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Reversal of warfarin anticoagulation in geriatric traumatic brain injury due to ground-level falls

Michael John Paisley ,[1] Arianne Johnson,[2] Spencer Price,[3] Bernard Chow,[3] Liliana Limon,[2] Rohit Sharma,[2] Stephen Kaminski[2]

[1]Surgery, Santa Barbara Cottage Hospital, Santa Barbara, California, USA
[2]Trauma, Santa Barbara Cottage Hospital, Santa Barbara, California, USA
[3]Radiology, Santa Barbara Cottage Hospital, Santa Barbara, California, USA

Correspondence to
Dr Michael John Paisley, Surgery, Santa Barbara Cottage Hospital, Santa Barbara, CA 93105, USA; mjpaisley@gmail.com

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ABSTRACT

Background The efficacy of prothrombin complex concentrate (PCC) compared with fresh frozen plasma (FFP) for reversal of oral anticoagulants has not been investigated in geriatric patients suffering intracranial hemorrhage (ICH) due to a ground-level fall (GLF).

Methods Patients 65 years and older who were treated at Santa Barbara Cottage Hospital between January 2011 and March 2018 with ICH after a GLF while taking warfarin were reviewed. Patients were reversed with either FFP (n=25) or PCC (n=27) and patient outcomes were compared. Separate analyses were conducted for patients who received adjuvant vitamin K administration and those who did not.

Results Mortality rates, hospital length of stay, intensive care unit admission and length of stay were similar for both FFP and PCC intervention. There was no difference in radiological progression of hemorrhage within the first 24 hours of admission (FFP: 36%, PCC: 43%, p=0.365). In patients who had international normalized ratio (INR) values measured prior to intervention, 81% (17 out of 21) of the PCC group reached an INR value below 1.5 within an 8-hour period, whereas only 29% (4 out of 14) of the FFP group did (p=0.002). Vitamin K was concomitantly given to 28% of the patients receiving FFP, and 81% of those patients receiving PCC. No significant differences in outcomes were found whether adjunctive vitamin K was administered or not, in either FFP or PCC group. However, when vitamin K was not administered, the PCC group had a higher rate of INR reversal (80% vs. 10% for FFP, p=0.006).

Conclusion Administration of PCC is as effective in short-term outcomes as FFP in treating geriatric patients on warfarin sustaining an ICH after a GLF. INR reversal was more successful, significantly faster, and required lower infusion volumes in patients receiving PCC.

Level of evidence Level III.

INTRODUCTION

Ground-level falls (GLF) are the most common mechanism of injury in the geriatric population.[1 2] Annually, the fall rate for people aged 64 is 35% which increases to 50% for those aged 85.[3 4] Furthermore, 30% to 50% of residents at long-term care facilities will suffer a fall each year, nearly half of which will suffer multiple falls.[4] Common in this age group, and compounding the risk of falling, is the concomitant use of anticoagulants for conditions such as atrial fibrillation, cardiac valvular disease, venous thromboembolism, and occlusive arterial disease. When an individual suffers an intracranial hemorrhage (ICH) while on anticoagulant therapy such as warfarin, the hemorrhage is at a heightened risk of expansion, resulting in worsened functional outcomes, and upwards of a 50% higher mortality rate.[5 6] Adults over the age of 64 will represent nearly one-quarter of our population by the year 2030, and thus it is vitally important to understand the risks and management of anticoagulant use such as warfarin in this population vulnerable to falling.[7 8]

Prior to the availability of multifactor prothrombin complex concentrates (PCC), emergent reversal of warfarin anticoagulation after injury could only be accomplished using infusion of fresh frozen plasma (FFP). Vitamin K infusion was concomitantly given to re-establish the endogenous pathways of coagulation factor synthesis that are impaired by warfarin use, but this treatment adjunct was not able to provide the rapid correction needed to reverse warfarin in the acute setting of life-threatening hemorrhage.[9] Fong *et al* compared PCC versus FFP infusion for warfarin reversal in geriatric patients with ICH and found better reversal of international normalized ratio (INR) values and less neurological impact when four-factor PCC was used.[10] Edavettal *et al* showed similar findings in geriatric trauma patients suffering an ICH; decreased neurological deterioration and faster INR reversal times after administration of three-factor PCC and FFP compared with FFP alone.[11] These aforementioned studies and numerous others have compared PCC and FFP for warfarin reversal after trauma, but often the mechanisms of injury included in the analysis were heterogeneous.[4 5 10–12] This heterogeneity can potentially muddy the interpretation of these studies, and so a focused assessment of these reversal agents is prudent and warranted. GLFs represent a unique, low-velocity mechanism of injury seen commonly in geriatric patients on anticoagulation. Understanding this injury pattern, and developing evidence-based treatment strategies is paramount to providing optimal care for this population at risk for life-threatening hemorrhage after seemingly minor injuries. In this study, we compared four-factor PCC versus FFP infusion for warfarin reversal in geriatric patients suffering ICH after GLF. Outcomes measured were mortality, hospital length of stay (LOS), intensive care unit (ICU) admittance, ICU LOS, radiological progression of hemorrhage, and INR reversal time.

