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Research Article

An Analysis of Outcomes after Administration of Four Factor Prothrombin Complex Concentrate for Urgent Reversal of Anticoagulation in Patients with Intracranial Hemorrhage

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ABSTRACT

Introduction: Four factor prothrombin complex concentrate (PCC4) and vitamin K are used for urgent reversal of coagulopathy in patients with intracranial hemorrhage while on vitamin K antagonists (VKA) and factor Xa inhibitors. Evaluation in a 'real world' population has not been performed.

Material and methods: Retrospective review of 110 patients with hemorrhagic stroke (n=75) or traumatic ICH (n= 35) at a comprehensive stroke and trauma center, from 9/2013 and 12/2016. PCC4 was used to reverse coagulopathy in VKA-related ICH in 75 patients and for factor Xa inhibitors in 35 patients.

Results: Between patient groups taking VKA and factor Xa inhibitors, there was no difference in Glasgow Coma Scale (GCS), or Marshall and Rotterdam CT scores. No differences were noted between VKA and factor Xa inhibitor-related ICH in median size of ICH on initial (p=0.69) or repeat (p=0.35) imaging. No difference was noted in ICH size progression (p=0.99). Rates of thromboembolic complications were noted in 13.3% of patients taking VKAs, higher than that reported in the literature. This relative hypercoagulable response was not noted in patients taking factor Xa inhibitors, as 0% suffered a thromboembolic event.

Conclusion: Despite arrest of ICH progression in most patients, the high rate of thromboembolic events in the VKA population suggests the risk of adverse events in a "real world" population is not insignificant and must be considered with respect to the clinical picture. Further studies are necessary to determine which patients are ideally suited to undergo repletion with PCC4 using expanded criteria.

Keywords: PCC4; Intracranial haemorrhage; Traumatic brain injury; Anticoagulation

Abbreviations: American College of Surgeons (ACS); Four factor Prothrombin Complex Concentrate (PCC4); Fresh Frozen Plasma (FFP); International Normalized Ratio (INR); Intracranial Hemorrhage (ICH); Joint Commission on Accreditation of Healthcare Organizations (JCHAO); Prothrombin Complex Concentrate (PCC); Skilled Nursing Facility (SNF); Vitamin K Antagonist (VKA)

INTRODUCTION

As the US population ages, more patients are being placed on therapeutic anticoagulation for a variety of indications [1]. This aging population has an increased propensity for both hemorrhagic strokes and falls, resulting in traumatic intracranial hemorrhage (ICH) [2-4]. Rates of major ICH in the setting of vitamin K antagonist (VKA) therapy range from 1.7-3.4% [5]. Studies have shown that VKA administration is associated with an increased risk of hematoma expansion and worse outcomes in the setting of ICH necessitating prompt reversal of anticoagulation to prevent progression of bleeding. Further, earlier time to reversal of international normalized ratio (INR) in VKA-associated ICH has been found to improve patient outcomes in both traumatic and spontaneous ICH [6-8]. Consequently, need has arisen for expeditious and full reversal of anticoagulation in patient with ICH.

Historically, reversal of anticoagulation required administration

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of both Vitamin K and fresh frozen plasma (FFP). An alternative treatment was found in prothrombin complex concentrate (PCC). When a four factor PCC was used to reverse VKA coagulopathy, observational studies showed improvement in time to reversal of INR when compared to FFP and vitamin K [9,10]. Two landmark phase III trials were conducted for comparison of FFP and PCC4 for "rapid" reversal of VKA-related coagulopathy. These trials demonstrated that PCC4 reversed an elevated INR much faster than FFP and overall outcomes were non-inferior to FFP [11,12]. The safety profile of PCC4 versus FFP was also similar with a 30 day mortality of around 6% and related thromboembolic events of around 4% [12]. Unfortunately, the study population in both of these landmark studies excluded many of the patients commonly seen in emergency clinical practice [11,12]. In 2012, the American College of Chest Physicians endorsed PCC over FFP for urgent reversal of VKA coagulopathy [13]. In 2016, a similar recommendation was made jointly by the Neurocritical Care Society and the Society of Critical Care Medicine [14].

