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Warfarin-associated intracerebral hemorrhage: Volume, anticoagulation intensity and location

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ABSTRACT

Background: Warfarin use increases mortality in patients with intracerebral hemorrhage (ICH). Larger hematoma volume and infratentorial location are both major determinants of poor outcome in ICH. Although warfarin-associated intracerebral hemorrhages have greater volumes, there is uncertainty about the effects of location. We aimed to investigate the influence of warfarin on hematoma volume and location.

Methods: We conducted a retrospective study of all patients hospitalized for ICH at a large stroke center from October 2007 to January 2012. Initial CT scans were used to quantify hematoma volumes using the computer-assisted planimetric analysis. Univariate and multivariable analyses determined the influence of warfarin on hemorrhage location. Median regression analysis was performed to estimate the effects of INR on hematoma volumes.

Results: We included 404 consecutive patients with ICH of whom 69 were on warfarin. Patients on warfarin had larger hematoma volumes (median 23.9 mL vs. 14.2 mL; $P = 0.046$). In patients excessively anticoagulated with warfarin (defined as INR > 3.0), compared with those in the therapeutic range, brainstem ICH was more frequent (24.0% vs. 6.1%; $P = 0.005$). Patients with INR > 3.0 had increased odds of infratentorial hemorrhage (OR 3.63; 95% CI 1.52–8.64; $P = 0.004$) when compared to non-warfarin ICH patients. After adjustment for hematoma location, there was no significant association between INR and hematoma volume.

Conclusions: Patients with warfarin-associated ICH have a predilection for brainstem ICH. After adjustment for ICH location, no relationship between admission INR and hematoma volume was found.

1. Introduction

Warfarin-associated ICH is a major clinical problem, more common than subarachnoid hemorrhage in the United States [1]. The use of warfarin to prevent atrial fibrillation-related stroke is increasing with aging populations and better recognition [2–4]. Oral anticoagulant therapy (OAT) not only increases the risk of intracerebral hemorrhage (ICH) [5], but also worsens the severity of ICH in a dose-dependent manner [6]. The underlying mechanism by which warfarin worsens ICH prognosis has not been well established.

Larger baseline hematoma volume and infratentorial location are two major determinants of poor outcome in spontaneous ICH [7,8]. Given that the risk of ICH increases significantly with increasing international normalized ratio (INR) in patients taking warfarin [9], it is possible that intense anticoagulation may affect the size of ICH. However, previous studies have reported conflicting results on the effect of warfarin on hematoma volume [10–13]. In addition, the correlation of anticoagulant therapy and hematoma location is controversial [14–17]. Some studies have suggested a higher proportion of lobar and thalamic location [10,17], but others reported a higher rate of cerebellar hemorrhage [14–16]. It follows that the relationship of OAT with hematoma volume and location remains unresolved.

The aim of the present study was to investigate in ICH patients whether higher INR values are associated with larger baseline hematoma volumes, and to determine the relationship between warfarin therapy and hematoma location.

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2. Methods

2.1. Study population

The study protocol was approved by the human research ethics committee of the Royal Melbourne Hospital. We identified all subjects aged ≥18 years who were hospitalized with ICH between October 1, 2007 and January 31, 2012 at this hospital. All potential cases were extracted from our prospective stroke database. Exclusion criteria were traumatic ICH, hemorrhagic transformation of cerebral infarction, ICH secondary to vascular malformation, aneurysm, vasculitis of the central nervous system, and recent endarterectomy. In addition, we excluded patients with primary intraventricular hemorrhage (IVH), liver cirrhosis, and those with missing INR values or CT scans on admission.

Patient demographics and putative risk factors, such as sex, age, hypertension, diabetes mellitus, atrial fibrillation, hypercholesterolemia, ischemic heart disease, previous transient ischemic attack (TIA) or stroke, and pre-ICH medications were abstracted from the stroke database and complemented by a chart review. Pre-ICH modified Rankin Scale (mRS), Glasgow Coma Scale (GCS) at presentation, mRS at discharge, and in-hospital mortality were retrieved. All presentations were within 7 days of symptom onset, including interhospital transfers. The initial baseline brain CT scans and INR values were evaluated. For warfarin-related ICH patients, initial INR values obtained before reversal were used for the analysis. Patients were both dichotomized by warfarin use and stratified by the level of anticoagulation (non-warfarin, warfarin therapy with INR < 2.0, 2.0–3.0, >3.0).

2.2. Neuroimaging analyses

All CT scans were reviewed and evaluated in consensus by two experienced neurologists (M.M, B.Y.) who were blinded to the patient's clinical status. The ICH and IVH volumes were determined from available CT scans. Images were transmitted digitally in DICOM format to a workstation and analyzed with the Analyze 10.0 software (Mayo Clinic, Rochester, MN). ICH and IVH were defined and outlined separately by using the tracing tools in the region of interest module from the Analyze software for planimetric volume calculation. Intraventricular blood was not included in the volume calculation. The hematoma location was categorized into lobar (with or without involvement of subcortical white matter), deep (basal ganglia, thalamus, internal capsule), cerebellum and brainstem. Location was also dichotomized into supra- and infratentorial site.

