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Warfarin and Statins are Associated with Hematoma Volume in Primary Infratentorial Intracerebral Hemorrhage

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Conflict of interest The following authors “Guido J. Falcone, H. Bart Brouwers, Alessandro Biffi, Thomas W.K. Battey, Alison M. Ayres, Anastasia Vashkevich, Kristin M. Schwab, Natalia S. Rost, Anand Viswanathan” have stated that they have no conflict of interest.

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Abstract

Background and purpose—Despite extensive studies of supratentorial intracerebral hemorrhage (ICH), limited data are available on determinants of hematoma volume in infratentorial ICH. We therefore aimed to identify predictors of infratentorial ICH volume and to evaluate whether location specificity exists when comparing cerebellar to brainstem ICH.

Methods—We undertook a retrospective analysis of 139 consecutive infratentorial ICH cases (95 cerebellar and 44 brainstem ICH) prospectively enrolled in a single-center study of ICH. ICH volume was measured on the CT scan obtained upon presentation to the Emergency Department using an established computer-assisted method. We used linear regression to identify determinants of log-transformed ICH volume and logistic regression to evaluate their role in surgical evacuation.

Results—Median ICH volumes for all infratentorial, cerebellar, and brainstem ICH were nine [interquartile range (IQR), 3–23], ten (IQR, 3–25), and eight (IQR, 3–19) milliliters, respectively. Thirty-six patients were on warfarin treatment, 31 underwent surgical evacuation, and 65 died within 90 days. Warfarin was associated with an increase in ICH volume of 86 % [$\beta = 0.86$, standard error (SE) = 0.29, $p = 0.003$] and statin treatment with a decrease of 69 % ($\beta = -69$, SE = 0.26, $p = 0.008$). Among cerebellar ICH subjects, those on warfarin were five times more likely to undergo surgical evacuation (OR = 4.80, 95 % confidence interval 1.63–14.16, $p = 0.005$).

Conclusions—Warfarin exposure increases ICH volume in infratentorial ICH. Further studies will be necessary to confirm the inverse relation observed between statins and ICH volume.

Keywords

Cerebellar hemorrhage; Brainstem hemorrhage; ICH volume; Anticoagulation; Warfarin; Statins

Introduction

The volume of intraparenchymal bleeding is a potent predictor of outcome following intracerebral hemorrhage (ICH) [1]. The association between hematoma volume and clinical outcome is equally strong in both supra- and infratentorial ICH [2]. For supratentorial hemorrhages, several factors have been reported to influence hematoma volume, including treatment with warfarin [3] and statins [4], leukoaraiosis [5], asymptomatic microbleeds [6], and the APOE epsilon-2 allele [7].

In contrast to supratentorial ICH, limited data are available regarding factors that influence hematoma volume in infratentorial ICH. One reason is the relative rarity of this event: Intraparenchymal hemorrhages in the cerebellum and brainstem account for ~10 % of all primary ICH [8]. In addition, the biologic mechanisms that determine the occurrence and extent of bleeding in infratentorial ICH may only partially overlap with those involved in supratentorial ICH. As a result, a majority of studies designed to identify determinants of supratentorial ICH volume excluded subjects with infratentorial hemorrhages as a way of reducing outcome heterogeneity [3, 7].

The size of the hematoma is particularly important for cerebellar ICH. Observational data suggest that, in properly selected patients, surgical evacuation improves clinical outcome in this type of ICH [9]. Importantly, subject selection for surgery in this setting is often based on the size of the hematoma [10]. In brainstem ICH, on the other hand, larger hemorrhages simply mean more damage and worse outcome, and surgery does not appear to offer any benefit.

Given the pivotal role of hematoma volume in infratentorial ICH, as well as the relative paucity of data concerning its determinants, we sought to identify predictors of hematoma volume for this specific type of intraparenchymal hemorrhage. Our primary aim was to assess whether pre-ICH treatment with warfarin, a wellknown determinant of supratentorial ICH volume, also increases infratentorial ICH volume. In addition, we also evaluated whether other factors influence the extent of bleeding in infratentorial locations.

