Individual Characteristics and Management Decisions Affect Outcome of Anticoagulated Patients with Intracranial Hemorrhage

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Key words
- Anticoagulation
- Central nervous system
- Complication
- Hemorrhage
- Optimization
- Outcome
- Stroke
- Thrombosis

Abbreviations and Acronyms
AC: Anticoagulation, anticoagulant
CNS: Central nervous system
GOS: Glasgow outcome scale
ICH: Intracerebral hemorrhage
LMWH: Low molecular weight heparin
TE: Thromboembolic, thromboembolism

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BACKGROUND: **Anticoagulated patients with intracranial hemorrhage represent a major management challenge. Our goal is to determine how patient characteristics and management decisions influence outcome.**

METHODS: **A systematic review of the literature identified relevant reported cases. Variables describing patient characteristics, management, and outcome were extracted. Statistical analyses were carried out using analysis of variance and Fisher's exact test.**

RESULTS: **A total of 242 patients from our updated dataset met inclusion criteria. Tissue plane of the hemorrhage ($P < 0.0001$), indication for anticoagulation ($P < 0.0001$), type of anticoagulant ($P = 0.0173$), and history of hypertension ($P = 0.0418$) were significantly associated with outcome. Older age ($P < 0.0001$), supratentorial index hemorrhages ($P = 0.0018$), failure to restart anticoagulation ($P < 0.0001$), and larger hematoma volume ($P < 0.0001$) were associated with worse outcome. Surgical evacuation was associated with improved outcome ($P = 0.0011$). There was a trend toward an association between the occurrence of a hemorrhagic or thromboembolic complication and risk of death ($P = 0.0882$). Sex and sidedness of the index hemorrhage were not significantly associated with outcome.**

CONCLUSIONS: **Our results provide prognostic information that may assist management of these patients. Our results also suggest that it may be unwise to withhold anticoagulation indefinitely after an index hemorrhage. As thromboembolic or hemorrhagic complications may be associated with worse outcome, efforts to avoid them may be wise. The studies that comprise our dataset have important limitations and a prospective study will be required to confirm these results.**

INTRODUCTION

Patients who present with central nervous system (CNS) hemorrhage complicating anticoagulant (AC) therapy are challenging to manage. These patients are at risk for progression or recurrence of their hemorrhage as well as thromboembolism (TE), either of which can have devastating consequences (35). In addition, aside from AC reversal and supportive management, no safe and effective therapy exists to treat this most highly morbid form of stroke (10, 37). Although such patients are frequently encountered (19), they have been subject to little study, likely because of their marked heterogeneity (18), as well as their high case fatality (9).

To inform decisions surrounding the management of these patients, we generated a dataset comprised of individual patient data extracted from relevant publications identified in a systematic review of the literature (18). Our initial work sought to identify an optimal timing and intensity for AC resumption, as well as a basis for individualizing therapy. We characterized the timing of hemorrhagic and TE complications subsequent to the first—or index—hemorrhage. We additionally identified predictors of these events. We found that hemorrhagic and TE complications occur with approximately equal frequency but that their temporal risks differ—hemorrhagic complications were more likely to occur within 24 hours of the index hemorrhage, whereas TE risk was highest 3 to 5 days after medical presentation, suggesting that 72 hours *may* be an optimal time to resume anticoagulant therapy for many patients.

Much remains, however, to be learned about decision making in these patients. One such controversy is whether AC should be restarted after an AC-related intracerebral hemorrhage (ICH) and if so, at what intensity (12). Also, the morbidity of hemorrhagic and TE complications subsequent to an index hemorrhage is unknown and it is unclear whether efforts to avoid them are justified (9). The relative morbidity of hemorrhagic and TE complications is unknown and it is possible that one should be avoided preferentially. Our

analysis has thus been performed with the goal of informing these issues. Improved understanding of how management decisions and patient characteristics influence outcome may assist in caring for patients with anticoagulant-related ICH.

