Perihematomal Edema and Functional Outcomes in Intracerebral Hemorrhage
Influence of Hematoma Volume and Location

Santosh B. Murthy, MD, MPH; Yogesh Moradiya, MD; Jesse Dawson, MD; Kennedy R. Lees, MD; Daniel F. Hanley, MD; Wendy C. Ziai, MD, MPH; for the VISTA-ICH Collaborators*
PHE as the interval increase in absolute volume during 24 hours and reported a significant association with poor outcomes. Edema growth occurs most rapidly during the first 48 hours, which suggests that a later assessment of edema expansion should better assess the relationship with outcome and in a time window where therapeutic intervention may be easier to deliver. We hypothesized that increase in PHE during 72 hours (iPHE) after ICH would be associated with worse functional outcome. We aimed to test this hypothesis and to explore whether there is a subset of ICH patients in whom PHE expansion is most detrimental.

Methods

Patient Selection
We used data contained in the Virtual International Stroke Trials Archive (VISTA-ICH). Eligibility for VISTA required the following: (1) documented entry criteria into a trial, with a minimum of 50 randomized patients with ICH; (2) documented consent or waiver of consent of local ethics board; (3) baseline assessment within 24 hours of stroke; (4) baseline assessment of neurological deficit; (5) confirmation of ICH by cerebral imaging within 7 days; (6) outcome assessment between 1 and 6 months with a validated stroke scale; and (7) data validation through monitoring. In addition, the VISTA cohort used in this study consisted of patients in the placebo-controlled arm (nonsurgical and nonintervention) presenting with Noncontrast Computed Tomography (NCCT) proven ICH within 6 hours of symptom onset, and with baseline clinical, radiological, and laboratory data. All patients had follow-up NCCT scan at 72 hours, and 90-day modified Rankin Scale (mRS) score and Barthel Index (BI) scores. Patients with early death or withdrawal of life support (<72 hours) were excluded.

Demographics and ICH Characteristics
Demographic variables of interest included age, sex, race, and ICH risk factors (comorbidities). All patients had admission Glasgow Coma Scale (GCS) scores. Baseline clinical data obtained on admission included systolic and diastolic blood pressures, and coagulation parameters (International Normalized Ratio and partial thromboplastin time). HV and PHE volume were calculated using semiautomated planimetry and were read centrally within each specific trial by a single trial neuroradiologist. Anatomic determination of ICH location was also performed by the central neuroradiologist, who visually distinguished involvement of the basal ganglia and cortex using a detailed mapping grid to semiquantitatively score the locations involved with hematoma. In addition, when the anatomic distinction was not clear, the ICHs in the VISTA database were scored as both basal ganglia and lobar. These ICHs were few and were eliminated from the study. Hematoma expansion (HE) was defined as an increase in the absolute baseline HV by either 33% or >12.5 mL on the NCCT at 72 hours. In the absence of a standardized measurement tool for PHE, we used a previously validated measure of PHE, defined as the absolute increase in PHE volume from baseline to 72 hours and designated it as iPHE.

Outcome Measures
The primary outcome measure was poor outcome at day 90 defined as an mRS score of ≥3. The secondary outcome was BI at day 90.

Statistical Analysis
Binary logistic regression was used to assess the relationship between iPHE (independent variable) and poor outcome on the mRS (response variable). Similarly, we also constructed linear regression models to study the effect of iPHE on BI scores (response variable) measured on a continuous scale. Our objective for using 2 different functional outcome scales was to test the consistency of our results. Covariates used for the models included age, admission GCS, baseline HV, HE, lobar location, infratentorial location, intraventricular extension, warfarin use, and time to baseline CT scan. These variables were identified based on significant relationships with outcome on the unadjusted analysis with P<0.05. We then performed 2 subgroup analyses. The first was based on the location of ICH (lobar and basal ganglia) and the second was based on baseline HV, which is a strong independent predictor of outcome.
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predictor of ICH outcomes and has also been shown to influence PHE.7,17 We controlled for this confounding effect in a 2-fold manner: (1) by subdividing the population based on HV and (2) by using HV as a covariate in the multivariate model for each subgroup. The study population was divided into 2 groups using a baseline HV cut-off threshold of 30 mL, which has been used in previous studies.9,18 The effect of iPHE on outcomes was assessed separately in each of these subgroups using logistic regression. Covariates included in the primary analyses were used in these models. Statistical analyses were performed using SPSS (version 21.0, Chicago, IL). All analyses were 2 tailed, and significance level was determined by \( P < 0.05 \).