Methods

Study design

We performed a retrospective analysis of data drawn from an ongoing prospective cohort study of ICH performed at Massachusetts General Hospital (Boston, MA, USA). The hospital's Institutional Review Board approved the study and written informed consent was obtained from all participants or their surrogates, when patients were unable to provide consent.

Subjects

ICH cases were ascertained by stroke neurologists and enrolled according to the methods previously described [11]. Study subjects were consecutive patients admitted to the Massachusetts General Hospital between January 1, 2000, and December 31, 2010, with primary and warfarin-related ICH. ICH was defined as a new neurologic deficit with compatible brain imaging showing the presence of intraparenchymal bleeding. Inclusion criteria were age >18 years and confirmation of ICH through computed tomography (CT). Exclusion criteria included trauma, brain tumor, hemorrhagic transformation of a cerebral infarction, vascular malformation, or any other suspected cause of secondary ICH.

Clinical Data

Patients (or their families or surrogates) were interviewed to determine age, sex, time of symptom onset, medical history, family history, pre-ICH treatment with warfarin, antiplatelets, antihypertensives and statins, and alcohol and tobacco use. Hospital charts were reviewed for Glasgow Coma Scale score upon arrival, admission arterial blood pressure, time to baseline imaging (time-to-scan), routine laboratory measurements, and in-hospital mortality. For patients who survived and were discharged, 90-day mortality was assessed by telephone by trained study staff and supplemented by regular surveillance of the Social Security Death Index [12].

Imaging analysis

For all study subjects, the first available head CT was evaluated. ICH location was assigned based on admission CT by study neurologists blinded to clinical data. Hemorrhages involving more than one territory were defined as mixed ICH and were excluded from the analysis. ICH volume was measured using Alice (PAREXEL International, Waltham, MA, USA) or Analyze 9.0 (Mayo Clinic, Rochester, MN, USA) software, using previously described methods [13]. Intraventricular bleeding was not included in volume calculations. Subjects with primary intraventricular hemorrhages, as well as those initially imaged beyond 72 h of symptom onset, were excluded from the analysis. Unless contraindicated, imaging of the intracranial vasculature (CT angiography, conventional angiography, or magnetic resonance angiography) was performed to rule out secondary causes of ICH. Hematoma expansion, defined as a relative increase of 33 % in hematoma volume, was assessed in subjects with available follow-up CTs.

Statistical Analysis

Covariates

Discrete variables are expressed as count (percentage) and continuous variables as mean [standard deviation (SD)] or median [interquartile range (IQR)], as appropriate. ICH volume was natural log-transformed to approximate normality. Following previous reports [3], subjects not on warfarin with missing International Normalized Ratio (INR) were assigned a value of 1. In primary analyses, INR was dichotomized at 2; in sensitivity analyses, other modeling strategies for INR were evaluated, including 3-bin categorization (INR < 2, 2–3, and >3) and inclusion of INR as a continuous covariate after natural log transformation.

Determinants of Infratentorial ICH Volume

Linear regression was utilized to model mean log-ICH volume. Univariate linear regression was initially implemented to evaluate unadjusted associations between log-ICH volume and covariates. Subsequently, multivariate linear regression was applied to identify independent associations after accounting for potential confounders. Model building proceeded as follows: age and sex were included in all models; covariates with p -values <0.2 in univariate analysis were entered into the model and backward eliminated to a significance level of 0.1; and finally, collinear factors (as measured through the variance inflation factor) were removed when appropriate. Analyses stratified by location (cerebellar and brainstem ICH) were subsequently performed.

Additional Outcomes

Surgical evacuation was evaluated by fitting logistic regression models. Model building proceeded as described above, and predictors of volume identified through linear regression were forced into these models. At our institution, surgical evacuation is indicated in cerebellar hemorrhages when the maximum diameter of the hematoma is >3 cm.