In recent years, factor Xa inhibitors have begun to replace VKA for patients requiring anticoagulation. As FFP is not effective in reversing coagulopathy from factor Xa inhibitors, PCC4 has been increasingly used in an attempt to urgently reverse coagulopathy from these anticoagulants [15]. However, studies have shown varied results in its ability to reverse coagulopathy from factor Xa inhibitors [16-18]. Critical care guidelines have promulgated usage of PCC for coagulopathy in patients using factor Xa inhibitors despite a paucity of high-quality evidence to support this use or an understanding of the full impact on these patients [19]. While AndexXa (Portola Pharmaceuticals, San Francisco, CA, USA) was recently approved by the FDA for targeted reversal of factor Xa inhibitors, it is limited by availability and cost, with minimal information available regarding the outcomes of patients receiving this treatment [20].

In our busy Joint Commission on Accreditation of Healthcare Organizations (JCHAO) Comprehensive Stroke and American College of Surgeons (ACS) Level I Trauma Center, the institutional urgent anticoagulation reversal guideline recommends PCC4/Vitamin K for reversal of VKA-related ICH. It recommends use of high dose (50 units/kg) of PCC4 as an option for urgent reversal in patients with an ICH who are anticoagulated with a factor Xa inhibitor. This "high dose" was recommended based on preclinical animal trials [16,21]. This observational study was conducted to analyze outcomes after the expanded use of PCC4 in ICH patients for reversal of both VKA-related and factor Xa inhibitor-related coagulopathy.

MATERIALS AND METHODS

The study was completed at a single center that is both an ACS-verified level 1 trauma center and JCHAO comprehensive stroke center. IRB approval was obtained prior to initiation of this study and informed consent was waived given the retrospective nature. All adult patients admitted with an ICH while on the VKA warfarin or the factor Xa inhibitors rivaroxaban and apixaban and who received PCC4 between 9/1/2013 and 12/31/2016 was identified. Dosing of PCC4 was based on the INR for patients taking warfarin with 25 units/kg given for INR 2<4, 35 units/kg given for INR 4-6, and 50 units/kg for INR>6. INR was assessed at time of admission and within six hours after PCC4 administration. Coagulopathy from rivaroxaban and apixaban were reversed with 50 units/kg of PCC4. Only individuals with incomplete documentation or a known active thrombotic comorbidity at time of admission were excluded from the analysis. Charts were analyzed for basic demographic information.

The primary endpoint was change in size of the ICH between the first and second CT scan in patients that did not have an intervening cranial drainage procedure (i.e. craniotomy or craniectomy). Repeat CT scans were typically completed at 8 hours after initial imaging, though some were as delayed as long as 12 hours given the clinical situation. The volumes (cm^3) were calculated based on CT measurements. Spherical hemorrhages were measured as ((A × B × C)/2) and abnormal shaped hemorrhages were measured as (A × B × C)/3) [21]. These measurements and volume calculations were performed by two senior general surgery residents who were blinded to the anticoagulant regimen. In addition to gross size change, a 35% change from initial imaging was used for secondary assessment of hemostasis for ICH. The secondary endpoints included: reduction of INR, mortality, length of stay (LOS), discharge status and symptomatic newly diagnosed thromboembolic events. Patients were only imaged for thromboembolic events if they were symptomatic. All patients initially had chemical venous-thromboembolism prophylaxis withheld due to active hemorrhage on arrival and it was restarted in 48 hours if the CT scan was deemed to be stable. Mechanical prophylaxis in the form of lower extremity pneumatic compression boots were applied after initial evaluation.

Parametric comparisons of continuous variables across anticoagulants used a linear regression model. Nonparametric comparisons used the Wilcoxon test. Comparisons of categorical variables across anticoagulants used a chi square test. The parametric tests of percent change of size being significantly different from zero within anticoagulant used a one-sample t-test. The nonparametric test of percent change used the Wilcoxon signed rank test. Logistic regression was used to test the interaction between operative intervention and class of anticoagulant for mortality. The alpha level of 0.05 without adjustment for multiplicity was used to denote statistical significance. SAS® 9.4 was used for statistical analysis.