METHODS

Database

Generation of our database has been previously described in detail (18). Briefly, patient data were extracted from publications identified in MEDLINE and EMBASE searches. These studies included reports of CNS hemorrhages that occurred while on AC (warfarin, heparin, or low molecular weight heparin [LMWH] with or without antiplatelet, but not antiplatelet therapy alone). Cases were included if the hemorrhage occurred in, or immediately adjacent to, the CNS and where computerized tomography or magnetic resonance imaging was used for diagnosis. Studies were excluded if there was doubt that hemorrhagic or thromboembolic complications after the initial hemorrhage would be reported. In addition, pregnant patients, those with infective endocarditis, or hemorrhagic transformation of an infarct were excluded when they could be identified. Three reviewers screened articles and extracted data regarding patient characteristics and management decisions. Collected variables included age, sex, location (supratentorial or infratentorial), sidedness (left, right, or bilateral), history of chronic hypertension, indication for anticoagulation (cardiac, deep venous thrombosis and/or pulmonary embolism, ischemic heart disease, cerebrovascular disease, multiple indications, or other), tissue plane of hemorrhage (intraventricular, intraparenchymal, subarachnoid, subdural, epidural, or multiple tissue planes), anticoagulation intensity at the time of the index hemorrhage (therapeutic, supratherapeutic, or subtherapeutic as defined in the source publication), anticoagulation type (heparinoids including unfractionated heparin and low-molecular weight heparin, warfarin or warfarin with an antiplatelet), presence of a hemorrhagic or thromboembolic complication after the index hemorrhage, whether AC was reversed at presentation, and the final intensity of anticoagulation after resumption (classed as no anticoagulation restart, the same intensity as before the index hemorrhage, or a lower intensity than preceding the index hemorrhage) that often differed from the intensity initially used on anticoagulation restart. The timing of AC restart was also recorded and grouped as early ($\leq$72 hours from the index hemorrhage) or late (>72 hours).

The dataset used for this study differs from the one used in our previous publication (18) in several respects. We updated our literature search, capturing an additional 2 years of studies meeting inclusion/exclusion criteria (completed February 22, 2011) leading to inclusion of five additional studies. For one of these studies (Goldstein et al., 17) the investigators provided us with the dataset of individual patient data used in their study. We also collected Glasgow outcome scale (GOS) scores for all patients where they were reported. The score most remote from the index hemorrhage was recorded. When not reported they could sometimes be computed in accordance with published criteria (20, 34). Patients without reported GOS scores were excluded from this analysis; in some cases GOS scores were available for only a subset of reported cases within a publication. Because GOS scores are not valid for patients with spinal cord deficits, patients with spinal index hemorrhages were excluded from this analysis. Also, because of the prognostic importance of hematoma volume and the rarity of reporting in our source literature, we contacted investigators of all studies included in our work requesting data on hematoma volume (22). Patients with ICHs resulting from traumatic causes were also excluded because of probable differences in their natural history.

Statistical Analysis

SAS version 9.2 (SAS Institute Inc., Cary, North Carolina, USA) was used for statistical analysis. Data analyses were performed using Fisher's exact test and analysis of variance with subsequent Bonferroni's correction for multiple comparisons.

RESULTS

Characteristics of Analyzed Patients

A total of 242 patients from 34 publications were included in the dataset used for our analysis. Characteristics of included studies are reported in Table 1 and the characteristics of the analyzed patients are reported in Table 2. Two pediatric patients anticoagulated for aortic valve replacements were included in the analysis.

Patient and Hemorrhage Characteristics as Predictors of Outcome

Significant predictors of outcome in univariate analysis included age ($P < 0.0001$), indication for AC ($P < 0.0001$), tissue plane of the index hemorrhage ($P < 0.0001$), hematoma volume ($P < 0.0001$), intracranial compartment of the index hemorrhage ($P = 0.0018$), and history of hypertension ($P = 0.0418$) (Figures 1 and 2). For these variables, worse outcome was associated with older age, a cerebrovascular indication for AC, larger hematoma volume, and supratentorial index hemorrhage. History of hypertension was associated with an increased risk of severe disability and decreased risk of mortality. With respect to tissue plane, subdural hemorrhages were associated with more favorable outcomes, whereas those with an index hemorrhage in multiple planes had poorer outcome. Although intraventricular hemorrhage would appear to have a favorable prognosis, this finding was based on a single case, preventing such a conclusion from being drawn. AC intensity on presentation was nearly significant as a predictor of poorer outcome ($P = 0.162$), with less favorable outcomes seen in those who presented with supratherapeutic AC levels at the time of their index hemorrhage (Figure 1). Sex ($P = 0.625$) and sidedness of the index hemorrhage ($P = 0.6664$) were not significantly associated with outcome. Considering all GOS classes, hemorrhagic or TE complications subsequent to the index hemorrhage did not affect outcome ($P = 0.4431$); however, the association between such complications and death was nearly significant ($P = 0.0882$) (Figure 3). There was no statistical evidence that TE or hemorrhagic complications differed in their morbidity ($P = 0.3299$) when we compared GOS scores for patients experiencing these complications using univariate analysis.

Management Decisions as Predictors of Outcome

In univariate analysis, outcome was significantly predicted by final AC intensity after resumption ($P < 0.0001$), surgical management ($P = 0.0011$), AC reversal