Prophylactic Fresh Frozen Plasma Infusion is Ineffective in Reversing Warfarin Anticoagulation and Preventing Delayed Intracranial Hemorrhage After Falls

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Abstract

Background: Elderly patients, with considerable fall risk, are increasingly anticoagulated to prevent thromboembolic disease. We hypothesized that a policy of prophylactic fresh frozen plasma (FFP) infusion in patients having falls would reverse vitamin K antagonists (VKAs) and that reversal would decrease delayed intracranial hemorrhage (ICH). **Methods:** A retrospective review of patients with trauma admitted to a level 2 community trauma center was performed from January 2010 until November 2012. Inclusion criteria were: ground level fall (GLF) with suspected head trauma, on VKA, an international normalized ratio (INR) of >1.5 , and a negative head computed tomography (CT). Patients were transfused with FFP to a goal INR of <1.5 while observed. Patients were classified as reversed (REV) if the lowest INR achieved within 4 to 24 hours after initial INR was <1.5 or unreversed (NREV) if lowest INR achieved was >1.5 . Chi-square and logistic regression were performed. **Results:** A total of 194 patients met the criteria. In all, 43 (22%) patients were able to be REV, and 151 (78%) patients remained NREV. Unreversed patients were male and younger ($P < .05$). There was no difference in mean FFP received. Unreversed patients had a higher initial INR of 3.0 compared to REV patients (2.5; $P = .018$). One patient developed a delayed ICH and belonged to the REV group. **Conclusion:** The incidence of delayed hemorrhage was 0.5%. A strategy of prophylactic FFP infusion was ineffective in VKA reversal. We recommend against prophylactic infusion of FFP during a period of observation for patients on VKA with suspected head trauma and a negative initial CT.

Keywords

brain hemorrhage, traumatic, trauma, nervous system, warfarin, anticoagulation, fall, elderly

Background

By 2030, the population of American adults aged >65 is expected to increase by 30%.¹ Many older adults are treated with anticoagulants for chronic health conditions. The most commonly used anticoagulant is warfarin.² The prevalence of warfarin use in the United States is unknown, but the Food and Drug Administration estimates that more than 31 million prescriptions for warfarin were written in 2004.³ One of 3 adults aged 65 and older experience fall each year.⁴ Falls are the most common cause of traumatic brain injuries (TBIs) in elderly patients.⁵ In 2000, TBIs accounted for 46% of fatal falls among older adults.⁶ Injury occurring while medically anticoagulated is associated with a worse outcome.⁷⁻⁹ Patients having a TBI while anticoagulated also experience significant morbidity.¹⁰

Traumatic brain injury in anticoagulated patients occurs not only acutely but can also develop more slowly and be

identified in a delayed fashion.^{11,12} Aggressive reversal of anticoagulation has been shown to improve outcome after traumatic intracranial hemorrhage (ICH).¹³ Options for reversal of anticoagulation include infusion of fresh frozen plasma (FFP), administration of vitamin K, and use of coagulation factors.¹⁴ We hypothesized that a policy utilizing prophylactic FFP infusion in patients having falls while anticoagulated with warfarin would be effective in reversing anticoagulation and that reversal of anticoagulation would decrease delayed ICH.

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Methods

After obtaining institutional review board approval which included a waiver of informed consent for study number 12-80r, data from the registry of Santa Barbara Cottage Hospital (SBCH) were collected and evaluated. The SBCH is a regional level 2 trauma center on the central coast of California. Patients were included in the study if they had a fall as a mechanism of injury while on warfarin with symptoms of head injury, loss of consciousness, or external signs of head trauma. All patients had a normal initial head computed tomography (CT) and were admitted to the trauma service from January 2010 to December 2012. The trauma service policy for the management of patients on warfarin anticoagulation and a negative initial head CT scan included admission for observation for a period of no less than 8 hours. During observation, patients had their anticoagulation prophylactically reversed with the infusion of FFP to a target international normalized ratio (INR) of <1.5 .