2.3. Statistical analysis

Continuous variables and categorical variables were compared using the Mann–Whitney rank-sum test and Fisher exact test as appropriate. The association between the baseline INR category and hematoma location was determined using multiple logistic regression analysis, including the factors that were found to be associated with ICH location in univariate analysis ($P < 0.20$). The following factors were considered: age, hypertension, hyperlipidemia, diabetes, and ischemic heart disease. Spearman rank correlation was estimated to determine the association between the baseline INR and hematoma volume for each ICH location category. Due to nonparametric hematoma volume distributions, median regression analysis was used to estimate the effects of INR on hematoma volumes, adjusted for the ICH location. Statistical analyses were performed using Stata/IC software package, version 12.0 (StataCorp, College Station, TX). All P values are 2-tailed; $P < 0.05$ was considered significant.

3. Results

There were 553 ICH patients treated at our hospital from October 1, 2007 to January 31, 2012. Of these, 28 were excluded due to secondary ICH, 12 due to primary IVH, 68 due to unavailable baseline CT scans or CT films unfit for computerized image analysis, and 47 due to missing initial INR values, leaving a study population of 404. Baseline characteristics of the study patients are described in Table 1.

The median age of the cohort was 74 years (interquartile range [IQR] 63 to 81), 58.9% of patients were male, and 17.1% (69/404) were taking warfarin at the time of their ICH. Patients on warfarin were older and more frequently had diabetes, ischemic heart disease, atrial fibrillation, and previous acute ischemic stroke. Patients on

Table 1
Baseline clinical characteristics of patients.

	All patients (n = 404)	Warfarin (n = 69)	Non-warfarin (n = 335)	*P* value
Male, no. (%)	238 (58.9)	43 (62.3)	195 (58.2)	0.527
Age, y (median, IQR)	74 (63–81)	77 (69–82)	73 (62–81)	0.031
Hypertension, no. (%)	297 (73.5)	48 (69.6)	249 (74.3)	0.414
Diabetes, no. (%)	88 (21.8)	24 (34.8)	64 (19.1)	0.004
IHD, no. (%)	69 (17.1)	26 (37.7)	43 (12.8)	<0.001
AF, no. (%)	75 (18.6)	52 (75.4)	23 (6.9)	<0.001
Hyperlipidemia, no. (%)	114 (28.2)	21 (30.4)	93 (27.8)	0.653
Previous AIS, no. (%)	39 (9.7)	15 (21.7)	24 (7.2)	<0.001
Previous TIA, no. (%)	17 (3.5)	5 (7.2)	12 (3.6)	0.185
Previous ICH, no. (%)	28 (6.9)	3 (4.3)	25 (7.5)	0.445
Preadmission statin use, no. (%)	110 (27.2)	25 (36.2)	85 (25.4)	0.065
Preadmission antiplatelet use, no. (%)	143 (35.4)	17 (24.6)	126 (37.6)	0.040
Pre-ICH mRS 3–5, no. (%)	110 (27.2)	20 (29.0)	90 (26.9)	0.629
Admission GCS (median, IQR)	14 (10–15)	13 (7–14)	14 (10–15)	0.029
Admission INR (median, IQR)	1.1(1.0–1.2)	2.6 (2.2–3.5)	1.1 (1.0–1.1)	<0.001
INR < 2.0, no. (%)	345 (85.4)	10 (14.5)	335 (100)	<0.001
INR 2.0–3.0, no. (%)	34 (8.4)	34 (49.3)	0	<0.001
INR > 3.0, no. (%)	25 (6.2)	25 (36.2)	0	<0.001
Baseline ICH volume, mL (median, IQR)	15.7 (5.3–42.1)	23.9 (6.4–59.0)	14.2 (5.2–37.4)	0.046
IVH, no. (%)	180 (44.6)	31 (44.9)	149 (44.5)	0.945
Baseline IVH volume, mL (median, IQR)	6.0 (1.6–22.2)	4.9 (1.4–39.6)	6.0 (1.7–22.2)	0.955
Midline displacement, no. (%)	187 (46.3)	36 (52.2)	151 (45.1)	0.516
In-hospital mortality, no. (%)	111 (27.5)	29 (42.0)	82 (24.5)	0.003
mRS at discharge (median, IQR)	4 (4–6)	5 (4–6)	4 (4–6)	0.053
mRS 4–6 at discharge, no. (%)	328 (81.2)	61 (88.4)	267 (79.7)	0.092

ICH = intracerebral hemorrhage; INR = international normalized ratio; IHD = ischemic heart disease; AF, atrial fibrillation; AIS, acute ischemic stroke; TIA, transient ischemia attack; GCS, Glasgow Coma Scale; mRS, modified Rankin Scale; IVH, intraventricular hemorrhage; IQR, interquartile range.