# Timing of Fresh Frozen Plasma Administration and Rapid Correction of Coagulopathy in Warfarin-Related Intracerebral Hemorrhage

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***Background and Purpose***—Anticoagulation-related intracerebral hemorrhage (ICH) is often fatal, and rapid reversal of anticoagulation is the most appealing strategy currently available for treatment. We sought to determine whether particular emergency department (ED) interventions are effective in reversing coagulopathy and improving outcome.

***Methods***—Consecutive patients with warfarin-related ICH presenting to an urban tertiary care hospital from 1998 to 2004 were prospectively captured in a database. ED records were retrospectively reviewed for dose and timing of fresh-frozen plasma (FFP) and vitamin K, as well as serial coagulation measures. After excluding patients with incomplete ED records, do-not-resuscitate orders established in the ED, initial international normalized ratio (INR) $\leq$1.4, and for whom no repeat INR was performed, 69 patients were available for analysis. The primary outcome was a documented INR $\leq$1.4 within 24 hours of ED presentation.

***Results***—Patients whose INR was successfully reversed within 24 hours had a shorter median time from diagnosis to first dose of FFP (90 minutes versus 210 minutes; $P=0.02$). In multivariable analysis, shorter time to vitamin K, as well as FFP, predicted INR correction. Every 30 minutes of delay in the first dose of FFP was associated with a 20% decreased odds of INR reversal within 24 hours (odds ratio, 0.8; 95% CI, 0.63 to 0.99). Dosing of FFP and vitamin K had no effect. No ED intervention was associated with improved clinical outcome.

***Conclusions***—Time to treatment is the most important determinant of 24-hour anticoagulation reversal. Although additional study is required to determine the clinical benefit of rapid reversal of anticoagulation, minimizing delays in FFP administration is a prudent first step in emergency management of warfarin-related ICH. (***Stroke*. 2006;37:151-155.)**

**Key Words:** anticoagulants ■ emergency medicine ■ intracerebral hemorrhage ■ warfarin

Intracerebral hemorrhage (ICH) is defined as bleeding into the brain parenchyma, which may extend into the ventricles and subarachnoid space. Spontaneous ICH accounts for 4% to 15% of cases of acute stroke but is the most fatal form of this disease.[1–6] Warfarin use increases both the risk of developing ICH[7–10] and its mortality.[1,11] The effect of warfarin on ICH severity appears to be related to an increased risk of continued in-hospital bleeding. When compared with ICH patients not on warfarin, patients on warfarin are at increased risk of hematoma expansion [odds ratio (OR), 6.2; 95% CI, 1.7 to 22.9].[6] Given the observed dose-response relationship between degree of elevation of the international normalized ratio (INR) and 3-month mortality,[1] intervention to decrease the INR is considered to be an important component of emergency management of warfarin-related ICH.

The acute phase of ICH, during which ongoing bleeding is most likely, generally occurs in the emergency department (ED). Management of ICH in the ED is, therefore, likely to be critical.[4] The volume of blood that extravasates from ruptured vessels is among the most important determinants of outcome.[11] This volume increases significantly in 18% to 38% of patients during the first 24 hours, indicating that ongoing bleeding is a common phenomenon in the ED.[12,13] For patients on warfarin, the risk of ongoing bleeding is over 50%.[6] Therefore, early intervention to minimize growth is likely to impact neurologic outcome. Indeed, the benefit of controlling ongoing bleeding in nonwarfarin-related ICH is supported by the results of a recent clinical trial of recombinant-activated factor VII.[14] Multiple guidelines suggest that patients diagnosed with warfarin-associated life–threatening hemorrhage, including ICH, receive emergent

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therapy to lower their INR.[15–17] There are 2 widely available interventions that accomplish this goal: clotting factor repletion and vitamin K.

We evaluated the effect of time to intervention on INR reduction in patients with warfarin-associated ICH. Interventions at our institution include fresh frozen plasma (FFP) and vitamin K, the standard treatments in our community. We hypothesized that higher doses and shorter times to initiation of therapy correlate with a higher rate of reversal of anticoagulation.

