematomas and limited neurological deficit, treatment should be instituted as soon as possible. It remains unproven that treatment influences mortality, although a recent retrospective analysis of health records showed a significant reduction in 30 day mortality in patients with ICH in whom the INR was corrected to less than 1.5 compared to those in whom it was not from 26.4 to 10.6%[10]. Others have suggested that INR correction and treatment with PCC are associated with a reduced risk of haematoma expansion[22,23]. All this emphasises the need for prompt treatment.

Finally, the time needed to obtain INR and CT scan results can cause significant delays. In the study by Dowlatshahi, the time to imaging resulted in significant delay in treatment[18].The BCSH guidelines suggest that treatment may be initiated in case of strong suspicion of intracranial bleeding after a clear head injury before CT and INR results are available[7]. In our institution CT scanning can be obtained in approximately 40 minutes and there was a delay of 1.3 hours before a sample for INR measurement arrived in the laboratory. The routine practice at the time of our audit was to wait for these results before administering treatment. To institute administration of PCC before availability of INR and CT scan results it is necessary to use a dosing regimen that is independent of INR. We used Beriplex® 30 units/kg with a maximum of 3,000 units, previously shown to normalise a median pre-treatment INR of greater than 20 and normalise thrombin generation[24]. The summary of product characteristics suggest a maximum infusion rate of 3 IU/kg/min which equates to an infusion time of approximately 10 minutes for a 70 kg adult. In practice we administered Beriplex® over 5-10 minutes. Similar infusion times have been described without safety concerns elsewhere[25,26].

In summary, in this paper we describe the real world usage of PCC to reverse warfarin induced coagulopathy in emergency situations. The data are limited by the single centre, retrospective nature of the study and incomplete data retrieval. The latter is representative of any study relying on data from clinicians not participating in a controlled study. Also, we only had a small number of patients in the individual subgroups. However, we have shown that there is potentially a significant group of patients (undergoing urgent surgery) in whom the use of PCC may have been avoided by better planning and prompt administration of vitamin K whilst in others there are significant delays in administering the PCC. We believe this is typical of the real world usage of PCC to "rapidly" reverse VKA associated coagulopathy and emphasizes the need for the development of local protocols and education of clinicians, in particular those working at emergency and surgical departments. In order to reduce delays there should be stocks of PCC in accident and emergency departments. Delays in obtaining an INR may be avoided by the availability of point of care INR testing. Although haematology advice should always be available, it should not be mandatory as it often adds additional delay. In clear life threatening bleeding, treatment may be given before INR results are available and should be facilitated by a simple single dosing schedule. In case of a strong suspicion of intracranial bleeding and a history of trauma, treatment should be started without waiting for CT scan results. Finally, to gain a better insight into the daily use of PCC and its effect, future studies should report the time from presentation to treatment.

Conflicts of interest disclosure

Michael Makris has received consultancy fees from CSL Behring and attended board meetings of CSL Behring.

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