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Treatment of Warfarin-Related Intracranial Hemorrhage: A Comparison of Prothrombin Complex Concentrate and Recombinant Activated Factor VII

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Key words
- Intracranial hemorrhage
- Prothrombin complex concentrate
- Recombinant activated factor VII
- Warfarin

Abbreviations and Acronyms
FFP: Fresh-frozen plasma
ICH: Intracranial hemorrhage
INR: International normalized ratio
PCC: Prothrombin complex concentrate
rFVIIa: Recombinant activated factor VII
SDH: Subdural hematoma


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OBJECTIVE: **Warfarin-related intracranial hemorrhage (ICH) is a devastating complication of warfarin therapy. Several studies have demonstrated successful correction of the international normalized ratio (INR) using prothrombin complex concentrate (PCC) or recombinant activated factor VII (rFVIIa). To our knowledge, no study has directly compared these agents for treatment of warfarin-related ICH.**

METHODS: **We retrospectively reviewed the charts of 15 patients who received rFVIIa and 9 who received PCC for treatment of warfarin-related ICH over a 2-year period. The primary objective was to compare the efficacy of rFVIIa and PCC in correcting the INR to 1.3 or less. Baseline INR was compared to INR obtained within 1, 3, 6, 12, and 24 hours after rFVIIa or PCC administration.**

RESULTS: **Six patients in the rFVIIa group and five in the PCC group had a follow-up INR within 1 hour of agent administration. In the rFVIIa group, the mean INR decreased from 6.1 to 1.1 and from 2.3 to 1.48 in the PCC group. At 6 hours, all rFVIIa patients and six (67%) PCC patients had at least one subsequent INR, with 93% and 50% correcting to an INR of 1.3 or less. Mean dose for all patients included was 53.4 ± 17.5 μg/kg and 27.8 ± 15.4 units/kg for rFVIIa and PCC, respectively.**

CONCLUSION: **Correction of the INR is more reliably obtained with rFVIIa when compared to PCC. Larger, prospective studies comparing these therapies for warfarin-related ICH are needed.**

INTRODUCTION

Intracranial hemorrhage (ICH) is a devastating complication of warfarin therapy. Patients developing ICH while receiving warfarin have approximately twice the mortality (18), and greater rates of hematoma expan-

sion (8) compared to patients not chronically receiving warfarin. Flibotte et al. (8) found that warfarin users were significantly more likely to experience hematoma expansion within 20 hours of an intracerebral hemorrhage than non-warfarin users, 54% versus 16% ($P = 0.007$) respectively. Therefore, timely correction of the international normalized ratio (INR) may decrease the rates of expansion. The American College of Chest Physicians recommendations for serious bleeding with warfarin therapy are to hold warfarin, administer vitamin K 10 mg IV, and supplement with fresh-frozen plasma (FFP), prothrombin complex concentrate (PCC), or recombinant activated factor VII (rFVIIa) (2). Intravenous vitamin K reliably lowers the INR but typically takes several hours to reach its full effect, whereas FFP infusion provides clotting factors but can be associated with volume overload. Several studies have examined the use of PCC and rFVIIa for correction of coagulopathy associated with warfarin therapy; however, none have directly compared them for warfarin reversal (5, 6, 9, 12, 19, 21, 22).

At our institution, patients with warfarin-related ICH are treated with vitamin K and FFP. If the INR is highly elevated or if the physician believes that it cannot be corrected in a timely manner, rFVIIa or PCC may be administered. Dosing of these agents for warfarin reversal is based primarily on physician experience and evidence from small studies (5, 6, 9, 12, 19, 21, 22). Thus, the purpose of this study is to evaluate the use of these products and compare their efficacy in correcting the INR to 1.3 or less.

Table 1. Baseline Characteristics

	rFVIIa ($n = 15$)	PCC ($n = 9$)
Age (years)	66.7	74.9
Caucasian	8 (53)	7 (78)
Weight (kg)	81.1	83.2
Admission GCS score	10.8	11.1
Baseline SBP (mm Hg)	152	159
Heart failure	9 (60)	4 (44)
Coronary artery disease	5 (33)	4 (44)
Chronic kidney disease	3 (20)	3 (33)
Stroke	3 (20)	1 (11)
Diabetes	8 (53)	5 (56)
Hypertension	10 (67)	7 (78)
Cancer	2 (13)	0
Warfarin indication		
Atrial fibrillation	5 (33)	6 (67)
Stroke	2 (13)	0
Venous thromboembolism	4 (27)	1 (11)
Valve replacement	1 (7)	1 (11)
Other/not specified	3 (20)	0
SDH	6 (40)	2 (22)
SAH	2 (13)	2 (22)
IPH	7 (47)	5 (56)
Baseline INR*	5.6 (1.6–10)	2.6 (1.3–3.4)

Note: Values are *n* (%) unless otherwise specified.
GCS, Glasgow Coma Scale; INR, international normalized ratio; IPH, intraparenchymal hemorrhage; PCC, prothrombin complex concentrate; rFVIIa, recombinant activated factor VII; SAH, subarachnoid hemorrhage; SBP, systolic blood pressure: SDH, subdural hematoma
*$P = 0.0117$.

METHODS

Patients admitted to our institution from November 2005 to November 2007 with ICH, subdural hematoma (SDH), intraparenchymal hemorrhage, or subarachnoid hemorrhage that received either rFVIIa or PCC were included in this study. Patients were excluded if they were younger than age 18 years, had an INR less than 1.3, or were not on chronic warfarin therapy. Patients were identified through a list of ICD-9 codes provided by health information management. All patients receiving either rFVIIa or PCC (Bebulin VH, Baxter Healthcare Corporation, Westlake Village, California, USA) during the same time period were identified via pharmacy billing records and cross-referenced with patients obtained from the ICD-9 list. This study was approved by our institutional review board.

The primary objective was to compare the ability of PCC and rFVIIa to correct the INR to 1.3 or less. INR correction was determined by comparing the INR nearest to agent administration with subsequent INR values. Total dosages of vitamin K and FFP were collected for each patient. Secondary objectives included time until surgical intervention, incidence of hematoma expansion and thrombogenic complications, disposition, and length of stay. Time to surgical intervention was defined as time from agent administration to surgical incision. Patients having external ventricular drains as the only surgical procedure were excluded from this analysis. Thrombogenic complications were defined as deep-venous thrombosis, pulmonary embolism, myocardial infarction, ischemic stroke, or disseminated intravascular coagulation occurring at any time after agent administration. Discharge summaries, imaging studies, and consultant reports were evaluated for thrombogenic complications. Presence of hematoma expansion was determined from CT scans obtained within 48 hours of the initial scan. Statistical analysis was performed using the χ^2 or Fisher's exact tests for categorical data and the Student's *t* test for continuous data.

RESULTS

There were 465 patients with ICH admitted to our institution during the study period. A total of thirty-four patients received either