Results

We identified a total of 685 patients with spontaneous ICH. Withdrawal of care and early death (<72 hours) occurred in 89 patients, leaving 596 patients with ICH who were included in the study. The demographics and comorbidities of the study cohort are shown in Table 1. The mean age was 66.0 years with predominantly males (65.1% versus 34.9% females) and white population (80.3% versus other ethnicities). Among comorbidities, hypertension had the highest prevalence (81.5%) followed by diabetes mellitus (18.5%) and hyperlipidemia (20.8%). At baseline, the median HV was 15.0 mL (IQR, 7.9–29.2), whereas the median PHE volume was 8.7 mL (IQR, 4.5–15.5). HE was observed in 122 (34.9%) patients. At 72 hours, the median HV was 22.6 mL (IQR, 10.1–44.5) and the median PHE volume was 26.4 mL (IQR, 12.8–48.5). The median iPHE was 14.7 mL (IQR, 6.6–30.3). Death occurred in 130 patients (21.8%), and poor outcome (mRS, 3–6) occurred in 424 patients (71.1%).

We assessed the effect of iPHE on functional outcome using logistic regression (Table 2). iPHE was associated with significantly greater odds of poor outcome (OR, 1.78; CI, 1.12–2.64; \( P = 0.011 \)) per 1 mL increase) after adjustment for confounding variables. It was also associated with 90-day BI (\( \beta \), −0.10; SE, 0.09; \( P = 0.035 \)). iPHE correlated with mRS 3 to 6 (OR, 1.78; CI, 1.12–2.64; \( P = 0.011 \)) and with 90-day BI (\( \beta \), −0.10; SE, 0.09; \( P = 0.035 \)). In the subgroup analysis based on ICH location, iPHE was significantly associated with functional outcome in basal ganglia ICHs. There was no relationship between iPHE and outcomes in lobar ICH patients.

<table>
<thead>
<tr>
<th>Covariates</th>
<th>mRS 3–6 at 90 d</th>
<th>PValue</th>
<th>Barthe Index at 90 d</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adj. OR (95% CI)</td>
<td>PValue</td>
<td>( \beta ) (SE)</td>
</tr>
<tr>
<td>Increase in absolute PHE volume during 72 h (iPHE)</td>
<td>1.78 (1.12–2.64)</td>
<td>0.011*</td>
<td>−0.10 (0.09)</td>
</tr>
<tr>
<td>Age, per year</td>
<td>1.33 (1.10–1.71)</td>
<td>&lt;0.001*</td>
<td>−0.32 (0.12)</td>
</tr>
<tr>
<td>Hematoma volume, per mL</td>
<td>1.22 (1.05–1.52)</td>
<td>0.045*</td>
<td>−0.16 (0.09)</td>
</tr>
<tr>
<td>Admission GCS, per point</td>
<td>0.78 (0.66–0.92)</td>
<td>0.004*</td>
<td>0.26 (0.79)</td>
</tr>
<tr>
<td>Hematoma expansion</td>
<td>2.82 (1.27–6.25)</td>
<td>0.011*</td>
<td>−0.23 (4.20)</td>
</tr>
<tr>
<td>Infratentorial location</td>
<td>5.22 (1.39–19.96)</td>
<td>0.016*</td>
<td>−0.14 (7.41)</td>
</tr>
<tr>
<td>Intraventricular extension</td>
<td>2.52 (1.46–4.32)</td>
<td>0.001*</td>
<td>−0.13 (3.09)</td>
</tr>
<tr>
<td>Warfarin use</td>
<td>3.19 (0.36–27.92)</td>
<td>0.644</td>
<td>−0.53 (4.55)</td>
</tr>
<tr>
<td>Time to baseline CT scan</td>
<td>0.96 (0.74–1.35)</td>
<td>0.354</td>
<td>−0.05 (1.49)</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; GCS, Glasgow Coma Scale; ICH, intracerebral hemorrhage; iPHE, increase in perihematomal edema; OR, odds ratio; and mRS, modified Rankin Scale. \( * \) indicates \( P \) value <0.05.