## Methods

### Study Design

This was a retrospective review of data collected as part of an ongoing prospective cohort study of ICH outcome.[1,18] Since 1994, consecutive patients with ICH presenting to Massachusetts General Hospital have been registered in a database and followed prospectively.[1] Patients are identified by systematic review of ED logs, hospital discharge diagnoses, and lists of all admissions to the neurology, neurosurgery, and internal medicine services.

### Study Setting and Population

We retrospectively reviewed ED management of consecutive patients with warfarin-associated ICH from January 1998 to June 2004. ICH was diagnosed on the basis of computed tomography (CT) scan obtained in the ED. Patients were excluded for age <18 years, lack of ED records, or if ICH was secondary to head trauma, ischemic stroke with hemorrhagic transformation, brain tumor, vascular malformation, or vasculitis. Do-not-resuscitate orders may be significant confounders in studies of ICH clinical care,[19,20] and patients with such orders, either preexisting or established in the ED, were excluded.

### Study Protocol

All aspects of the study were approved by the Institutional Review Board. Patients were prospectively characterized as described previously.[1] ICH volumes were determined from baseline CT scans as described previously.[6]

Chart review was performed by 1 physician and 2 research assistants; research assistants were trained in data abstraction, and 10 charts from each were reviewed with >95% interrater reliability. Data abstracted included initial Glasgow Coma Scale (GCS) score, initial INR, intubation status, time from presentation to initial CT scan, time from CT to first dose of FFP, total dose of FFP, and time from CT to vitamin K, as well as dose and route of administration and total time in the ED after diagnosis. Time from symptom onset to presentation was documented from the admission note or discharge summary. For patients who received no FFP or vitamin K in the ED, their doses were scored as zero, and times to treatment were scored as time in the ED after diagnosis plus 60 minutes to account for the minimum delay expected in initiating the administration of blood products once a patient was transferred from the ED to an intensive care unit. No patient received prothrombin complex concentrate or recombinant factor VIIa.

### Outcome Measures

The primary outcome was INR reversal within 24 hours. This time point was chosen based on previous studies[21–25] and the irregular frequency with which serial coagulation measures were performed, in order to minimize confounding by unmeasured factors that might influence the frequency of serial INR measures. Any documented follow-up INR ≤1.4 within 24 hours of arrival in the ED was scored as positive. Patients for whom no repeat INR was performed were excluded. Mortality and Glasgow Outcome Scale (GOS) score at 3 months were determined as described.[1] GOS score was chosen as a simple, highly reproducible scoring system for neurologic outcome that can be performed over the telephone with a high degree of inter-rater reliability.[26]

**TABLE 1. Patient Characteristics and Mortality**

| Characteristic | Proportion (n=69) | 90-Day Mortality (%) | OR (95% CI) |
|---|---|---|---|
| Sex | | | |
| Female | 46 | 41 | |
| Male | 53 | 54 | 1.7 (0.7 to 4.5) |
| Age | | | |
| ≤75 | 54 | 49 | |
| >75 | 46 | 47 | 0.9 (0.4 to 2.4) |
| Hypertension | | | |
| No | 15 | 60 | |
| Yes | 85 | 46 | 0.6 (0.1 to 2.2) |
| Diabetes | | | |
| No | 80 | 45 | |
| Yes | 20 | 46 | 1.0 (0.3 to 3.5) |
| Coronary artery disease | | | |
| No | 68 | 42 | |
| Yes | 32 | 55 | 1.7 (0.6 to 4.9) |
| Atrial fibrillation | | | |
| No | 33 | 36 | |
| Yes | 67 | 43 | 1.4 (0.4 to 5.1) |
| Any antiplatelet use | | | |
| No | 74 | 47 | |
| Yes | 26 | 47 | 1.0 (0.3 to 3.0) |
| Initial INR | | | |
| <2.0 | 12 | 37 | |
| 2.0 to 3.0 | 39 | 41 | |
| >3.0 | 49 | 56 | 1.6 (0.3 to 7.3) |
| Initial GCS | | | |
| >8 | 78 | 38 | |
| ≤8 | 22 | 79 | 6.0 (1.5 to 24) |
| Hematoma volume | | | |
| <30 mL | 53 | 36 | |
| 30 to 60 mL | 28 | 69 | |
| >60 mL | 19 | 89 | 6.0 (1.7 to 22) |
| Hemorrhage location | | | |
| Deep | 61 | 50 | |
| Lobar | 39 | 50 | 1.0 (0.4 to 2.8) |
| Time from symptom onset to presentation | | | |
| >4 h | 49 | 28 | |
| ≤4 h | 51 | 62 | 4.1 (1.5 to 11.6) |
| Transfer from outside hospital | | | |
| Yes | 47 | 48 | |
| No | 53 | 48 | 1.0 (0.4 to 2.6) |