Additional Analyses

In sensitivity analysis, we removed outlier observations (>4 SD from the mean) and included time-to-scan in the models described above. Time-to-scan was not included in primary analyses because data were missing for 18 (20 %) of subjects.

All statistical analyses were performed using SAS 9.3. The results of the statistical tests were considered significant at $p < 0.05$ (2-tailed).

Results

During the study period, 1,253 patients were admitted to the Emergency Department with a diagnosis of ICH (Fig. 1). Of these, 157 (13 %) corresponded to infratentorial hemorrhages. Among infratentorial ICH cases, three subjects were imaged beyond 72 h and 15 had no CT data available, yielding a total of 139 cases to be included in the current analysis; mean age was 71 (SD 4) and 63 (45 %) patients were females. Ninety-five subjects (68 %) had cerebellar hemorrhages and 44 (32 %) had brainstem ICH (Table 1).

A number of baseline characteristics differed across infratentorial locations (Table 1). Compared to subjects with brainstem ICH, subjects with cerebellar hemorrhages were older (73 vs 64 years, $p < 0.001$), less likely to smoke (8 vs 20 %, $p = 0.002$), and more likely to be treated with statins (36 vs 18 %, $p = 0.04$). Upon admission to the hospital, subjects with cerebellar hemorrhages had lower mean diastolic blood pressure (92 vs 103 mm of mercury, $p = 0.007$) and were imaged later than subjects with brainstem ICH (median time-to-scan 6 vs 3 h, $p < 0.001$). Ninety days after the bleeding episode, 65 out of 139 patients (47 %) had died. Mortality in cerebellar and brainstem ICH was 36 and 70 %, respectively ($p < 0.001$). Follow-up CTs were available in 73 subjects (51 %), of which 8 (11 %) presented hematoma expansion; all expanders required surgical evacuation of the hematoma.

Predictors of Infratentorial ICH Volume

Radiologic findings were similar across infratentorial locations. For all (cerebellar and brainstem combined), cerebellar, and brainstem hemorrhages, median ICH volumes were nine (IQR 3–23), ten (IQR 3–25), and eight (IQR 3–19) milliliters (mL), respectively. Relevant predictors of ICH volume identified in univariate analysis (Table 2) included pre-ICH treatment with warfarin ($p = 0.02$), admission INR ≥ 2 ($p = 0.02$), pre-ICH treatment with statins ($p = 0.04$), and history of diabetes ($p = 0.05$). In addition, pre-ICH treatment with antiplatelets, pre-ICH treatment with antihypertensives, and admission blood glucose reaching the <0.2 criterion were considered in multivariate modeling.

Of the predictors described above, pre-ICH treatment with warfarin and statins remained significant in multivariate analysis. As expected, admission INR ≥ 2 was collinear with pre-ICH treatment with warfarin, the latter purporting the higher association strength. The remaining univariate predictors, including pre-ICH treatment with antiplatelets and antihypertensives, as well as admission blood glucose, lost their initial significance in multivariate modeling (all $p > 0.1$). Considering together all infratentorial ICHs, multivariate modeling indicated that pre-ICH treatment with warfarin increased mean ICH volume by 86 % [or 7.7 mL, beta (b) = 0.86, SE = 0.29, $p = 0.003$] and pre-ICH treatment with statins

decreased it by 69 % (or 6.2 mL, $\beta = -0.69$, SE = 0.26, $p = 0.008$; Table 3). Stratified analysis based on location revealed that these associations were even stronger for cerebellar hemorrhages (warfarin $p < 0.001$ and statins $p = 0.002$) and null for brainstem hemorrhages (warfarin $p = 0.70$ and statins $p = 0.92$; Table 3). Of note, the available sample size for brainstem ICH had 90 % power to detect an effect of either exposure, assuming a similar effect size to that observed for cerebellar ICH. These results remained unchanged when incorporating time-to-scan into the model, removing outlier volumes in sensitivity analysis and modeling INR using different strategies (data not shown).