METHODS

After Institutional Review Board approval, we conducted a retrospective review of patient records maintained in our trauma database at Santa Barbara Cottage Hospital (SBCH). SBCH is an academic regional referral center and an American College of Surgeons verified Trauma Center which went from level II to level I status in 2017. We identified patients seen between January 2011 and March 2018 who were over the age of 64 and suffered a GLF (International Classification of Diseases, Ninth Revision codes: 880.1, 880.9, 885.0, 885.9, 888.1) while taking warfarin. Patients found to have ICH at admission head CT (defined as having an Abbreviated Injury Scale-Head compartment (AIS-H) score greater than 2) who were then subsequently treated with FFP or PCC for warfarin reversal were compared. FFP was the primary agent used for warfarin reversal in our institution prior to 2013 after which PCC became our primary agent. Patient demographics (age, gender, race), Glasgow Coma Scale (GCS), Injury Severity Score (ISS), AIS-H, findings on head CT scan (subdural hematoma, epidural hematoma, intraparenchymal hemorrhage, subarachnoid hemorrhage), volume of PCC or FFP transfused, and neurosurgical procedure data were collected. Primary outcome measures included mortality, ICU admission, ICU LOS, and hospital LOS. Subset analyses were completed for INR reversal and radiological progression as follows. Concomitant to FFP or PCC infusion, vitamin K use was evaluated and subset analysis was performed. For patients with preintervention INR values, the time needed to reach the goal INR value of 1.5 was interpolated via a linear plot where the x-axis value (hours) intersected with an INR value (y-axis) of 1.5. For patients who underwent a follow-up CT within 24 hours of diagnosis, the index and subsequent CTs were evaluated for progression of hemorrhage by a radiologist blinded to which reversal agent was used. Progression of hemorrhage was determined when any of the following occurred: blood products qualitatively appeared to increase by at least 20% from baseline; new subdural, intraventricular, or subarachnoid extension of blood with the appearance not attributable to redistributed hemorrhage; or new serious sequelae such as worsening hydrocephalus, cerebral edema, mass effect, or brain herniation were observed. For all measures, the two groups were compared using a two-sample t-test assuming equal variance for continuous variables, and a Pearson's χ^2 test for categorical variables.

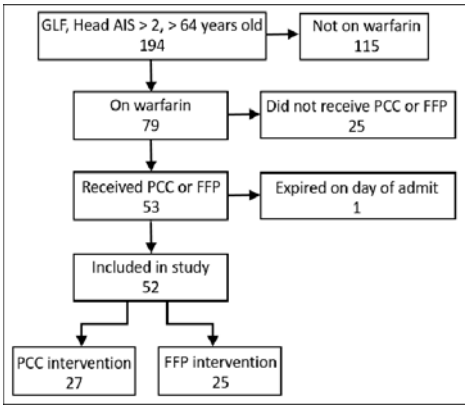

Figure 1 Inclusion and exclusion of patients. AIS, Abbreviated Injury Scale; FFP, fresh frozen plasma; GLF, ground-level fall; PCC, prothrombin complex concentrate.

Table 1 Patient baseline characteristics, treatments, and outcomes

	Intervention		
	FFP (n=25)	PCC (n=27)	P value
Age*	83.8 (6.51)	85.8 (7.10)	0.290
Number of females (%)†	16 (64)	10 (37)	0.096
Number of white patients (%)†	22 (88)	27 (100)	0.208
Congestive heart failure†	1 (4)	3 (11)	0.336
History of falls (%)†	9 (36.0)	11 (40.7)	0.725
Glasgow Coma Scale (SD)*	14.32 (2.44)	14.04 (2.70)	0.693
Injury Severity Score (SD)*	15.72 (4.08)	16.93 (5.57)	0.375
AIS-Head and Neck (SD)*	3.64 (0.70)	3.85 (0.72)	0.287
Initial scan			
Subdural hematoma (%)	14 (56)	21 (78)	
Subarachnoid hemorrhage	6 (24)	2 (7)	
Intraparenchymal hemorrhage (%)	4 (16)	7 (26)	
Infusion volume, mL (SD)*	910 (370)	87 (33)	<0.001‡
Neurointervention (%)†	2 (8.0)	3 (11.1)	0.704
Mortality (%)*	0 (0.0)	3 (11.1)	0.262
Hospital LOS, days (SD)*	4.16 (2.56)	3.73 (1.42)	0.335
Admitted to ICU (%)†	17 (68)	21 (78)	0.630
ICU LOS, days (SD)*	2.29 (1.16)	2.43 (0.68)	0.676
Proportion that reached INR <1.5 within 8 hours (%)†	4/14 (29)	17/21 (81)	0.002‡
CT progression within 24 hours (%)†	5/14 (36)	10/23 (43)	0.365