### Data Analysis

Categorical variables were compared between groups using Fisher exact test for significance. The Kruskal-Wallis and Spearman rank correlation tests were used for continuous variables, which are

**TABLE 2. ED Management and Successful INR Reversal**

| | INR Reversed at 24 h | | |
|---|---|---|---|
| Characteristic | No (n=12) Median (25% to 75%) | Yes (n=57) Median (25% to 75%) | *P* Value |
| Door to CT time | 65 (30 to 90) min | 40 (25 to 85) min | 0.5 |
| CT to FFP time | 210 (100 to 375) min | 90 (60 to 205) min | 0.02 |
| Dose of FFP | 2 (1 to 5) units | 4 (2 to 6) units | 0.1 |
| CT to Vit. K time | 245 (37 to 361) min | 87 (25 to 210) min | 0.2 |
| Any Vit. K given | 58% | 81% | 0.1 |
| Dose of Vit. K | 7.5 (0 to 10) mg | 10 (5 to 10) mg | 0.5 |
| IV route | 0% | 30% | 0.2 |
| SC/IM route | 100% | 70% | 0.2 |
| Time in ED after CT | 242 (200 to 412) min | 227 (185 to 340) min | 0.3 |
| Intubated | 42% | 44% | 1.0 |

Continuous variables are presented as the median value with interquartile ranges; dichotomous variables are presented as proportions. Vit. indicates vitamin; IV, intravenous route of delivery; SC, subcutaneous route of delivery; IM, intramuscular route of delivery. No patient in this cohort received oral vitamin K.

represented in the tables as dichotomous variables with the breakpoint set at the group median for the purposes of convenient presentation. GOS score was analyzed first as an ordinal variable then dichotomized with scores of 4 to 5 representing "good" neurologic outcome and scores of 1 to 3 representing "poor" outcome.[1] Multivariable analysis for odds of INR reversal at 24 hours was performed by logistic regression controlling for initial severity of disease; variables included in the model were baseline INR, initial hematoma volume, initial GCS, and whether the patient was intubated. All of the analyses were performed with Stata software (Stata Corp).

## Results

Of 160 patients with primary warfarin–related ICH, 114 (71%) had ED records available. Of the patients excluded for missing ED records, 87% had been transferred from an outside hospital ED. Patients with missing records did not differ from those with intact records with regard to age, sex, comorbidities, or mortality. Thirty-eight patients were made do-not-resuscitate in the ED and were excluded. In addition, 2 of the remaining patients had a baseline INR ≤1.4, and 5 did not have a repeat INR drawn at any time, leaving 69 patients for analysis of INR reversal (Table 1). Among patients who knew their indication for warfarin use, 40% reported atrial fibrillation. Indications for the remaining patients were distributed among cerebrovascular, cardiovascular, and peripheral vascular disorders.

Table 1 shows the demographics for this cohort and 90-day mortality. Continuous variables were categorized for the purposes of presentation, but all of the statistics were performed on the original data set. Demographic features associated with increased mortality were low GCS score, large hematoma volume, and early time to presentation.