RESULTS

This study included 110 total patients. Basic demographic data is summarized in Table 1. Seventy-five patients (68.2%) suffered hemorrhagic strokes and thirty-five patients (31.8%) had a traumatic intracranial injury. 34.5% of patients in the study required an emergent intracranial operation. There was no difference in the population subgroups of trauma versus spontaneous ICH with respect to GCS, Marshall, or Rotterdam CT scores.

52 patients received two CT scans without interval drainage between the scans. Stratified by anticoagulant, there was no difference in the median size of the ICH on initial and repeat imaging. Additionally, there was no statistically significant median percent change for ICH size (Table 2). There was no difference between groups of patients with hemorrhage size changing by 20%. A non-parametric comparison of the distribution of percent changes between 1st and 2nd scans demonstrated that there was very little change in the warfarin and rivaroxaban hemorrhages after the administration of PCC4 in patients who did not have an interval

Table 1: Basic demographic information stratified by anticoagulation type.

Anticoagulant	Age	GCS	Marshall (Max=6)	Rotterdam (Max=6)	% Trauma	% Operation
Warfarin (75)	75	11.1	4.0	3.4	32.0	36.0
Rivaroxaban (21)	77	11.1	3.6	2.6	23.8	33.3
Apixaban (14)	78	12.2	4.3	3.1	42.9	28.6
p-value	0.41	0.81	0.71	0.19	0.49	0.86

GCS-Glasgow Coma Score

Table 2: Initial and repeat intracranial hemorrhage size in patients without an interval drainage procedure.

Anticoagulant	Median size (cm^3) (Q1-Q3)	Median repeat size (cm^3) (Q1-Q3)	Median % change (cm^3) (Q1-Q3)
Warfarin (33)	1.5 (0.6, 19.1)	1.7 (0.6, 18.1)	6.7 (-7.1, 44.8) (p=0.15)
Rivaroxaban (11)	4.2 (0.7, 14.0)	7.8 (0.7, 14.0)	-1.5 (-5.2, 33.3) (p=0.92)
Apixaban (8)	5.2 (0.9, 42.5)	10.3 (2.7, 54.7)	10.7 (-8.0, 916.1) (p=0.30)
p-value	0.88	0.48	0.71