*Pearson's χ^2 test.
†Two-sample t-test assuming equal variance.
‡Significant result
AIS, Abbreviated Injury Scale; FFP, fresh frozen plasma; ICU, intensive care unit; INR, international normalized ratio; LOS, length of stay; PCC, prothrombin complex concentrate.

RESULTS

Fifty-two patients had a GLF while on warfarin and met the inclusion criteria (figure 1). Twenty-five patients received FFP and 27 patients received PCC intervention. Baseline characteristics were similar between the two groups, including age, sex, race, GCS, ISS, AIS-H, and initial INR value (table 1). Overall, the mean age was 84.8 years, mean GCS was 14, ISS was 16.4, and AIS-H score was 3.8. On average, 910±370 mL of FFP was infused compared with 87±33 mL of PCC (p<0.001). Neurosurgeries occurred in two FFP patients (both received craniotomy for SDH) and three PCC patients (one craniotomy and two burr holes for SDH). FFP and PCC patients had similar short-term outcomes, including mortality (0% vs. 11.1%, respectively, p=0.262), ICU admittance (68% vs. 78%, respectively, p=0.630), mean hospital LOS (4.16 days vs. 3.73 days, respectively, p=0.335), and mean ICU LOS (2.29 days vs. 2.43 days, respectively, p=0.676). Table 2 summarizes these findings.

Vitamin K was administered to 7 of the 25 patients who received FFP (28%), and 22 out of 27 patients (81%) (p<0.01). Subset analyses of clinical outcomes based on whether or not patients received vitamin K in addition to FFP or PCC showed no statistically significant differences in outcomes between the FFP and PCC groups, except for INR reversal (tables 2 and 3). Twenty-two of the 27 PCC patients (81%) and 15 of the 25 FFP patients (60%) had INR values taken before intervention. Each treatment group had one patient who had an initial INR value less than 1.5, and both of these patients were excluded from further analysis. Initial INR values were similar between

Table 2 Patient treatments, INR reversal, radiological progression, and outcomes for patients given vitamin K

	Intervention		
	FFP (n=7)	PCC (n=22)	P value
Neurointervention (%)*	0 (0.00)	2 (9.09)	0.408
Mortality (%)*	0 (0.00)	3 (13.60)	0.302
Hospital LOS, days (SD)†	5.29 (4.02)	3.86 (1.32)	0.392
Admitted to ICU (%)*	7 (100.00)	17 (77.27)	0.166
ICU LOS, days (SD)†	2.43 (.79)	2.53 (.72)	0.776
Preintervention INR (SD)†	3.38 (1.34)	2.77 (1.22)	0.346
Proportion that reached INR <1.5 within 8 hours (%)*	4/4 (100)	14/16 (87.50)	0.456
CT progression observed within first 24 hours (%)*	4/7 (57.14)	9/19 (47.37)	0.658

*Pearson's χ^2 test.
†Two-sample t-test assuming equal variance.
FFP, fresh frozen plasma; ICU, intensive care unit; INR, international normalized ratio; LOS, length of stay; PCC, prothrombin complex concentrate.

the two groups (FFP=2.78±1.03, PCC=3.01±1.79, p=0.655). In patients with a preintervention INR value greater than 1.5, we found no difference in successful reversal within 8 hours to a goal INR value of less than or equal to 1.5 between the FFP and PCC groups when vitamin K was given (100% vs. 87%, respectively, p=0.456) (table 2). However, when vitamin K was not given, PCC was able to accomplish reversal in 80% of patients compared with only 10% of patients administered FFP (p=0.006) (table 3). Follow-up CT scans occurred within 24 hours of diagnosis for 14 of the 25 FFP patients (56%) and 23 of the 27 PCC patients (83%). Radiological progression of hemorrhage was similar between the two groups, with 36% of FFP patients showing progression and 43% of PCC patients showing progression (p=0.365, table 1).