Median initial INR (interquartile range) was 3.0 (2.2 to 3.9). Median time to second INR was 300 (195 to 470) minutes, and median follow-up INR was 1.5 (1.4 to 1.7), with a median reduction in INR of 1.4 (0.7 to 2.3). The median number of INR measurements over the first 24 hours was 3

**TABLE 3. Demographic and Clinical Characteristics Associated With Time to Initial FFP Administration**

| Characteristic | Mean Time±SD (min) to FFP Administration | *P* Value |
|---|---|---|
| Age, y | | |
| ≤75 | 159±133 | |
| >75 | 146±124 | 0.6* |
| GCS | | |
| >8 | 153±114 | |
| ≤8 | 122±124 | 0.9* |
| Initial INR | | |
| <2 | 187±99 | |
| 2 to 3 | 156±148 | |
| >3 | 144±119 | 0.5* |
| ICH volume | | |
| <30 mL | 148±121 | |
| 30 to 60 mL | 168±133 | |
| >60 mL | 160±153 | 0.8* |
| ICH location | | |
| Lobar | 126±106 | |
| Deep | 188±159 | 0.2** |
| Time to ED | | |
| >4 h | 177±157 | |
| ≤4 h | 131±92 | 0.3* |
| Transferred | | |
| No | 113±96 | |
| Yes | 208±144 | 0.003** |
| Intubated | | |
| No | 156±133 | |
| Yes | 150±123 | 0.8** |
| Door to CT | | |
| <60 min | 136±112 | |
| ≥60 min | 179±149 | 0.4* |
| FFP dose | | |
| ≥4 units | 120±108 | |
| <4 units | 190±140 | <0.001* |
| Vit. K dose | | |
| ≥5 mg | 147±119 | |
| <5 mg | 170±153 | 0.7* |
| Vit. K route | | |
| IV | 109±101 | |
| SC, IM | 157±120 | 0.1** |
| CT to Vit. K | | |
| ≤100 min | 112±85 | |
| >100 min | 198±152 | <0.002* |

For convenience of presentation, continuous variables have been broken into dichotomous variables with the breakpoint set at the population median. Statistics were performed on the original continuous variables. Vit. indicates vitamin; IV, intravenous route of delivery; SC, subcutaneous route of delivery; IM, intramuscular route of delivery. *Spearman rank correlation test; **Kruskal-Wallis nonparametric test.

(2–4). Two patients with a documented INR ≤1.4 within 24 hours were noted to have an INR rise back above this threshold: 1 at 20 hours which was recorrected at 33 hours and 1 at 6 hours, which was recorrected by 10 hours.

Table 2 shows that of the ED interventions evaluated, only timing of FFP was associated with successful INR reversal. Median time to first dose of FFP was 90 (60 to 205) minutes for patients who had an INR ≤1.4 within 24 hours, and 210 (100 to 375) minutes in those who did not ($P=0.02$). No demographic or clinical characteristic, including referral from an outside hospital, predicted INR reversal (data not shown). A low initial INR was not associated with an increased likelihood of INR reversal ($P=0.3$). In addition, initial INR was not associated with FFP dose ($P=0.08$) or timing ($P=0.5$) or vitamin K dose ($P=0.1$) or timing ($P=0.2$).

We next analyzed determinants of prompt FFP administration. Time to FFP was associated with both dose of FFP and time to vitamin K (Table 3), suggesting that timing of FFP administration reflects more aggressive overall care. Multivariable analysis was performed to adjust for variables that reflect clinical severity of disease including GCS, initial INR, hematoma volume, and intubation status. Every 30-minute delay in FFP administration was independently associated with a 20% decrease in the probability of successful INR reversal within 24 hours (OR, 0.8; 95% CI, 0.63 to 0.99). Rapidity of administration of vitamin K had a similar independent effect in this model (OR, 0.8; 95% CI, 0.65 to 0.98). These results were not altered by inclusion of interhospital transfer or frequency with which serial INR assays were drawn (data not shown).

Finally, we examined whether earlier time to treatment is associated with improved clinical outcome (Table 4). Early time to treatment and successful INR reversal did not improve outcomes. On multivariable analysis, including GCS, initial INR, and hematoma volume, the only ED intervention that affected outcome was intubation, which was strongly associated with increased mortality ($P<0.001$).

