The Effect of Warfarin and Intensity of Anticoagulation on Outcome of Intracerebral Hemorrhage

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Background: Warfarin sodium is highly effective for prevention of embolic stroke, particularly in nonvalvular atrial fibrillation, but its expected benefit can be offset by risk of intracerebral hemorrhage (ICH). We studied the determinants of ICH outcome to quantify the independent effect of warfarin.

Methods: Consecutive patients with supratentorial ICH treated in a tertiary care hospital with a neurointensive care unit were prospectively identified during a 7-year period, and data on hemorrhage location, clinical characteristics, and warfarin use were collected. Independent predictors of 3-month mortality were determined using multiple logistic regression analysis.

Results: Of 435 consecutive patients aged 55 years or older, 102 (23.4%) were taking warfarin at the time of ICH. Three-month mortality was 25.8% for those not taking warfarin and 52.0% for those taking warfarin. Independent predictors of death were warfarin use (odds ratio [OR], 2.2; 95% confidence interval [CI], 1.3-3.8), age 70 years or older (OR, 2.4; 95% CI, 1.4-4.0), and presence of diabetes mellitus (OR, 1.8; 95% CI, 1.0-3.3). Although 68.0% of all warfarin-related hemorrhages occurred at an international normalized ratio (INR) of 3.0 or less, increasing degrees of anticoagulation were strongly associated with increasing risk of death compared with no warfarin use.

Conclusions: Patients taking warfarin had a doubling in the rate of intracerebral hemorrhage mortality in a dose-dependent manner. The data suggest that careful control of the INR, already known to limit the risk of warfarin-related ICH, may also limit its severity.

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(hemorrhage originating in the lobes or the deep structures of the cerebral hemispheres) who presented to the Massachusetts General Hospital (MGH) emergency department (ED). Patients with ICH located in the brainstem and cerebellum were not included in our cohort. During the study, we systematically reviewed ED logs and lists of all admissions to the neurology, neurosurgery, and internal medicine services. In addition, we performed a retrospective review of ED and hospital discharge diagnoses several times per year to identify any missed subjects. Patients with secondary causes of ICH, including antecedent head trauma, acute ischemic stroke with hemorrhagic transformation, brain tumor, vascular malformation, or vasculitis of the central nervous system, were excluded. All aspects of this study were approved by the institutional review board.

Among 501 patients with ICH identified, 60 had hemorrhages located in the brainstem or cerebellum, 4 had primary intraventricular hemorrhage, and 2 had uncertain warfarin use status. The remaining 435 patients formed the study cohort. We categorized patients in 2 groups for separate analysis: those who presented directly to the MGH ED and those who were transferred to the MGH ED after brief evaluation in a community hospital ED. Of the 435 patients in the cohort, 203 (46.7%) were admitted directly and 232 (53.3%) were admitted after transfer from a referring ED. Directly admitted patients were older than transferred patients (mean±SD age, 75.6±9.2 vs 73.2±9.2 years) but otherwise did not differ with regard to clinical features, including diabetes mellitus, coronary artery disease, hypertension, use of warfarin, use of an antiplatelet agent, ICH location, 3-month mortality, and functional outcome. We therefore pooled these 2 groups for all further analyses.

All 435 patients received computed tomographic scans of the brain on admission to the MGH ED. Hemorrhages were prospectively classified as lobar or deep hemispheric on the basis of the computed tomographic scan by one of the study neurologists without knowledge of clinical outcome. Hemorrhages centered in the subcortical white matter of the frontal, parietal, temporal, or occipital lobes were defined as lobar. Hemorrhages in the thalamus and basal ganglia were identified as deep hemispheric. Patients with primary intraventricular hemorrhage were not included in the study cohort.

All subjects or their family informants were interviewed in the MGH ED by a neurologist or neurosurgeon who obtained clinical data on medications, indication for warfarin use, and features of the medical history. In addition, we systematically reviewed the medical records of all subjects after death or discharge. Hemorrhages were categorized as warfarin-related if warfarin was reported as a regularly ingested medication. The intensity of anticoagulation, recorded as the international normalized ratio (INR) of the prothrombin time, was the value determined in the ED on presentation. For those patients initially evaluated at a referring hospital, the INR recorded is the value determined in the referring ED before the administration of therapy. Patients were identified as hypertensive on the basis of clinical history or if they required antihypertensive therapy at least 2 weeks after the onset of ICH.

Coronary artery disease was defined by history of coronary artery disease, angina, or myocardial infarction. Diabetes mellitus was defined by history of the diagnosis or by regular use of insulin or an oral hypoglycemic agent.

The primary outcome was death assessed 3 months after ICH onset. Of the 139 patients who were dead at 3 months, 111 (79.9%) died during the hospitalization for their ICH. Of the remaining 28 patients who died, 11 were identified through follow-up telephone calls to family members, 9 through review of the medical record, and 8 through a search of the Social Security Death Index, a database updated weekly containing vital information for individuals whose deaths were reported to the US Social Security Administration.21.22 We used the Social Security Death Index to confirm vital status of all patients at 3 months.