Hematoma Evacuation in Cerebellar Hemorrhages

Association analyses involving surgical evacuation of the hematoma aimed to evaluate the downstream effect of predictors of infratentorial ICH volume described above. As surgery has no proven benefit in brainstem ICH, only cerebellar hemorrhages were considered in this analysis. A total of 30 (32 %) subjects with cerebellar ICH underwent hematoma evacuation. Multivariate logistic regression (Table 4) indicated that treatment with warfarin was independently associated with a 5-fold increase in risk of requiring surgical evacuation of the hematoma (OR = 4.80, 95 % confidence interval [CI] 1.63–14.16, $p = 0.005$). This association faded when including ICH volume in the model, suggesting that ICH volume mediates the relationship between warfarin and surgical evacuation (Table 4). In addition, age was inversely correlated with the same risk (OR = 0.96, 95 % CI 0.92–0.99, $p = 0.03$).

Discussion

These results indicate that pre-ICH treatment with warfarin and statins may influence the size of intraparenchymal bleeding in infratentorial ICH. This study also suggests that the effect of these determinants is location specific, disproportionately affecting infratentorial ICH located in the cerebellum. Importantly, these factors were also associated with clinical management in these patients. Warfarin treatment correlated with requirement of surgical evacuation of the hematoma, an expected finding given that hematoma volume is the most important factor driving the decision of pursuing hematoma evacuation.

The observed association between pre-ICH treatment with warfarin and infratentorial ICH volume is in line with the known biology of this condition. In triggering clinically evident episodes of intracerebral bleeding, anticoagulation is believed to interact with underlying small vessel vasculopathies of the brain known to cause ICH [14]. Treatment with warfarin, and more specifically the intensity of anticoagulation measured by the INR, is associated with increased hematoma size in supratentorial ICH [3]. For infratentorial hemorrhages, some studies suggest that pre-ICH treatment with warfarin could result in worse clinical outcome and increased mortality [15, 16]. Our study brings together these two observations. We show that the effect of warfarin treatment on ICH volume also applies to infratentorial ICH, providing a plausible explanation for the reported negative effect of warfarin on outcome. Of note, in the present analysis, the association between warfarin and infratentorial ICH volume was specifically driven by the effect of the former on cerebellar hematomas.

Previous evidence surrounding the role of statin treatment in ICH volume and outcome is contradictory. Furthermore, studies on this topic reported thus far pertain mainly to

supratentorial ICH, making direct extrapolations to infratentorial ICH difficult. A recent study found a positive association between exposure to statins and favorable clinical outcome following ICH [17]. Moreover, a large metaanalysis on statins and ICH found a significant decrease in mortality after ICH in subjects who were receiving these drugs [18]. However, a third report specifically focused on determinants of ICH volume found that exposure to statins could increase the size of the hematoma [4].

Unfortunately, the known biology of statins cannot be used to inform the discussion presented above. Due to the multitude of biologic pathways affected by these drugs, a plausible explanation for either option exists. On one hand, it could be hypothesized that the effect of statins on vascular outcomes, mediated through their impressive effect on lipid levels, reduces the burden of small vessel disease in the parenchyma surrounding the vessel responsible for the hemorrhage. In turn, this could reduce hematoma growth by limiting the cascading effect generated by rupture of diseased vessels located on the periphery of the hematoma [19]. On the other hand, mechanisms suggested to mediate a possible increase in ICH risk in subjects with a previous history of ischemic stroke, reported in two large clinical trials [20], could also apply to ICH volume. These include the mild antithrombotic effect exerted by statins [21] as well as the observation that the strong reduction in lipid levels achieved by these drugs could affect the integrity of phospholipid membranes [22], thus increasing their frailty. In light of this evidence, it is clear that further studies are warranted to elucidate the causal role of statins on infratentorial ICH volume.