## Discussion

Our data demonstrate that earlier administration of FFP increases the likelihood of successful 24-hour correction of coagulopathy after warfarin-related ICH. The effect of FFP administration was independent of markers of disease severity, suggesting that clinical presentation alone does not determine the timing of INR reversal strategies. The finding that time to vitamin K and time to FFP were strongly correlated suggests that these time markers reflect more aggressive care overall and that more aggressive care improves anticoagulation reversal.

We found strikingly long delays in both time to intervention and in time to INR correction and low frequencies with which serial coagulation measures were repeated. Most expert guidelines recommend rapid reversal of anticoagulation for ICH.[15,27] These findings have led to the dissemination of formal guidelines within our institution, as well as educational sessions regarding appropriate reversal strategies.

It was interesting to note that more rapid correction of the INR did not reduce morbidity or mortality. This likely reflects the reality that even those patients in our cohort who did achieve an INR ≤1.4 within 24 hours were nonetheless not reversed quickly enough to alter outcome. Improving outcome probably requires ultra-early reversal of coagulopathy. Such intervention requires not only rapid ED respond time, but that patients arrive as quickly as possible after symptom onset, a continued challenge in the care of stroke patients.[28] Patients in our cohort presented a median of 4 hours after symptom onset, and most may have presented too late in the course of their disease for treatment to influence outcome. In addition, the time to anticoagulation reversal may be too slow with both vitamin K and with FFP. Future studies may include more rapid acting agents; although preliminary work suggests a benefit of recombinant activated factor VII in nonwarfarin-related ICH,[14,29] its efficacy and risks in warfarin-related ICH[30] remain to be clarified. In addition, the use of more sensitive measures of neurologic outcome (such as National Institutes of Health Stroke Scale Score) at specified time points may detect subtle improvements in morbidity that we could not evaluate here.

Our study has several limitations. The most important is its retrospective design. Care was not standardized across the cohort, and the timing of serial coagulation measures was irregular and determined by physician choice. In addition, we were not able to measure potential determinants of time to FFP administration related to physician practice. It remains

**TABLE 4. ED Interventions and Outcomes**

| | Alive at 90 Days | | GOS Score at 90 Days | |
|---|---|---|---|---|
| Characteristic | Yes | No | Good | Poor |
| CT to FFP (min) | 105 (65 to 260) | 85 (60 to 210) | 97 (60 to 210) | 110 (72 to 255) |
| Dose FFP (units) | 3 (2 to 6) | 4 (2 to 6) | 2 (2 to 6) | 3 (1 to 4) |
| Door to CT (min) | 45 (30 to 90) | 42 (25 to 75) | 45 (20 to 80) | 60 (33 to 97.5) |
| CT to vitamin K (min) | 120 (35 to 240) | 55 (20 to 226) | 135 (45 to 245) | 90 (30 to 226) |
| Dose of vitamin K (mg) | 10 (1 to 10) | 10 (5 to 10) | 10 (1 to 10) | 10 (5 to 10) |
| Vitamin K given IV | 22% | 31% | 25% | 23% |
| 24 hour INR reversal | 83% | 82% | 60% | 82% |
| Time to disposition (min) | 230 (190 to 390) | 235 (180 to 350) | 230 (185 to 420) | 240 (195 to 320) |
| Intubated | 17% | 73%* | 10% | 64%** |

Continuous variables are presented as the median (interquartile range). *$P<0.001$; **$P<0.002$.

possible that unmeasured practice variation may play an important role in the correction of coagulopathy. Future prospective trials with standardized protocols will be necessary to better control for any potential confounders.

Overall, our study demonstrates that prompt intervention improves INR reversal in acute warfarin–related ICH. Whereas no mortality benefit was detected, the established relationship between the degree of anticoagulation and both hematoma growth and mortality in warfarin-related ICH imply that emergent reversal should be the cornerstone of ED management strategies. We recommend that formal pathways be put in place to standardize the rapid use of warfarin reversal agents in ICH (the protocol for our institution, instituted after the completion of the present analysis, can be found online at http://www.stopstroke.org). This may minimize the effect of provider team or other unmeasured factors on aggressiveness of treatment.

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