As a secondary analysis, we examined functional outcome among survivors using the 3-month Glasgow Outcome Scale (GOS), a 3-point scale (1 indicates dead; 2, persistent vegetative state; 3, severe disability; 4, moderate disability; and 5, recovery of normal premorbid activities).23,24 Good outcome was defined as independence in activities of daily living (GOS, >3). There were no survivors in persistent vegetative state (GOS, 2). Glasgow Outcome Scale score at 3 months was determined from systematic telephone interview and medical chart review for 204 survivors and at discharge from review of hospital records in an additional 87 for whom 3-month follow-up information was unavailable. We thus were able to determine GOS score in 291 (98.0%) of 297 survivors.

**STATISTICAL ANALYSIS**

Categorical variables were compared between groups using Fisher exact test for significance. Age was first analyzed as a continuous variable and subsequently as dichotomous (age, <70 vs ≥70 years). International normalized ratio was grouped into 3 categories according to clinically meaningful cutpoints (<2.0, 2.0-3.0, and >3.0). Association between mortality and INR was determined using the Mantel-Haenszel χ² test for trend. Multivariate analysis for odds of 3-month mortality from ICH was performed by multiple logistic regression analysis, controlling for ICH location, factors found to be associated (P<.10) with mortality in univariate analysis, sex, use of an antiplatelet agent, and factors associated with warfarin use. In this analysis, a categorical variable with no warfarin use and 3 levels of INR range (using the 3 INR cutoffs) was included in the model. The overall effect of warfarin use was then estimated from the model by taking the mean of the 3 levels of INR range, using contrast rows estimation. A 2-tailed P=.05 was required for significance. Except for the multivariate model, which was analyzed using SAS software (SAS Institute, Cary, NC), all analyses were performed with Stata software (Stata Corp, College Station, Tex).

Of the 435 consecutive patients aged 55 years or older with deep hemispheric and lobar ICH, 102 (23.4%) were taking warfarin at the time of their ICH, 138 (31.7%) were taking an antiplatelet agent, and 22 (5.1%) were taking both. The mean±SD age was 74.7±9.3 years. There were 194 patients (44.6%) with deep ICH and 241 (55.4%) with lobar ICH. The mean±SD age of patients with deep ICH was younger than that of patients with lobar ICH (72.7±9.9 vs 75.7±8.6, P<.01). Three-month mortality was 31.7% for the entire cohort. Significant predictors of 3-month mortality in univariate analysis included use of warfarin, advanced age, lobar location, diabetes mellitus, and coronary artery disease (Table 1). For patients taking warfarin, increasing intensity of anticoagulation was strongly associated with increasing risk of death (P<.01 for trend).

Use of an antiplatelet agent had no apparent effect on mortality (Table 1). In patients not taking warfarin, mortality for users and nonusers of an antiplatelet agent at the time of hemorrhage was 25.9% and 25.2%, respectively (odds ratio, 1.0; 95% confidence interval, 0.6-1.5). Mortality in the subgroup taking warfarin and an antiplatelet agent was higher compared with that in pa-
patients taking warfarin alone (59.1% vs 48.1%; odds ratio, 1.5; 95% confidence interval, 1.0-2.6) but the difference was not significant.

We compared the characteristics of those taking warfarin vs those not taking warfarin. The mean ± SD age for the warfarin group was slightly older than that of the non–warfarin group (75.7 ± 8.4 vs 74.0 ± 9.6 years, P = .11). Proportions of deep hemispheric ICH and lobar ICH were similar among those with warfarin-associated (42.2% vs 57.8%) vs non–warfarin-associated (45.4% vs 54.7%) hemorraghes. Clinical characteristics significantly associated with warfarin use included presence of diabetes mellitus (28.0% in the warfarin subgroup vs 13.6% in the subgroup not taking warfarin), coronary artery disease (41.0% vs 20.2%), and hypertension (80.2% vs 67.0%). The primary indication for warfarin use was atrial fibrillation in 49.5% of patients. Indications for the remaining patients were distributed among cerebrovascular, cardiovascular, and peripheral vascular disorders.

In multivariate analysis (Table 2), warfarin use, age, and diabetes mellitus status remained significant predictors of mortality at 3 months. Increasing INR among patients taking warfarin independently predicted fatal outcome. Intracerebral hemorrhage location, sex, and concurrent use of an antiplatelet agent did not affect mortality. Controlling for comorbid conditions associated with warfarin use, including diabetes mellitus, hypertension, coronary artery disease, and atrial fibrillation, did not alter these results. Furthermore, adding terms for interaction between warfarin use and use of an antiplatelet agent, presence of hypertension, or coronary artery disease status did not alter the results of the analysis. In contrast to the effect of warfarin on mortality, secondary analysis suggested a small, if any, effect of warfarin on functional outcome among patients who survived their ICH (Figure). Among survivors of warfarin-ICH, 34.7% achieved a good clinical outcome, ie, GOS score greater than 3, compared with 42.3% of survivors of ICH unrelated to warfarin use. In multivariate analysis controlling for hemorrhage location, sex, warfarin use, antiplatelet use, diabetes mellitus, hypertension, and coronary artery disease, only age independently predicted poor clinical outcome among survivors, ie, GOS score less than 4 (odds ratio for age ≥ 70 years, 4.2; 95% confidence interval, 2.5-7.4; P < .01).