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<td>Adj. OR (95% CI)</td>
<td>PValue</td>
<td>( \beta ) (SE)</td>
</tr>
<tr>
<td>Lobar ICH only (n=164, 27.5%)</td>
<td>0.97 (0.93–1.26)</td>
<td>0.220</td>
<td>0.04 (0.18)</td>
</tr>
<tr>
<td>Basal Ganglia ICH only (n=413, 69.3%)</td>
<td>1.49 (1.12–1.95)</td>
<td>0.005*</td>
<td>−0.15 (0.09)</td>
</tr>
<tr>
<td>HV &lt;30 mL (n=451, 75.7%)</td>
<td>1.97 (1.24–3.34)</td>
<td>0.035*</td>
<td>−0.13 (0.11)</td>
</tr>
<tr>
<td>HV &gt;30 mL (n=145, 24.3%)</td>
<td>1.11 (0.97–1.31)</td>
<td>0.513</td>
<td>−0.16 (0.14)</td>
</tr>
</tbody>
</table>

Each model was adjusted for age, baseline hematoma volume, admission GCS, hematoma expansion, infratentorial location, intraventricular extension, warfarin use, and time to computerized tomographic scan. CI indicates confidence interval; GCS, Glasgow Coma Scale; HV, hematoma volume; ICH, intracerebral hemorrhage; iPHE, increase in perihematomal edema volume during 72 h; mRS, modified Rankin Scale; and OR, odds ratio.
on HV (Table 3), iPHE was significantly associated with poor outcome in the HV <30 mL group (OR, 1.97; CI, 1.24–3.34; P=0.035) and also with BI (β, −0.13; SE, 0.11; P=0.024). However, iPHE did not correlate with outcomes in the HV >30 mL subgroup. The distribution of baseline ICH variables in the 2 HV categories is shown in Table II in the online-only Data Supplement.

Discussion

In this study, iPHE was significantly associated with poor functional outcomes after ICH. This association was location-dependent and volume-dependent effect, that is, in small to moderate volume hematomas and basal ganglia ICHs.

Several studies have reported an association between PHE and functional outcomes after ICH. Our findings corroborate a similar effect of PHE on functional outcomes of a recent pooled analysis of the INTERACT 1 and 2, where PHE had a significant impact on death or 90-day disability. This study in comparison with ours assessed PHE at 24 hours and did not correct for HE. In addition, we also observed that the influence of PHE on functional outcomes is likely dependent on HV. A similar observation was made in a small single-center prospective study (n=133), where PHE was associated with poor functional outcome (mRS>3) at discharge with smaller ICH volumes (<30 mL), with a 3-fold increase in the odds of severe disability with every 10 mL increase in PHE volume. Use of absolute PHE volumes only on admission and assessment of functional outcomes at discharge were notable shortcomings of the study. As to why PHE has a larger impact in case of smaller volume hematomas could be because of following reasons—first, HV is a strong predictor of ICH mortality, and mortality rates approaching 90% are seen with HV >30 mL. This implies that PHE may have a lesser independent influence on outcomes in large ICH. Second, smaller hematomas tend to have larger PHE volumes relative to HV, and PHE may hence have a stronger effect on outcomes in this subset. Because the majority of our study population was composed of patients with small (61.6%) and moderate hematomas (25.4%), the relationship between PHE and functional outcome in these 2 cohorts may have driven the overall effect of PHE on disability.

We report for the first time, that the effect of PHE on ICH outcomes is observed in basal ganglia hemorrhages after adjusting for HV. Although ICH location has not been shown to be a predictor of PHE (lobar versus basal ganglia ICHs), whether location has an influence on the relationship between PHE and outcomes has not been studied. Presumably, patients with PHE accompanying basal ganglia ICH location may have had higher cerebral herniation events, which may have predisposed to poorer outcomes. Nonavailability of extent of midline shift and herniation events in the VISTA database limited further exploration of these factors. Despite iPHE being significantly larger in lobar ICHs compared with basal ganglia hematomas, there was no association with functional outcome at this location. It is possible that the relatively smaller sample size of the lobar population may not have been powered to detect a significant association, or that larger HV in the lobar group drives the association with outcome. Another limitation is that the distinction between lobar and basal ganglia location in cases with overlap may have biased the results toward one group or the other.