Patients were defined as anticoagulated if they were taking warfarin and had a baseline INR >1.5 less than 4 hours after emergency department triage. Additional data collected from the trauma registry included patient demographics, hospital outcomes, initial INR, amount of FFP received per patient, lowest INR between 4 and 24 hours after admission, and evidence of ICH on follow-up CT. Patients were then divided into 2 groups. Anticoagulation reversed by prophylactic FFP administration was defined as an INR of <1.5 within 4 to 24 hours after admission (REV). Anticoagulation was determined not reversed if INR <1.5 was not achieved within 4 to 24 hours after admission (NREV). Units of FFP ranged from 400 to 450 cm³ in volume. Diagnoses and procedures were identified by *International Classification of Diseases, Ninth Revision*, codes. The primary outcome was rate of mortality between the 2 groups. Secondary outcomes included complications, hospital length of stay, intensive care unit length of stay, incidence of delayed bleed, and effective reversal of INR. The following complications were tracked during the study period: drug/alcohol withdrawal, pulmonary embolism, acute renal failure, urinary tract infection, unplanned return to intensive care, and myocardial infarction. Patients were excluded if they did not undergo head CT imaging, they received an alternate reversal agent such as prothrombin complex concentrate, they were found not to be anticoagulated (INR <1.5 on admit), or follow-up INR testing was not available. No patients excluded were identified as having developed an ICH in delayed fashion after their trauma.

Continuous data were summarized using means with standard deviation in parenthesis or medians with interquartile range in parenthesis based on the distribution of the data. Discrete data were summarized as number in group with percentage of group in parenthesis. Univariate analysis was performed with *t* test, Wilcoxon Rank Sum test, and chi-square test where appropriate. Prehospital characteristics and

comorbidities that were significant on univariate analysis were entered into a multivariate logistic regression model. Data from the multivariate model were summarized using odds ratios. All statistical tests were 2-sided and a *P* value less than .05 was considered statistically significant. The analysis was performed using the R Statistical Computing Environment (R Core Team 2012).¹⁵

Results

During the 35-month study period, there were 392 patients who fell while taking warfarin with 194 meeting inclusion criteria and 198 patients excluded (Figure 1). Forty-three (22%) patients were able to be REV using a prophylactic FFP transfusion strategy, while 151 (78%) remained anticoagulated. Patient characteristics and outcomes are shown in Table 1. The REV group was more likely to be female, older, and to have a lower INR. There was no difference between the groups in the initial set of vital signs, baseline Glasgow Coma Scale, or Injury Severity Score. The median units of FFP administered to patients were not significantly different between the reversal group and those patients who did not have their anticoagulation reversed. A higher initial INR was observed in the NREV compared to REV patients ($P < .05$).

The median lowest follow-up INR within 4 to 24 hours was 1.8 and 1.4 in the NREV and REV groups, respectively. Figure 2 is a visual display of within patient change in INR from initial to follow-up separated by whether patients had their anticoagulation reversed. Mortality was 2.3% in the REV group and 0.7% in the NREV group ($P = .391$). Only 1 patient during the study period developed an ICH in a delayed fashion; this patient belonged to the REV group and was identified by neurologic changes. The CT scan subsequently demonstrated that this patient had developed a subdural hemorrhage.

The multivariate model contained age, gender, and initial INR. All variables entered in to the multivariate model were significant (Table 2). A higher initial INR (odds ratio [OR] 0.49), younger age (OR 1.05), and male gender (OR 0.43) were associated with NREV.

Eight complications were observed to occur in the 194 patients, that is, 2 drug/alcohol withdrawals, 1 pulmonary embolism, 1 acute renal failure, 2 urinary tract infections, 1 unplanned return to intensive care, and 1 myocardial infarction. There was no observed difference in the number of complications between the groups.

Discussion

In this retrospective analysis, 78% of 194 studied patients admitted after ground-level falls did not have their INR normalized to less than 1.5 within 24 hours with a policy of prophylactic FFP infusion. The rate of delayed ICH (0.5%) does not appear to have been affected. One patient

Figure 1. Flowchart for anticoagulation reversal.

Table 1. Patient Characteristics and Hospital Outcomes.