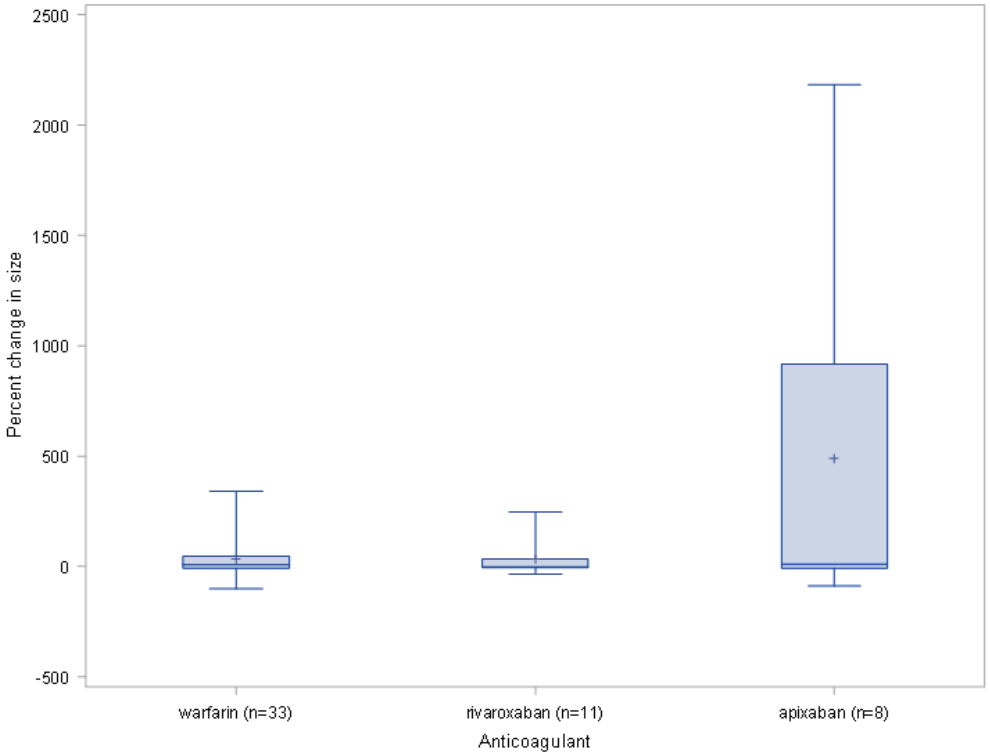

Figure 1: Distribution of percent change in ICH size between 1st and 2nd CT scans in patients that did not have an interval neurosurgical procedure (p=0.67).

neurosurgical procedure. While the apixaban group hemorrhages appeared to increase despite PCC4, the distribution was quite wide and the change was not statistically significant (Figure 1). 80.8% of all groups remained stable after PCC4 administration (p=0.67) (Table 3).

In the VKA group, the mean INR was found to decrease from 4.3 to 1.3 within four to six hours of administration. Although INR is not validated to assess chemical level of anticoagulation in factor Xa inhibitors, the mean INR of patients on factor Xa inhibitors was 1.6 on initial presentation and was not rechecked.

Approximately half of all patients died during their hospital stay, typically within three days of admission (Table 4). One third of the combined population required a drainage procedure which was not statistically associated with increased mortality (p=0.5). However, when comparing anticoagulant groups, requiring a procedure

Table 3: Subjective change in ICH size between first and second CT scans using a 35% change as clinically meaningful.

Anticoagulant	Decreased	Stable	Increased
Warfarin (33)	9.1%	60.6%	30.3%
Rivaroxaban (11)	9.1%	72.7%	18.2%
Apixaban (8)	0%	62.5%	37.5%

Table 4: Discharge disposition and median time to mortality stratified by anticoagulant. Overall discharge disposition p=0.99.

Anticoagulant	Home %	Rehab %	SNF %	Death %	Median time to mortality (days)
Warfarin (75)	13.3	14.7	22.7	49.3	2 (n=37)
Rivaroxaban (21)	19.1	14.3	19.1	47.6	5 (n=2.5)
Apixaban (14)	14.3	21.4	21.4	42.9	3.5 (n=6)

on admission was not associated with increased mortality in the VKA group (p=0.53) but was with the factor Xa inhibitors group (p=0.03) (Table 5). The majority of patients who survived required additional nursing care at the time of discharge. There was no significant difference in discharge disposition among the anticoagulant groups (Table 4).

Newly diagnosed symptomatic thromboembolic events were noted in 13.3% of the patients with VKA-related ICH (10/75). Six of the ten events were lower extremity deep vein thrombosis. Other events included three strokes and one mesenteric thromboembolus. Four of the events developed within hours of receiving PCC4 and two of the events resulted in death. There was no association with the presenting INR or subsequent PCC4 dose and the development of a thromboembolic event (p=0.34). There were no symptomatic thromboembolic events identified in the factor Xa inhibitor-related ICHs treated with PCC4 (Table 6).

DISCUSSION

Two landmark studies have evaluated both the safety and efficacy of administering PCC4 for urgent reversal of coagulopathy from VKAs [11,12]. However, inclusion and exclusion criteria for these studies were stringent. More than 80% of patients on VKAs in this study would have been excluded from enrollment in these phase III trials suggesting that PCC4 being used in a "real world" population that has never been studied.

