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ORIGINAL ARTICLE

Role of Antiplatelet Agents in Hematoma Expansion During The Acute Period of Intracerebral Hemorrhage

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Abstract
Background Oral anticoagulants have been associated with greater hematoma expansion in patients with intracerebral hemorrhage (ICH). The purpose of this study was to determine whether the reported use of antiplatelet agents also results in greater hematoma expansion.
Methods Retrospective review of patients with spontaneous supratentorial ICH diagnosed within 6 h of onset, who underwent follow-up head CT approximately 48 h later. Digital imaging analysis of initial and second CT scans was performed for comparison of hematoma volume changes between patients reporting and those not reporting antecedent antiplatelet use. Statistical analyses to determine predictors of ICH volume change and in-hospital mortality were also performed via multivariate regression models.
Results Of the 70 patients included, 17 were documented as taking antiplatelet agents. Groups were comparable regarding baseline demographic, clinical and laboratory characteristics, and the timing of CT scans was similar. Patients reporting antiplatelet use experienced greater absolute increase (7.7 ml vs. 5.5 ml) and proportional increase (110% vs. 21%) in ICH volume than those not reporting antiplatelet use, but these differences were not statistically significant ($P = 0.94$ and 0.61 respectively; Wilcoxon test). Baseline hematoma volume tended to correlate with percentage volume increase ($P < 0.1$), whereas IVH was inversely associated with percent volume increase ($P < 0.05$). Age ($P < 0.05$), absolute volume increase ($P < 0.005$), and final volume ($P < 0.001$) were associated with in-hospital mortality, the rates of which were similar between the two study groups (18% vs. 17%).
Conclusions Patients reporting antiplatelet use experienced similar degrees of hematoma expansion compared to patients not reporting antiplatelet use.

Keywords Antiplatelet · Intracerebral hemorrhage · Hemorrhage · Hematoma · Expansion · Enlargement · Acute · Digital image analysis · Volume

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Introduction

Intracerebral hemorrhage (ICH) represents 10–15% of all cerebrovascular events [1], and carries a 30-day mortality rate of approximately 40% [2]. Disability and mortality from ICH have been correlated with hematoma expansion [3], which occurs mostly during the first few hours after the onset [2]. Predictors of ICH expansion have included larger initial size [4], contrast extravasation into the hematoma [5], and the use of oral anticoagulants [6, 7]. Warfarin use

has been consistently linked to hematoma expansion [6–8], but studies assessing the contribution of antiplatelet agents to hematoma expansion have yielded conflicting results [4, 9–13]. The purpose of this study is to determine the impact of reported antiplatelet use on hematoma enlargement, and to identify predictors and document the extent of hematoma enlargement during the acute phase of supratentorial ICH.

Methods

Patient Selection and Data Collection

Using the ICD-9 code for ICH [431], the institutional databank of Columbia University Medical Center was queried for all patients given a diagnosis of ICH between January 1, 2001 and December 31, 2006. From this list, the most recent 1,000 cases were selected. For all patients, electronic medical records were first reviewed and then supplemented by paper charts when data were missing or incomplete. Demographic, clinical, laboratory, and radiological data were systematically abstracted. Cases were reviewed to identify patients whose ICH was attributed to hypertension or amyloid angiopathy, and therefore considered primary. Patients were excluded if the ICH was secondary to a vascular abnormality, venous thrombosis, mass lesion, infectious or inflammatory process, neurosurgery, trauma, systemic illness, hemorrhagic diathesis, or oral anticoagulant use. Also excluded were patients <18 years old, those enrolled in the Factor Seven for Acute Hemorrhagic Stroke Trial [14], those undergoing surgical evacuation prior to the second CT, patients with posterior fossa ICH (due to the possible limitation in hematoma expansion as a result of anatomic restrictions), and those lacking a follow-up CT.

Patients presenting during the acute period of the event who were diagnosed by head CT scan within 6 h of symptom onset were included in this study, so as to select those cases at greatest risk for hematoma enlargement [2]. Initial CT (CT1) was compared to a repeat imaging study done as close to 48 h postictus as possible (CT2). Digital image analysis was performed by a blinded interpreter using a program capable of computing hematoma area at each tomographic level. The areas were added and multiplied by the CT segment dimension (0.5 cm) to yield final ICH volume. The location of hemorrhage (deep versus lobar), and the presence or absence of intraventricular hemorrhage (IVH), were also noted. Deep locations included the thalamus, putamen, pallidum, caudate, and internal capsule. Lobar locations included hemispheric cortical and/or juxtacortical regions, sparing the deep nuclear structures.