DISCUSSION

The use of warfarin remains a mainstay of medical management in patients at risk for thromboembolic events, and is a common medication used in the elderly. Elderly adults are at heightened risk of falling, and understanding how best to reverse the anticoagulant effects of warfarin in these patients after injury is paramount. Prior to the availability of PCC, FFP was the only available agent for the emergent reversal of warfarin, and serves as the standard for comparison. In our study of elderly adults with ICH after GLFs while on warfarin, we found that PCC performed as well as FFP in clinically relevant outcomes, including mortality, radiological progression of hemorrhage, ICU LOS, and hospital LOS. Notably, PCC achieved INR reversal faster, more reliably, with lower required infusion volumes, and without the risks inherent to blood component therapy.

Table 3 Patient treatments, INR reversal, radiological progression, and outcomes for patients not given vitamin K

	Intervention		
	FFP (n=18)	PCC (n=5)	P value
Neurointervention (%)*	2 (11.11)	1 (20.00)	0.602
Mortality (%)*	0 (0.00)	0 (0.00)	NA
Hospital LOS, days (SD)†	3.72 (1.67)	2.40 (1.34)	0.104
Admitted to ICU (%)*	10 (55.56)	4 (80.00)	0.322
ICU LOS, days (SD)†	2.20 (1.40)	2.0 (0.00)	0.662
Preintervention INR (SD)	2.40 (.52)	4.16 (2.88)	0.244
Proportion that reached INR <1.5 within 8 hours (%)*	1/10 (10)	4/5 (80)	0.006†
CT progression observed within first 24 hours (%)*	1/7 (14.29)	1/4 (25)	0.658

*Pearson's χ^2 test.
†Two-sample t-test assuming equal variance.
FFP, fresh frozen plasma; ICU, intensive care unit; INR, international normalized ratio; LOS, length of stay; NA, not applicable; PCC, prothrombin complex concentrate.

When compared with FFP reversal, similar clinical outcomes were achieved with more successful and faster times to INR reversal with PCC. Our results are consistent with findings from previous studies showing reliably faster INR reversal after PCC compared with FFP administration.[10–12] As PCC does not require thawing or cross-matching, it has the added benefit of being administered faster than FFP and with significantly smaller volume of infusion. This is particularly relevant when treating elderly patients as they are more likely to be physiologically frail and sensitive to volume overload.[12] Additional factors such as the logistics associated with maintaining a thawed and ready stock of FFP, and monitoring for and managing transfusion reactions, when weighed against the lower efficacy of FFP in reversing warfarin on the whole, would suggest that PCC and vitamin K be considered the agents of choice when attempting emergent warfarin reversal.

This study was a retrospective review of a single institution's trauma database and so is vulnerable to errors in coding and retrieval of data. In 2013, our institution switched to PCC as our primary agent for the reversal of warfarin, and so this study was not randomized or blinded to the interventions employed. Vitamin K was intended to be administered concomitantly to FFP or PCC per institutional protocol, but adherence to this was clearly suboptimal; only 28% of our FFP group received vitamin K in comparison to 81% of the PCC group. Subgroup analyses showed no difference in outcomes or rates of INR reversal in the FFP and PCC groups when vitamin K was concomitantly given; however, when vitamin K was not given, PCC was more successful at obtaining reversal within 8 hours. It is important to note that the small size of our cohorts limits our ability to conduct deeper subgroup analyses, and a dedicated study is warranted to properly evaluate the adjuvant use of vitamin K alongside FFP and PCC. Patients on other anticoagulants and antiplatelet agents were excluded, as were those taking multiple agents in addition to warfarin; the impact these patients have on our understanding of ICH after GLF is not assessed by our analysis. Our rates of neurosurgical procedures is low, and so we are unable to make any meaningful analyses comparing the two reversal modalities on this critical issue. Lastly, we identified only 52 patients suffering ICH after GLF on warfarin over the course of 8 years. This small sample size potentially limits our ability to detect true differences in the intervention groups and thus may lead to type II statistical errors. Our findings correlate and build on other studies evaluating the efficacy of PCC versus FFP, and thus lending to the validity of our findings, but clearly a multicenter trial will be able to better detect true differences and thus provide better clarity in the optimal management of this important patient group.[9–12]

CONCLUSION

Prothrombin complex concentrate achieves rapid reversal of warfarin-induced anticoagulation in geriatric patients with ICH after suffering GLFs. When compared with FFP reversal, similar clinical outcomes were achieved with faster times to INR reversal with PCC.

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ORCID iD

Michael John Paisley http://orcid.org/0000-0002-0236-9579

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