	Anticoagulation Not Reversed (n = 151)	Anticoagulation Reversed (n = 43)	P Value
Age	82.2 (10)	85.8 (5.9)	.004
Number of males	74 (49%)	11 (25.6%)	.005
Heart rate	80.2 (18.5)	82.0 (16.1)	.532
Respiratory rate	17.7 (3.2)	17.6 (3.1)	.852
Systolic blood pressure	147.9 (27.5)	155.1 (27.6)	.139
Diastolic blood pressure	73.4 (15.5)	75 (18.5)	.607
Glasgow Coma Scale	14.8 (0.8)	14.8 (0.4)	.920
Red blood cells	0 (0.3)	0.1 (0.5)	.378
Fresh frozen plasma	1.6 (0.8)	1.6 (0.7)	.968
Platelets	0 (0.1)	0 (0)	.319
Total blood products	1.5 (0.9)	1.6 (0.9)	.516
Hospital length of stay	2.7 (1.8)	2.7 (1.4)	.986
ICU length of stay	0.2 (0.9)	0.3 (0.9)	.565
Abbreviated Injury Scale—head	0.8 (0.9)	0.9 (1)	.453
Injury Severity Scale	3.8 (3.2)	4.7 (4.6)	.250
Mortality	1 (0.7%)	1 (2.3%)	.391
INR—initial	3.0 (1.7)	2.5 (1.0)	.018
INR—follow-up	1.8 (0.4)	1.4 (0.1)	<.001
Time between laboratory test results, hours	9.7 (4.6)	9.1 (4.0)	.425

Abbreviations: ICU, intensive care unit; INR, international normalized ratio.

developed a delayed ICH and was in the group that was successfully reversed with FFP to an INR of less than 1.5 within 24 hours. This is the first study, to the author's knowledge, to report on whether or not there is benefit to the prophylactic reversal of warfarin anticoagulation following falls in patients with a negative head CT during a period of observation.

Given that unintentional injury is among the top 10 causes of death in the elderly patients¹⁶ and TBI after falls is a

common occurrence, attempts to improve outcome are justified. Survival after traumatic ICH in anticoagulated patients is improved when patients are treated with an aggressive reversal of their anticoagulation.¹³ Recent practice management guidelines from the Eastern Association for the Surgery of Trauma advocate that patients receiving warfarin with a posttraumatic ICH should receive initiation of therapy to correct their INR toward a normal range within 2 hours of admission.¹⁷ For those patients with a negative initial head CT but who are at risk of the delayed development of ICH, a period of observation after injury is recommended.¹⁸

In 1 survey of trauma surgeons, over two-thirds of respondents stated they would reverse the anticoagulation of a patient with a negative head CT on warfarin anticoagulation. In the same survey, of those surgeons choosing to reverse anticoagulation in the setting of a negative head CT, nearly 75% would choose to do so with plasma infusion.¹⁹ In this study, it was hypothesized that there would be a benefit to the reversal of anticoagulation for those patients who are at risk of the delayed development of ICH. In this retrospective analysis of patients admitted after falls, prophylactic FFP infusion was ineffective in reversing warfarin anticoagulation. The 0.5% rate of delayed development of ICH is similar to previously published reports.^{11,20}

There are a number of reasons that the use of plasma to reverse warfarin anticoagulation may be ineffective. According to the results of a systematic review of 80 randomized clinical trials, the current guidelines for the administration of FFP are largely empirical.²¹ In the United States, FFP at a dose of 10 to 15 mL/kg is used to reverse the warfarin effect; however, there is a paucity of evidence supporting its efficacy.²² Moreover, FFP transfusion has several disadvantages, that is, (1) a delay in therapeutic effect because of the time required to obtain the ABO blood type and to thaw and transfuse several hundred milliliters of FFP; (2) transfusion-associated circulatory overload, especially in elderly patients with cardiac disease; (3) allergic reactions; (4) infection from exposure to multiple donors; and (5) transfusion-related acute lung injury, the most common cause of transfusion-related deaths in the United States.²³