Absolute hematoma volume change was calculated as CT2-CT1, and percentage change as $[CT2/CT1 - 1] \times 100$. Since volume changes are typically not normally distributed, comparisons were based on Wilcoxon's nonparametric test. For comparisons of proportions, Fisher's exact test was used because of small expected values. Spearman's tests were performed for correlation coefficients. Multivariate regression models to identify determinants of ICH expansion were also explored. For all analyses a P-value of <0.05 was considered statistically significant.

Results

Of the 1,000 patients screened, 70 met the inclusion criteria. Main reasons for exclusion were diagnosis later than 6 h after onset (37%), hemorrhage related to aneurysm, arteriovenous malformation, ischemic conversion, infratentorial location, or extracerebral hematoma (24%), hemorrhage secondary to trauma, neoplasm, infection, or

Table 1 Baseline characteristics and clinical data of patients taking and not taking antiplatelet agents, and for entire study group

	Entire cohort ($n = 70$)	Antiplatelet ($n = 17$)	No antiplatelet ($n = 53$)	P value
Age (years)	66 ± 15	72 ± 16	64 ± 14	0.10
Male (%)	59	65	57	0.59
Hypertension (%)	81	88	79	0.50
PT (s)	14 ± 1	14 ± 1.2	14 ± 1	0.64
PTT (s)	30 ± 6.4	30 ± 3.7	30 ± 7.1	0.50
Platelets (per μl)	228 ± 72	228 ± 50	228 ± 79	0.71
Hemorrhage				
Deep (%)	73	88	68	0.13
IVH (%)	41	41	42	1
Platelet transfusion (n)	3	1	2	1
Time to transfusion (min)	143 (120–180)	120	155 (130–180)	0.22

All continuous variables reported as mean ± SD, except for the time to transfusion category which reports mean (range). Continuous variables compared using Wilcoxon's nonparametric test, and proportions compared using Fischer's exact test

hemorrhagic diathesis (21%), moribund condition at presentation and no repeat CT performed (11%), and age <18 years (6%). Three patients were excluded due to lack of follow-up CT, and two patients were excluded due to surgical evacuation. Of the 70 patients included for analysis, 17 (24%) reported taking antiplatelet agents at the time of the event (15 ASA and 2 Clopidogrel). The demographic, clinical, and laboratory characteristics of the study groups are presented in Table 1.

No substantial difference was noted in the time intervals from onset to first CT, or from first CT to follow-up CT between the two groups (Table 2). For the entire study group, a total of 1,051 individual images were analyzed. Initial and final ICH volumes, and absolute volume changes, were similar between patients reporting and not reporting antiplatelet agents (Table 2). Despite a marked numerical difference in proportional mean hematoma volume expansion, no statistical differences were observed between the two groups (Table 2). Over 50% of all patients experienced some degree of ICH expansion, the distributions of which appear in Fig. 1. A breakdown for the extent of hematoma expansion by antiplatelet status is shown in Fig. 2.

Baseline hematoma volume tended to be positively associated with percentage volume increase, whereas IVH tended to be inversely associated with percent volume increase (Table 3a). In the multivariate model incorporating factors that may predispose to IVH (initial size and deep location), IVH more definitively emerged as a negative predictor of ICH expansion (Table 3b). Age, absolute volume increase, and final volume were associated with in-hospital mortality (Table 4). Mortality rates during hospitalization were essentially identical in patients reporting and those not reporting antiplatelet utilization. The 30- and 90-day mortality rates were unavailable for comparison.