A large sample size and careful ascertainment of cases constitute important strengths of our study. One important limitation stems from the approach utilized to ascertain drug exposures before ICH: We lack information on dosage and duration of exposure before the hemorrhage occurred. This is probably not relevant for warfarin, as the INR is an accurate measure of the intensity of anticoagulation at the time of the ICH and was found in this and other studies [3] to be equally associated with hematoma volume. However, this lack of data could have introduced some misclassification and consequent information bias in the case of statin treatment. The direction of this bias, nonetheless, was probably toward the null, as the misclassification is likely to have been independent and non-differential.

Summary

Exposure to warfarin and statins seems to play a role in determining hematoma volume in infratentorial ICH. Given the effect of warfarin on coagulation-related pathways, as well as previous evidence regarding the role of this drug in determining supratentorial ICH volume, it seems reasonable to conclude that warfarin has a causal, positive effect on infratentorial hematoma volume. We show that exposure to warfarin has important management implications as patients exposed to this drug are more likely to undergo surgical evacuation. In light of the conflicting results described by previous reports, and the heterogeneity of pathways affected by statins, further studies are required to elucidate the meaning of the observed association between statin treatment and decreased ICH volume.

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Fig. 1.
Study flowchart

Table 1

Cohort characteristics

Covariate	<u>All infratentorial ICH</u>		<u>Cerebellar ICH</u>		<u>Brainstem ICH</u>		<i>p</i>
	<i>n</i> = 139		<i>n</i> = 95		<i>n</i> = 44		Cerebellar versus brainstem
Age, mean (SD)	71	(14)	73	(13)	64	(22)	<0.001
Female sex, <i>n</i> (%)	63	(45)	45	(47)	18	(41)	0.48
Hypertension, <i>n</i> (%)	116	(83)	79	(83)	37	(84)	0.89
Diabetes, <i>n</i> (%)	25	(18)	15	(16)	10	(23)	0.29
Hypercholesterolemia, <i>n</i> (%)	37	(27)	40	(42)	12	(27)	0.13
Coronary artery disease, <i>n</i> (%)	26	(19)	21	(22)	5	(11)	0.16
Atrial fibrillation, <i>n</i> (%)	25	(18)	20	(21)	5	(11)	0.18
Previous ICH, <i>n</i> (%)	6	(4)	4	(4)	2	(5)	0.90
Previous ischemic stroke, <i>n</i> (%)	26	(19)	18	(19)	8	(18)	0.96
Current smokers, <i>n</i> (%)	17	(12)	8	(8)	9	(20)	0.002
Ever smokers, <i>n</i> (%)	38	(27)	28	(29)	10	(23)	0.16
Warfarin treatment, <i>n</i> (%)	36	(26)	26	(27)	10	(23)	0.56
Antiplatelet treatment, <i>n</i> (%)	59	(42)	44	(46)	15	(34)	0.18
Anti-hypertensive treatment, <i>n</i> (%)	90	(65)	65	(68)	25	(57)	0.18
Statin treatment, <i>n</i> (%)	42	(30)	34	(36)	8	(18)	0.04
Admission systolic BP, *mean (SD)	184	(42)	180	(37)	193	(49)	0.11
Admission diastolic BP, *mean (SD)	95	(22)	92	(20)	103	(25)	0.007
Admission blood glucose, **mean (SD)	172	(59)	160	(47)	179	(78)	0.35
INR 2, <i>n</i> (%)	30	(22)	21	(22)	9	(20)	0.78
ICH volume, ***median (IQR)	9	(3–23)	10	(3–25)	8	(3–19)	0.71
IVH volume, ***median (IQR)	2	(1–8)	2	(1–9)	2	(1–7)	0.38
Intraventricular extension, <i>n</i> (%)	54	(39)	33	(35)	21	(48)	0.16
Time-to-scan, ****median (IQR)	5	(3–7)	6	(4–8)	3	(2–6)	0.007
90-day mortality	65	(47)	34	(36)	31	(70)	<0.001