Our results indicate that warfarin use increases risk of death from ICH and that intensity of anticoagulation independently predicts 3-month mortality for patients with warfarin-ICH. Although warfarin even at the most commonly used therapeutic levels of anticoagulation (INR,
2.0-3.0) appears to increase risk of fatal outcome, our data indicate that this risk rises further as the INR increases. Careful control of the INR may therefore reduce not only the risk of developing ICH but also the mortality of those hemorrhages that occur. In addition, the link between intensity of anticoagulation and clinical outcome may support the possibility that rapid reversal of warfarin effect through emergency administration of vitamin K, fresh frozen plasma, or clotting factor concentrates may improve the otherwise dismal outcome of warfarin-ICH.

A plausible mechanism for the increased mortality associated with high INR is the generation of greater hematoma volumes. A recent study has found that increased hemorrhage size predicted outcome in warfarin-ICH. Furthermore, some studies comparing patients with warfarin-ICH with those with non-warfarin-ICH have found increased hematoma volumes in the warfarin group. The exact relationship between intensity of anticoagulation and hematoma volume, arguably the most powerful predictor of outcome in ICH, remains controversial. Some investigations have suggested a correlation, while others have not. Future studies will be needed to assess the correlation of INR elevation with hematoma volume and expansion.

The role of age in predicting outcome from ICH may reflect the fact that the neurologic injury caused by ICH is worse in older persons or that capacity for recovery is more limited. Alternatively, it may reflect the consequences of attenuated aggressiveness of care for older patients with ICH. Age also determines risk of cerebral amyloid angiopathy, an important cause of spontaneous ICH and warfarin-ICH in lobar brain regions. This is the likely explanation for the observation that patients with lobar hemorrhage were on average older than those with deep hemorrhage in our cohort. Because cerebral amyloid angiopathy can affect cerebral vessels in a wide distribution, it may play a role in impairing regenerative capacity after ICH. Despite the plausibility of these potential mechanisms, there remains controversy over the degree to which age determines prognosis from ICH. Among previously published smaller studies, advanced age has been identified as an independent risk factor for poor outcome in some but not others.

The presence of diabetes mellitus also independently predicted death in our cohort. Although it has not been linked as an independent risk factor for the development of ICH, diabetes mellitus has indeed been previously identified as a marker for increased ICH mortality. One possible explanation is that persons with diabetes mellitus are more likely to be hyperglycemic on presentation. Known to worsen ischemic brain damage and to predict worse outcome in patients with stroke, hyperglycemia has also been implicated as a contributor to poor outcome in a wider range of brain injuries.

Lobar ICH has traditionally been viewed as less devastating than deep hemispheric hemorrhage. The differences we observed in mortality rates between patients with lobar and deep hemispheric hemorrhage suggest that this may not be the case. Mortality rates, however, reflect factors other than hemorrhage location, such as hematoma volume, displacement of midline structures, ventricular extension, and cause of hemorrhage. A more detailed analysis of the ICH characteristics of our cohort will therefore be necessary to investigate whether there may be important underlying explanations for the trend toward increased lobar ICH mortality that we observed. Nonetheless, when applied to the decision to anticoagulate patients at risk for lobar hemorrhage, an important implication of our data is that outcome from lobar ICH appears to be no better than that associated with deep hemorrhage.

There are important limitations to the present study. Any study of prognosis is susceptible to unmeasured confounding when care is not standardized throughout the cohort. Nonetheless, all patients in this study received treatment within a single tertiary care center with an active neurological intensive care unit, assuring some degree of consistency. One potentially powerful confounder is withdrawal of support for the sickest or oldest patients. Although it is unlikely that the INR on presentation might have affected the likelihood of withdrawal of support, this possibility requires further investigation. In addition, because of the nonrandomized nature of warfarin allocation, it is possible that the effect of warfarin use on mortality may have been confounded by the treatment indication for warfarin. Although adjustment for warfarin indication and for warfarin-associated comorbidities did not alter the independent effect of warfarin on fatal outcome, the possibility remains that unmeasured comorbidities associated with warfarin use may have confounded our analysis. We attempted to minimize loss to follow-up for our primary end point by relying on the Social Security Death Index to confirm vital status, thereby accounting for 98.6% of survivors at discharge or at 3 months. Data for our secondary end point, functional outcome at 3 months, however, were incomplete. For those lost to follow-up, we used the GOS score measured at the time of discharge as a substitute. Because of the possibility that patients improve between discharge and 3 months, we may have underestimated the functional outcome in this group of patients.

Our data confirm the devastating effect of warfarin use on ICH outcome and suggest that rapid correction of coagulopathy may be of benefit in the severe setting. In addition, these results can play a role in clinical decision making for patients being considered for warfarin therapy. The outcome data in the present study provide empiric information necessary for the development of decision-analysis models that can be used to evaluate various clinical scenarios involving anticoagulation, such as whether to offer anticoagulant therapy to ICH survivors who are at high risk for thromboembolic stroke.

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