Rapid Warfarin Reversal in the Setting of Intracranial Hemorrhage: A Comparison of Plasma, Recombinant Activated Factor VII, and Prothrombin Complex Concentrate

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Key words
- Intracranial hemorrhage
- Plasma
- Prothrombin complex concentrate
- Recombinant activated factor vii
- Reversal
- Warfarin

Abbreviations and Acronyms
EMR: Electronic medical record
FFP: Fresh-frozen plasma
FVIIa: Activated factor VII
INR: International normalized ratio
PCC: Prothrombin complex concentrate
Vit K: Vitamin K
WICH: Warfarin-related intracranial hemorrhage

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OBJECTIVE: **To compare the safety and effectiveness of three methods of reversing coagulopathic effects of warfarin in patients with potentially life-threatening intracranial hemorrhage.**

METHODS: **A retrospective electronic medical record review of 63 patients with warfarin-related intracranial hemorrhage between 2007 and 2010 in an integrated health care delivery system was conducted. The three methods of rapid warfarin reversal were fresh-frozen plasma (FFP), activated factor VII (FVIIa; NovoSevenRT [Novo Nordisk, Bagsværd, Denmark]), and prothrombin complex concentrate (PCC; BebulinVH [Baxter, Westlake Village, California, USA], ProfilnineSD [Grifols, North Carolina, USA]), each used adjunctively with vitamin K (Vit K, phytonadione). We determined times from reversal agent order to laboratory evidence of warfarin reversal (international normalized ratio [INR]) in the first 48 hours and compared INR rebound rates and complications in the first 48 hours.**

RESULTS: **Reversal with FFP took more than twice as long compared with FVIIa or PCC. To reach an INR of 1.3, mean (±SD) reversal times were 1933 ± 905 minutes for FFP, 784 ± 926 minutes for FVIIa, and 980 ± 1021 minutes for PCC ($P < 0.001$; $P < 0.01$ between FFP and FVIIa, $P < 0.05$ between FFP and PCC). INR rebound occurred in 0 of 31 patients for FFP, 4 of 8 for FVIIa, and 0 of 7 for PCC ($P = 0.001$). Complications were uncommon. FVIIa was 15 and 3.5 times as expensive as FFP and PCC, respectively.**

CONCLUSION: **As an adjunct to Vit K for rapid warfarin reversal, FVIIa and PCC appear more effective than FFP. Either FVIIa or PCC are reasonable options for reversal, but FVIIa is considerably more expensive and may have greater risk of INR rebound.**

INTRODUCTION

Warfarin, an oral vitamin K (Vit K) antagonist, remains the most commonly used form of outpatient anticoagulation despite recently developed alternative forms of oral anticoagulation becoming available (4). Bleeding is the major risk of warfarin anticoagulation, and the various forms of intracranial hemorrhage (e.g., intracerebral hemorrhage, subdural hematoma, subarachnoid hemorrhage, and traumatic brain injury) are the most feared complications of warfarin anticoagulation. Warfarin is a strong independent predictor of intracranial hemorrhage (ICH) expansion (14), which is known to predict increased mortality in ICH (7, 10). Therefore, when warfarin-related intracranial hemorrhage (WICH) occurs, the anticoagulant effect of warfarin needs to be reversed as rapidly as possible (5). The administration of Vit K is necessary to reverse warfarin anticoagulation, but its use as a sole reversal agent is generally accepted to be insufficient because it can take many hours to days to reverse the international normalized ratio (INR) (5). Three rapid reversal strategies are available that can be given in addition to Vit K to more quickly treat WICH: fresh-frozen plasma (FFP), activated factor VII (FVIIa), and prothrombin complex concentrate (PCC).

Unfortunately, few studies exist in which the efficacy and safety of these three approaches have been compared. ICH management guidelines discuss each approach, but in the absence of data, the guidelines do not favor one approach over the others (5). Here, we present the results of a retrospective electronic medical record (EMR) analysis in which we compared the effectiveness and safety of FFP, FVIIa, and PCC in combination with Vit K to rapidly reverse warfarin coagulopathy in a neurosurgical emergency.

METHODS

Study Design and Setting

This study design was a retrospective EMR review to compare the relative rates of warfarin reversal and the safety of three

methods in reversing warfarin coagulopathy in the setting of ICH. The study setting was all emergency departments and hospitals in Kaiser Permanente Northern California, a large integrated health care delivery system (15).