Table 2 Imaging, volumetric, and mortality data

	Antiplatelet	No antiplatelet	*P* value
Onset to CT1 (min)	146 ± 102	151 ± 86	0.72
CT1 to CT2 (h)	38 ± 32	38 ± 22	0.44
Initial CT1 volume (ml)	13.8 ± 11.4	19.2 ± 15.4	0.25
Final CT2 volume (ml)	21.5 ± 24.6	24.6 ± 25.1	0.50
Volume change (ml)	7.7 (±22.7)	5.5 (±14.3)	0.94
Volume change (%)	110.4 (±363.4)	20.8 (±47.9)	0.61
Vol change >33% (%)	29 (±11)	28 (±6)	1
In-hospital mortality (%)[a]	18	17	1

Continuous variables reported as mean (±SD). Continuous values compared using Wilcoxon's nonparametric test, and proportions compared using Fisher's exact test

[a] Mortality rates do not include approximately 10% of patients moribund upon presentation who did not undergo repeat CT

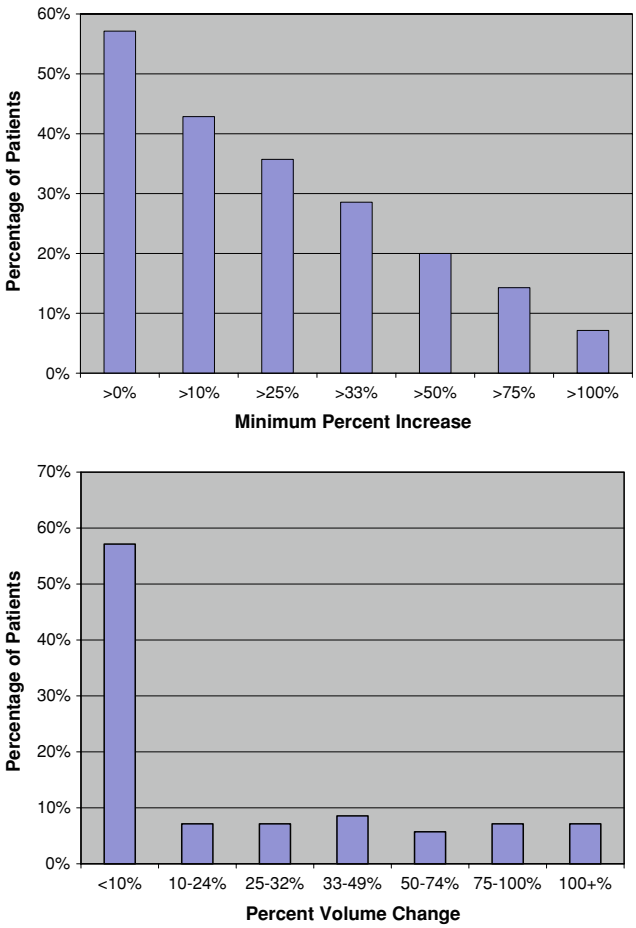

Fig. 1 Cumulative and categorical distributions of hematoma expansion

Discussion

Prior studies have consistently demonstrated an association between warfarin use and hematoma expansion, using both planimetric computerized volume analysis and the simplified equation for calculating ellipsoid volume (ABC/2) [6–8]. Recent studies have shown a predisposition for asymptomatic cerebral microhemorrhages among patients taking platelet inhibitors [15], and a propensity for ICH expansion in patients with reduced platelet activity as measured by aggregometry [16]. Two studies utilizing the ellipsoid calculation equation suggested an association between antiplatelet agents and ICH enlargement [9, 10], yet studies employing more precise computerized planimetric methods have yielded conflicting results [4, 11–13].

In our study, patients reporting antiplatelet use experienced similar absolute and proportional increases in hematoma volume compared to patients not reporting antiplatelet use. Our findings are in contrast to those of Saloheimo et al. [11], who found greater mean hematoma expansion among patients using aspirin than among

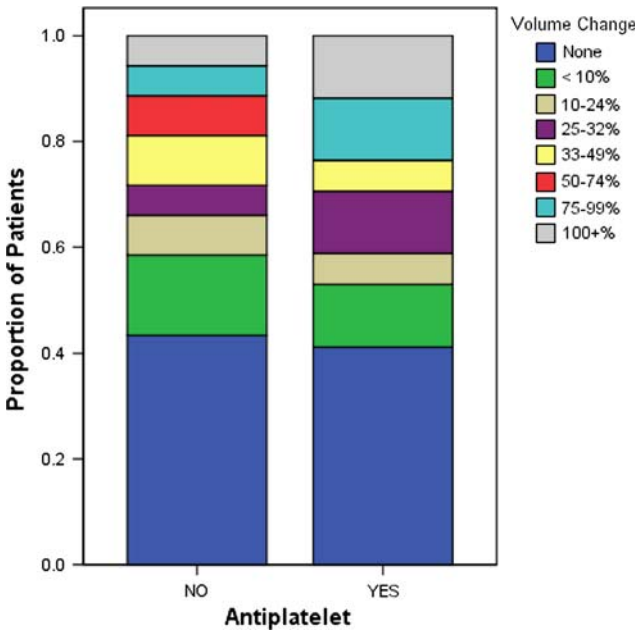

Fig. 2 Categorical breakdown of relative hematoma volume increase according to antiplatelet status