ICH intracerebral hemorrhage, *n* number, *SD* standard deviation, *IVH* intraventricular hemorrhage, *IQR* interquartile range, *BP* blood pressure, *INR* international normalized ratio, *oz* ounces

* In millimeters of mercury;

** in milligrams/deciliter;

*** in milliliters,

**** in hours

Table 2

Univariate linear regression results. Dependent variable: log-transformed hematoma volume

Covariate	β	SE	<i>p</i>
Location (Ref.: cerebellar)	−0.04	0.27	0.87
Age	−0.05	0.01	0.58
Sex (Ref.: female)	0.24	0.25	0.32
Hypertension	−0.33	0.33	0.31
Diabetes	−0.64	0.32	0.05
Hypercholesterolemia	−0.30	0.26	0.24
Coronary artery disease	−0.19	0.31	0.53
Atrial fibrillation	0.16	0.32	0.63
Previous ICH	−0.14	0.61	0.82
Previous ischemic stroke	−0.12	0.32	0.72
Current smokers	−0.12	0.36	0.75
Ever smokers	−0.18	0.28	0.53
Warfarin treatment	0.67	0.28	0.02
INR 2	0.39	0.17	0.02
Antiplatelet treatment	−0.41	0.25	0.10
Anti-hypertensive treatment	−0.37	0.26	0.14
Statin treatment	−0.55	0.26	0.04
Admission systolic BP	−0.002	0.003	0.60
Admission diastolic BP	−0.003	0.01	0.64
Admission blood glucose	0.004	0.002	0.07

ICH intracerebral hemorrhage, *n* number, *SE* standard error, *Ref.* reference category, *BP* blood pressure, *INR* international normalized ratio

Table 3

Multivariate linear regression—dependent variable: log-transformed hematoma volume

Covariate	All infratentorial ICH			Cerebellar ICH			Brainstem ICH		
	<i>n</i> = 139			<i>n</i> = 95			<i>n</i> = 44		
	β	SE	<i>p</i>	β	SE	<i>p</i>	β	SE	<i>p</i>
Age	0.001	0.001	0.27	−0.007	0.01	0.51	−0.01	0.02	0.48
Sex (Ref.: female)	0.25	0.24	0.30	0.18	0.30	0.55	0.24	0.42	0.63
Pre-ICH Tx with warfarin	0.86	0.29	0.003	1.19	0.34	<0.001	0.21	0.55	0.70
Pre-ICH Tx with statins	−0.69	0.26	0.008	−0.94	31.00	0.002	−0.06	0.52	0.92

Log logarithm, *ICH* intracerebral hemorrhage, *n* number, *SE* standard error, *Ref.* reference, *Tx* treatment

Table 4

Multivariate logistic regression, dependent variable: surgical evacuation

Covariate	<u>Model without ICH volume</u>			<u>Model with ICH volume</u>		
	<u>Cerebellar ICH (<i>n</i> = 95)</u>			<u>Cerebellar ICH (<i>n</i> = 95)</u>		
	OR	95 % CI	<i>p</i>	OR	95 % CI	<i>p</i>
Age	0.96	(0.92–0.99)	0.03	0.95	(0.90–0.99)	0.02
Sex (Ref.: female)	0.95	(0.36–2.48)	0.91	0.77	(0.24–2.47)	0.66
Pre-ICH Tx with warfarin	4.80	(1.63–14.16)	0.005	2.01	(0.55–7.36)	0.30
Pre-ICH Tx with statins	0.63	(0.23–1.75)	0.37	2.27	(0.55–9.40)	0.26
ICH hematoma volume	–	–	–	5.12	(2.30–11.41)	<0.0001

ICH intracerebral hemorrhage, *CI* confidence interval, *Ref* reference, *INR* international normalized ratio