In this population, as shown previously, PCC4 was effective at reversing an elevated INR in the VKA population. The primary endpoint was radiographic progression of the ICH between the first and second CT scan in patients that did not have an intervening cranial operation. In Sarode's phase III study, hemorrhage control was dichotomized to "effective" or "noneffective" based on the requirement of additional hemostatic products. ICH volume analysis was only used to exclude patients. Specifically, they excluded hemorrhages greater than 30 cm^3, subdural hemorrhages greater than 10 mm and midline shift greater than 5 mm [12]. This study included all ICH, regardless of size, and more closely evaluated progression of hemorrhage by radiographic measurement. Not surprisingly, larger hemorrhages were more likely to require an interval drainage procedure. The median ICH sizes at the time of presentation and on repeat imaging after PCC4 was administered were not significantly different (Table 2). This was likely related to the large size variability at both imaging points, particularly with the factor Xa inhibitor medications. This variability was addressed in two ways. First, a 35% change was selected as a threshold for hemostasis and hemorrhage size change was classified as decreased, stable or increased. Interestingly, most (70-82%) hemorrhages in all anticoagulant groups decreased or remained stable after the administration of PCC4 (Table 3). Secondly, a nonparametric analysis of the distribution of percent hemorrhage size change was utilized to limit the statistical effect of very small bleeds with minimal, but relatively large percent, changes. Using this analysis, the distribution of size changes were found to be very small and similar between the warfarin and rivaroxaban groups. However, the apixaban related hemorrhages had a much larger increase in the distribution of size change after PCC4 treatment; this was not statistically significant due to the small sample size and wide distribution of size change (Figure 1). Despite no statistically significant differences in ICH size change in patients who did not have an interval operation, a difference in mortality was identified in the VKA and factor Xa inhibitor patients treated with PCC4 who received an operation (Table 5). This could be related to the smaller factor Xa inhibitors population size compared to VKA but it does stand as one of the few differences between the groups and would warrant further assessment in a larger population.

Table 5: Mortality by OR and anticoagulant.

OR	Alive	Dead
Grouped Mortality by OR (p=0.50)		
NO	39 (54.2%)	33 (45.8%)
YES	18 (47.4%)	20 (52.6%)
Mortality by OR for warfarin (p=0.53)		
NO	23 (47.9%)	25 (52.1%)
YES	15 (55.6%)	12 (44.4%)
Mortality by OR for Xa Inhibitors (p=0.03)		
NO	16 (66.7%)	8 (33.3%)
YES	3 (27.3%)	8 (72.7%)

Table 6: Thromboembolic events in VKA patients that were reversed with Kcentra.

Thromboembolic event (n)	Detection time	Anticoagulation indication	Disposition
DVT (6)	3: <1 day 3: 2-3 weeks	5: A. fib 1: DVT/PE	6: SNF/Rehab
Strokes (3)	1: <1 day 1: 3 days 1: 1 month	2: A. fib 1: Aortic valve	1: Death 2: SNF
Mesenteric thromboembolus (1)	1: 2 days	1: A. fib, Mitral valve	1: Death

DVT-deep venous thrombosis; SNF-skilled nursing facility; A. fib-atrial fibrillation; Rehab-rehabilitation center

Usage of PCC4 is not without risks. Rates of thromboembolic complication in the reported literature are 2.9-7% [11,12] whereas the rate in this study was slightly higher at 13.3%. Importantly, patients were only tested for symptomatic thrombotic events and nearly 50% of all patients with VKA-related ICH died. The median time to death or institution of comfort measures in this population was within three days of admission, while just under half of the thromboembolic complications were noted after three days. It is possible the thromboembolic rate would be higher if given enough time for symptoms to appear from the hypercoagulable state and warrant testing. Still, more than half of the patients who received PCC4 ultimately survived, suggesting patient selectivity is important. Balancing the risk of hemorrhage versus the risk of exposing the patient to a thrombophilic state is critical as the morbidity of this thromboembolic risk is high. As an example, in the VKA-related hemorrhage group, three separate patients suffered strokes, one being fatal, and one patient succumbed to a mesenteric thromboembolism approximately 36 hours after administration of PCC4.