Table 3 Predictors of ICH expansion

	>25%	>33%	>50%
a			
Age	0.50	0.77	0.60
HT	0.10	0.82	0.86
Antiplatelet	0.81	0.93	0.64
CT1 volume	**0.09**	0.13	0.25
Deep	0.13	0.21	0.52
IVH	**0.05**	**0.05**	**0.09**
Overall model	0.35	0.46	0.61
b			
CT1 volume	**0.08**	**0.09**	0.20
Deep	0.10	0.14	0.37
IVH	**0.04**	**0.04**	**0.06**
Overall model	0.08	0.08	0.18

Values represent *P* values

a—Statistical analyses based on multivariate logistic regression model incorporating the variables age, HT, antiplatelet, CT1, deep, and IVH. Results suggest that IVH may be associated with less ICH expansion >25% (OR = 0.33, 95% CI = 0.1–1.01) and >33% (OR = 0.31, 95% CI = 0.08–1.02). For >50% expansion, the statistical impact is less robust but comparable (OR = 0.31, 95% CI = 0.06–1.21)

b—Statistical analyses based on multivariate logistic regression model incorporating the variables CT1, deep, and IVH. Results suggest that IVH may be associated with less ICH expansion >25% (OR = 0.32, 95% CI = 0.1–0.95) and >33% (OR = 0.29, 95% CI = 0.08–0.94). For > 50% expansion, the statistical impact is less robust but comparable (OR = 0.28, 95% CI = 0.06–1.06)

nonusers (22.6% vs. 16.1%, $P = 0.006$). The study by Saloheimo was, however, limited by available imaging in only about 70% of patients within the first day of symptom onset, and follow-up scans were done a median of 7 days later. Our findings are also in contrast to those of Sorimachi et al. [12], whereby substantial (>20%) hematoma expansion was more frequent among aspirin users than nonusers (63% vs. 8%, $P = 0.0003$). However, the study by Sorimachi differed from ours in that patients were diagnosed as late as 24 h after symptom onset, and were uniformly treated with antifibrinolytic therapy.

Conversely, our findings are consistent with those of the recent large study by Sansing et al. [13], which involved a similar time interval from symptom onset to diagnosis by CT scan (approximately 2 h). Differences between our study and that of Sansing, however, include the randomized use of a neuroprotectant agent (CHANT Trial), the inclusion of posterior fossa hemorrhages and thus the possible need for evacuation of large cerebellar hematomas (>3 cm), and the longer time interval from initial to repeat head CT (72 h) which may have allowed for greater hematoma resolution. Our findings are also consistent with the study by Broderick and colleagues which failed to demonstrate a substantial (>33%) difference in hemorrhage enlargement among users of antiplatelet agents [4]. Unlike our study, the study by Broderick entailed randomized treatment to rF-VIIa, and also included posterior fossa hemorrhages.

We suspect that our negative findings may be due to several factors, including the unreliability of reported antiplatelet use (or nonuse), and the variable antiaggregant activity of different agents at different doses [17]. Most importantly, however, may be the fact that even verified antiplatelet use may fail to produce platelet inhibition [18], as evidenced by antiplatelet "resistance" among certain ICH patients [18]. That some nonusers actually exhibit intrinsically impaired platelet activity may additionally attenuate differences between the two populations [18]. As such, an analysis of hematoma enlargement based on reported antiplatelet therapy may markedly underestimate the true impact of effective antiaggregant therapy. As is the case for warfarin-related hemorrhages where serologic tests are used to measure degree of anticoagulation, physiologic tests of platelet function may represent the most appropriate means for determining risk of hematoma expansion due to antiplatelet medications.