The current study demonstrates the difficulty in reversing warfarin anticoagulation within 24 hours with standard dosing of FFP. A potential cause for the difficulty may be in the dosing. When INR is >1.5, a relationship between dose and target INR is found.^{24,25} In one study, it was shown that 33 mL/kg was more effective in achieving target levels of coagulation factors compared to 12 mL/kg.²⁵ However, the range of dosage in that study was wide. In the current study, a lower initial INR was associated with reversal of anticoagulation. It is possible a higher dose of plasma may result in more complete reversal of INR, but this would be associated with an increase in the risks. Appropriate dosing of FFP for warfarin reversal remains an area of active research.²⁶ Our data support previously reported claims that male patients may be more difficult to have their anticoagulation reversed but it may be

Figure 2. Change in international normalized ratio (INR) from initial to follow-up measurement. Bold line indicates the population mean. The average time difference between initial and follow-up measurement was 9.5 hours.

Table 2. Multivariate Model for Anticoagulation Reversal.

	OR for Anticoagulation Reversal (95% CI)	P Value
Age	1.1 (1.0-1.1)	.034
Male	0.40 (0.2-0.9)	.017
INR initial	0.7 (0.4-1.0)	.039

Abbreviations: CI, confidence interval; INR, international normalized ratio; OR, odds ratio.

easier in older patients.²⁷ This heterogeneity emphasizes the challenges of attempting to reverse anticoagulation with FFP in these groups.

Alternate agents for the immediate reversal of warfarin anticoagulation have recently become available. Warfarin prevents thromboses by blocking posttranslational modification of coagulation factors II, VII, IX, and X, which results in the production of dysfunctional proteins.²⁸ Initially developed for the prevention and control of bleeding in patients with factor IX deficiency due to hemophilia B, prothrombin complex concentrate (PCC) contains these coagulation factors. Several PCC products are available worldwide but differ in the amount of factor VII.²⁹ Prothrombin complex concentrate has been recommended as a supplemental therapy option with vitamin K for reversal of warfarin anticoagulation in serious or life-threatening bleeding.³⁰ Prothrombin complex concentrate used with or without additional FFP has been shown to provide rapid reversal of the INR in neurosurgical patients and patients with trauma.³¹⁻³⁴ With effective rapid reversal strategies now available as well as the demonstrated ineffectiveness of plasma, a policy of prophylactic reversal of anticoagulation appears unwarranted.

This study has several limitations. During the study period, the reported rate of allergic transfusion reactions for FFP infusion at the institution was 0.3%. This is much lower than the reported 1% to 3% overall incidence of allergic

reactions for transfusions.³⁵ Similarly, while a recent study found transfusion-associated cardiac overload to occur in 6% of patients receiving transfusions,³⁶ it was rarely recognized or reported at our institution. Such low and inaccurately reported transfusion complication rates make any group comparisons of these events or conclusions inappropriate. This is a single-center study and the findings may not be generalizable to other trauma centers with a different population with trauma. Although trauma registry data are accumulated prospectively, they are studied retrospectively and this study is limited by its nature and inherent potential coding errors and biases.³⁷ The multivariate model used was overfitted and prone to type 1 error and thus its results are only hypothesis generating. This is a retrospective study of a trauma service protocol for the reversal of warfarin anticoagulation that was applied to all patients, but there was not a specific required uniformity to its execution in terms of the timing and amount of FFP infusion or the interval at which the follow-up INR was to be obtained. Follow-up CT scan was done based on changes in clinical examination, not in a standardized fashion and thus some cases with ICH may have been missed. Finally, as patients were without a defined emergency requiring rapid reversal, it is unclear how these results would have changed if a greater urgency for anticoagulation reversal were present. Nonetheless, only 22% of our patients were successfully reversed to an INR < 1.5 utilizing only the infusion of FFP.

Conclusion

A prophylactic strategy of FFP infusion to reverse warfarin anticoagulation in patients having traumatic falls resulted in a low proportion of patients who had their anticoagulation effectively reversed. It did not appear to impact the rate of delayed ICH. We recommend against prophylactic infusion of FFP during a period of observation for patients taking VKA with suspected head trauma and a negative initial CT.

Authors' Note

SR, JG, LF, and SK designed this study. SR and SK conducted the literature search. SR, JG, and SK collected the data which JG analyzed. All authors interpreted the data. SR, RS, and SK wrote the article. JG prepared figures and tables. LF and SK edited the final article.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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