The factor Xa inhibitors present a unique challenge. Several small studies have demonstrated variable efficacy for reversal of coagulopathy in animal models and healthy volunteers through the use of PCCs [15]. Recommendations from different organizations reflect a hesitancy to routinely promote use of a PCC for factor

Xa inhibitor-related ICH. The institutional guideline for this study allows for use of 50 units/kg of PCC4 as an option to reverse coagulopathy from factor Xa inhibitors. Radiographic progression of ICH in this study was variable for rivaroxaban and apixaban. While not statistically different given the small sample size and wide variability, apixaban may be associated with higher rates of bleeding, perhaps related to dosing regimen or clearance. Further studies will be needed to better delineate *in vivo* reactions to these different medications. As these findings are comparable to the VKA group, which has been well studied and is supported in the literature, it suggests that PCC4 may be effective for factor Xa inhibitor coagulopathy reversal at least for rivaroxaban (Figure 1). However, this should be interpreted with caution due to the limited sample size and high rates of mortality in this study. Interestingly, with zero thromboembolic events noted in the factor Xa inhibitor patients; a question is posed regarding chemical reversal of factor Xa inhibitors. It is possible that these medications are not being fully reversed, allowing for an ongoing mild anticoagulated state that prevents thromboembolic events from occurring. More likely, as PCC4 directly reinserts the vitamin K derived factors being altered by VKA medications, it may be abruptly changing the clotting physiology in the VKA group, making them more prone to developing events, while a more gradual change is occurring in patients anticoagulated with factor Xa inhibitors. This evaluation is limited by sample size.

This study is the largest to date directly assessing outcomes in ICH patients who had their anticoagulation reversed with PCC4. In addition, it utilizes a patient population excluded in the initial trials for the severity of their illness, suggesting that an expanded usage criterion for PCC4 is effective for arrest of progression of hemorrhage growth. Historically, mortality rates of ICH while on anticoagulation are 44%, similar to the mortality rate observed after administration of PCC4 in this study [22]. Further studies are necessary to characterize the impact on morbidity for ICH survivors. Although the sample size is small, these data would further support the usage of PCC4 to reverse coagulopathy in patients that sustain a factor Xa inhibitor-related ICH while on rivaroxaban. While there are only eight apixaban patients included in the interval size change analysis, PCC4 did not seem as effective in reducing hemorrhage growth in these patients (Figure 1). Several other studies have been released which reveal difficulty with hemostasis using PCC4 for factor Xa inhibitors, noting anywhere from 15-30.9% ineffective or poor hemostasis, explained potentially by underdosing of PCC4 compared to active circulating volume of factor Xa inhibitors [23,24]. It does appear that the risk of thromboembolic complications in VKA-related ICH patients that were given PCC4 is higher than previously estimated, 8%, also confirmed by other recent studies [23,25]. With multiple strokes and deaths identified in this study, the risk profile in a "real world" population is striking and certainly needs to be considered with respect to a patient's clinical picture. The recent Food and Drug Administration approved medication, AndexXa, may be a viable alternative to PCC4, with an efficacy of 82% for hemostasis. However, thromboembolic complication rates were noted to be 10%, and the cost continues to be a limiting factor in clinical practice [26]. As timing of administration compared to previous anticoagulant dosing, concentration and volume of distribution of circulating anticoagulant, degree of injury or bleeding, and the current physiologic status of the patient all are considerations for efficacy of anticoagulation reversal and risk of adverse event, caution must be used in the approach to intracranial hemorrhage and reversal of anticoagulation.

CONCLUSION

As this is an observational and retrospective study of a combined stroke and trauma population, heterogeneity and bias can impact the results. Additionally, without a non-reversed group overall benefit of anticoagulation reversal cannot be definitively determined. Further studies are necessary to better define an inflection point in which PCC4 use for anticoagulation reversal optimizes the risk/benefit ratio when considering administering a potent thrombophilic agent in these high-risk patients.

Despite arrest of ICH progression in most patients, the high rate of thromboembolic events in the VKA population suggests the risk of adverse events in a "real world" population is not insignificant and must be considered with respect to the clinical picture. Further studies are necessary to determine which patients are ideally suited to undergo repletion with PCC4 using expanded criteria.

CONFLICT OF INTEREST

Dr. Painter, Dr. Farrell, Dr. Wiedner, Dr. Perza and Dr. Cipolle have no conflicts of interest to disclose.

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