Despite the absence of a statistical difference between the two groups, patients reporting antiplatelet use experienced a greater mean increase in hematoma volume. The greater proportion of patients developing volume increases of more than 75% and 100% in the antiplatelet group probably explains this finding, and raises the possibility that these patients may possess the greatest degree of platelet inhibition. Also, since antiplatelet users may

Table 4 Predictors of in-hospital mortality

	Absolute volume		Percent volume	
	P value	OR (95% CI)	*P* value	OR (95% CI)
Age	**0.025**	1.06/year (1.01–1.14)	**0.021**	1.06/year (1.01–1.12)
IVH	0.11	3.41 (0.77–18.24)	0.14	2.76 (0.73–11.67)
Volume increase	**0.0016**	1.06/ml (1.02–1.12)	0.41	1/% inc (1.00–1.004)
CT2 volume[a]	0.059	1.05/ml (1.00–1.12)	**0.0002**	1.06/% inc (1.03–1.13)
Overall model	0.0008	–	0.061	–

Statistical analyses based on multivariate linear regression model incorporating age, IVH, and absolute or relative volume increase

[a] For CT2 volume, same variables were included along with final hematoma volume. Results suggest that when absolute volume is considered, age and volume increase are associated with mortality. When relative volume is considered, age and final volume are associated with mortality. IVH was not associated with mortality

exhibit an overall greater degree of platelet inhibition than nonusers [18], it is possible that larger study numbers may have demonstrated a more statistically robust difference between the two groups. However, the largest study to date (which most closely resembles ours in methodology) similarly demonstrated a lack of association between reported antiplatelet use and ICH expansion [13].

As in prior studies, our results suggest that baseline hematoma volume may correlate to the extent of subsequent hematoma enlargement [4]. Interestingly, our study also demonstrated a possible negative association between IVH and hematoma enlargement, which may theoretically be explained by hemorrhage "decompression" into the low resistance ventricular system [19]. Previous studies have investigated the connection between hematoma volume and IVH [19], but we are not aware of any prior reports specifically correlating the extent of ICH expansion to presence of IVH, and therefore our findings may be somewhat novel. Finally, mortality was markedly associated with age, hematoma volume increase, and final hematoma volume, as has been observed in previous reports [3, 20, 21].

Limitations to our study include the use of ICD codes for identifying cases, the retrospective nature of data collection, the small number of patients studied, and the absence of data on excluded patients which may introduce bias into our results. Nevertheless, every effort was made to carefully review medical records and imaging studies so as to identify all acute ICH patients who were most likely to experience hematoma enlargement. This study is also limited by the lack of documentation regarding systemic pressures upon admission, and the uncertain degree or duration of any hypertensive management employed. One observational study found no association between hypertension and hematoma expansion [22], thus possibly negating the need to correct for this variable in our analysis. However, a randomized clinical trial showed that hypertensive treatment may decrease ICH expansion [23], and official AHA/ASA practice guidelines recommend antihypertensive therapy [24]. A final criticism of our study is the lack of clinical data for functional outcome assessments. However, in-hospital mortality rates were recorded, and were consistent with the findings of some [13, 25], but not all [9–11], previous reports investigating the relationship between antiplatelet agents, ICH and mortality.

Positive aspects of our study include the selection of patients presenting during the acute period when ICH enlargement is most likely to occur [2], the precise computerized method used for volume analysis [26], the objective manner in which this analysis was performed, and the availability of early and late CT scans for all patients. We believe that the exclusion of posterior fossa hemorrhages is also an attribute to our study, given that hematoma enlargement may be limited by anatomic restrictions, yet this may also represent a limitation in that our results may not apply to hemorrhages in these regions. The results of this study are reinforced by the fact that initial hematoma volume was comparable between the two groups, given that initial hematoma volume is a predictor of hematoma expansion [4]. These results were also not confounded by a disproportion of IVH between the groups, which may theoretically limit ICH expansion [19]. Finally, we report an important inverse association between IVH and ICH expansion, possibly explained by decompression of cerebral hemorrhage in to the ventricular system.

The results of this study fail to provide support for the premise that reported use of antiplatelet agents contributes to ICH expansion. Given the conflicting evidence available from the literature at the present time, and therefore the clinical uncertainty that exists regarding the impact of antiplatelet agents upon ICH, additional large prospective observational studies may more conclusively resolve this controversy. More importantly, however, will be to confirm the results of physiologically based studies that directly measure platelet function in patients with ICH so as to confirm the reported connection between platelet inhibition and hemaotma expansion.

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