Subjects

Patients were included in this study if they were admitted to a Kaiser Permanente Northern California medical center between January 1, 2007, and December 31, 2010; had a diagnosis of ICH; had an active prescription for warfarin; had an INR $\geq$1.5 at the time of hospital admission, and were $\geq$18 years of age. Patients were excluded if they did not receive Vit K or did not receive one of the three options for warfarin reversal (FFP, FVIIa, or PCC) or who received both PCC and FVIIa. Subject inclusion and exclusion criteria were applied by a combination of programmer query and clinician EMR review, as follows: the initial screen to capture appropriate cases was by programmer query of clinical databases for the following criteria: (a) time window January 1, 2007 to December 31, 2010; (b) acute inpatient hospitalization with a discharge diagnosis of ICH (ICH, subdural hematoma, epidural hematoma, or traumatic brain injury) by *International Classification of Diseases*, 9th Revision code (348.4, 430, 431, 432.0,432.1, 432.9, 800.1x, 800.2x, 800.3x, 800.4x, 800.6x, 800.7x, 800.8x, 800.9x, 801.1x, 801.2x, 801.3x, 801.4x, 801.6x, 801.7x, 801.8x, 801.9x, 802.6x, 802.7x, 803.1x, 803.2x, 803.3x, 803.4x, 803.6x, 803.7x, 803.8x, 803.9x, 852.4x); (c) active prescription for warfarin; (d) elevated INR (1.5 or greater) at presentation; (e) age 18 or older. A clinician EMR review by a physician and/or pharmacist was then performed to confirm the aforementioned inclusion/exclusion criteria and to additionally apply the following criteria: (a) complete inpatient and outpatient EMR status; (b) treatment (based on order and administration record) with Vit K; and (c) treatment (based on order and administration record) with FFP, FVIIa, or PCC. Additional patient data such as medical comorbidities (hypertension, diabetes mellitus, hypercholesterolemia, atrial fibrillation or flutter, coronary artery disease/myocardial infarction, stroke, previous ICH), reason for warfarin anticoagulation, and survival to hospital discharge was recorded based on programmer query and EMR review.

Pharmacy Analysis

We examined the following methods for rapid reversal of warfarin coagulopathy: FFP plus Vit K, PCC plus Vit K, or recombinant FVIIa plus Vit K. During the search period of full implementation of a Kaiser Permanente-wide EMR, ordering physicians had access to a rapid reversal electronic order set with prespecified options for FFP, FVIIa, and PCC dosing. Dosing decision support for FFP administration included a weight and INR-based dose calculator based on a published formula for FFP warfarin reversal (22). Dosing options for FVIIa in the order set were 40 μg/kg and 80 μg/kg, and dosing options for PCC were based on patient weight and current INR, according to a published formula for PCC warfarin reversal (22). Ordering physicians could also choose to order FFP, FVIIa, or PCC as individual "a la carte" electronic orders outside the order set. Patients who received both FFP and one of either PCC or FVIIa were included in the appropriate PCC, FVIIa, or FFP group as follows: patients who received full-dose FVIIa or PCC in combination with $\leq$4 units of FFP in the first 24 hours were categorized as receiving FVIIa or PCC. Patients receiving >4 units of FFP in the first 24 hours together with a low dose of FVIIa (<30 μg/kg) or PCC (<60% expected dose based on the standard weight and INR based calculator) (22) were categorized as receiving FFP. Patients receiving any other combination of rapid reversal agents were excluded from our analysis. Total number of administered units of FFP, milliliters of FFP, micrograms of FVIIa, and international units of PCC were determined by EMR review based on order and administration record. Total mg and route of Vit K administered in the first 24 hours was determined by EMR review. Patient weight (in kg) during the first 24 hours was recorded by EMR review.

Laboratory Analysis

All INR values and the date/time stamp of the laboratory result from immediately prior to the hospital admission through the first 48 hours of hospital admission were extracted from laboratory databases. For all laboratory analyses, time zero was the time of rapid reversal agent order as recorded in the EMR. As a specific a priori goal INR for adequate warfarin reversal in a neurosurgical emergency cannot be assumed, we separately compared the times to reach an INR of 1.3 or less, 1.4 or less, and 1.5 or less. Times to reach target INR were calculated from the timestamp of the rapid reversal agent order in the EMR to the timestamp of the first INR resulted at or below the indicated level. If the INR was not reversed within 48 hours (not documented for any reason, including failure to reverse, death, or discharge), then the INR at 48 hours was assumed to be last measured value (last observation carried forward). For comparisons of time to reversal within 48 hours, maximum reversal time was capped at 48 hours (2880 minutes). For graphing of INRs over time, if no INR was resulted prior to time zero (time of physician order for rapid reversal agent), then the first documented INR was carried back to time zero. To look for the possibility of rebound of the INR after initial warfarin reversal, we defined rebound as follows: INR of 1.3 or less reached in the first 48 hrs then INR rebound occurred to 1.5 or higher in the first 48 hours.

Complications

Specific clinical complications were recorded by clinician EMR review. Any potential complications after the administration of the reversal agent were recorded, specifically myocardial infarction, venous thromboembolism (deep vein thrombosis and/or pulmonary embolus), ischemic stroke, disseminated intravascular coagulation, congestive heart failure exacerbation/pulmonary edema, rash, anaphylaxis, or rebound in the INR (as described previously).

Statistical Analysis

For time to reversal of INR, comparisons across the three rapid reversal agents (FFP, FVIIa, and PCC) were made by nonparametric analysis of variance (Kruskal-Wallis test). For significant ($P < 0.05$) results of the Kruskal-Wallis test, post-test comparisons (FFP vs. FVIIa, FFP vs. PCC, and FVIIa vs. PCC) were made by the use of Dunn multiple comparisons test. Categorical data in contingency tables were analyzed with Fisher exact test. Comparison of the actual and predicted International Units (IU) of PCC administered was performed by paired Student *t*-test after we tested the normality assumption by the method of Kolmogorov and Smirnov. All statistical tests were two-sided with an alpha = 0.05.