Our study has some important limitations. First, the VISTA population had low ICH severity because these patients were selected from clinical trials that incorporate stringent selection criteria. The observed mortality rate of 21.8%, which is substantially lower that reported in population-based studies, and the overall low baseline HV limit the generalizability of our results to the general population. Second, like most studies, we only studied the effects of iPHE over 72 hours, although it is well known that edema can evolve well beyond this time frame. Caution is warranted before drawing firm conclusions about the lack of association between iPHE and outcomes in larger hematomas because our study may have lacked statistical power.

Although information was available on admission blood pressure parameters, subsequent blood pressure data were not available. It is possible that blood pressure control had a role to play in the higher proportion of patients with HE in our study; however, it seems less likely that blood pressure had a role in the evolution of PHE because 2 large ICH trials have demonstrated no relationship between these 2 factors. We accounted for this limitation by using HE as one of the covariates in the determination of the effect of iPHE on ICH outcomes. Despite these limitations, large prospectively collected databases like VISTA provide a unique opportunity to study outcomes in selective ICH cohorts.

Conclusions

PHE seems to have a significant impact on functional outcomes after spontaneous ICH, particularly in patients with small to moderate volume hematomas. PHE seems to correlate with disability in basal ganglia ICH more than lobar ICH. These findings suggest that basal ganglia hematomas and ICHs with HV<30 cc may represent an optimal target for interventions designed to ameliorate secondary injury in ICH.

Appendix


Sources of Funding

Dr Hanley was awarded significant research support through grant numbers 1U01NS062851 for Clot Lysis Evaluation of Accelerated Resolution of Intraventricular Hemorrhage III and for Minimally Invasive Surgery Plus Recombinant Tissue-Type Plasminogen Activator for Intracerebral Hemorrhage Evacuation (MISTIE) III 1U01NS08082.

Disclosures

None.

References


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Stroke. 2015;46:3088-3092; originally published online September 22, 2015;
doi: 10.1161/STROKEAHA.115.010054

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/46/11/3088

Data Supplement (unedited) at:
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SUPPLEMENTAL MATERIAL

Perihematomal Edema and Functional Outcomes in Supratentorial Hemorrhage: Influence of Hematoma Volume and Location

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<table>
<thead>
<tr>
<th>ICH characteristics</th>
<th>Lobar ICH N=164 (27.5%)</th>
<th>Basal Ganglia ICH N=413 (69.3%)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Admission GCS, median (IQR)</td>
<td>14 (13-15)</td>
<td>14 (13-15)</td>
<td>0.764</td>
</tr>
<tr>
<td>GCS &lt;9</td>
<td>36 (21.7)</td>
<td>74 (17.9)</td>
<td>0.487</td>
</tr>
<tr>
<td>Median Baseline NIHSS (IQR)</td>
<td>12 (8-18)</td>
<td>14 (10-18)</td>
<td>0.190</td>
</tr>
<tr>
<td>Hematoma volume at baseline (cc), median (IQR)</td>
<td>29.3 (18.1-53.5)</td>
<td>13.4 (7.9-22.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hematoma Volume at 72 hours (cc), median (IQR)</td>
<td>38.9 (25.4-71.7)</td>
<td>18.3 (9.8-35.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hematoma Expansion</td>
<td>43 (26.2)</td>
<td>82 (19.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PHE at baseline (cc), median (IQR)</td>
<td>16.7 (9.7-28.2)</td>
<td>7.7 (4.7-12.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PHE at 72 hours (cc), median (IQR)</td>
<td>45.9 (22.5-77.2)</td>
<td>22.7 (11.9-38.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Absolute increase in PHE over 72 hours (IQR)</td>
<td>25.2 (8.6-46.9)</td>
<td>13.2 (6.5-25.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Median Time to Initial CT scan (in hours, IQR)</td>
<td>1.9 (1.5-2.9)</td>
<td>1.9 (1.5-2.7)</td>
<td>0.443</td>
</tr>
</tbody>
</table>

**Supplemental Table I**: Baseline ICH characteristics of patients with intracerebral Hemorrhage based on location of the hematoma
CT: Computerized Tomography, GCS: Glasgow Coma Scale, PHE: Perihematomal edema, IQR: Inter Quartile Range
**Supplemental Table II**: Baseline ICH characteristics of patients with intracerebral hemorrhage based on hematoma volumes

CT: Computerized Tomography, GCS: Glasgow Coma Scale, HV: Hematoma Volume, ICH: Intracerebral Hemorrhage, PHE: Perihematomal edema, IQR: Inter Quartile Range