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Rate of Perihaematomal Oedema Expansion is Associated with Poor Clinical Outcomes in Intracerebral Haemorrhage

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Abstract

Background—Perihaematomal oedema (PHE) expansion rate may be a predictor of outcome after intracerebral haemorrhage (ICH). We determined whether PHE expansion rate in the first 72 hours after ICH predicts outcome, and how it compares against other PHE measures.

Methods—We included patients from the Virtual International Stroke Trials Archive. We calculated PHE expansion rate using the equation: (PHE at 72 hours- PHE at baseline)/(Time to 72 hour computerized tomography scan – Time to baseline computerized tomography scan). Outcomes of interest were mortality and poor 90-day outcome (modified Rankin Scale score of 3). Logistic regression was used to assess relationships with outcome.

Results—A total of 596 patients with ICH were included. At baseline, median haematoma volume was 15.0 mL (IQR: 7.9–29.2) with median PHE volume of 8.7 mL (IQR: 4.5–15.5). Median PHE expansion rate was 0.31 mL/hr (IQR: 0.12–0.55). The odds of mortality were greater with increasing PHE expansion rate (OR: 2.63, CI: 1.10–6.25), while the odds of poor outcome

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also increased with greater PHE growth (OR: 1.67, CI: 1.28–2.39). Female sex had an inverse relationship with PHE growth, but baseline hematoma volume had a direct correlation. Among other PHE measures, only interval increase in PHE correlated with poor outcome. There was no significant difference between the two measures of PHE volume expansion.

Conclusions—Rate of PHE growth over 72 hours was an independent predictor of mortality and poor functional outcomes following intracerebral haemorrhage. Baseline haematoma volume and gender appear to influence PHE growth.

Keywords

Intracerebral haemorrhage; perihematoma oedema; mortality; functional outcome

Introduction

Perihematoma oedema (PHE) is a radiological marker for secondary injury following spontaneous intracerebral haemorrhage (ICH).¹ PHE is hypothesized to occur following the activation of inflammatory pathways by haeme products.² Studies assessing the association between PHE and ICH outcomes have yielded conflicting results, perhaps due to small sample sizes, retrospective design and selection bias, and heterogeneity in the measurement techniques and timing of imaging. For instance, the relative oedema volume, a ratio obtained by dividing PHE by the baseline haematoma volume³, is limited by strong collinearity between PHE and haematoma volume and the tendency to be disproportionately higher in small haematomas compared to larger ones.³ Studies that measured absolute baseline PHE volume⁴ and interval increase in PHE over 24 hours⁵ have both shown that these measurements correlate with poor functional outcomes but not with mortality.

Although PHE evolves over the first week after ICH, its growth is believed to be fastest in the first 48–72 hours.⁶ We previously reported that absolute increase in PHE over 72 hours was associated with worse functional outcomes following ICH, particularly with basal ganglia ICH and haematomas <30 mL.⁷ In a single center cohort in which subjects with significant intraventricular haemorrhage (IVH) and warfarin related ICH were excluded, we reported that PHE growth rate at 24 hours was independently associated with death or disability.⁸ However, at 72 hours, PHE growth rate correlated with functional outcome but not with mortality.⁸ This may have been due to the small sample size of the study that limited the power to detect a significant association. These results need to be replicated in a large multicenter cohort that has greater external validity. Emerging data suggest that PHE growth is a feasible biomarker for secondary injury that reduces the sample size in ICH studies required to find a statistically significant difference in outcomes, and is therefore a good clinical trial endpoint in phase II, proof of concept ICH trials.⁹ If PHE expansion rate is predictive of outcome in multiple independent cohorts, it may provide an attractive therapeutic target for future clinical trials aimed at improving outcome after ICH, a disease with a high rate of mortality and neurological morbidity and with no current therapy beyond blood pressure management.

The rapidity of oedema enlargement is a time-sensitive function, and from a mathematical standpoint requires precise time based plots. Unfortunately, neuroimaging in the clinical

setting often tends to occur at variable time periods based on logistic factors such as patient's hemodynamic stability, bedside procedures etc. Hence we aimed to quantify PHE expansion more accurately by considering the exact time lapsed from the initial neuroimaging scan. In the present study, we quantified PHE expansion as 'rate of growth per hour' in the first 72 hours - the time period of rapid PHE growth. Our aim was three fold-one, to study the relationship between PHE expansion rate and ICH outcomes, two, to study factors associated with PHE expansion, and three to compare PHE expansion rate with previously reported measures.

Methods

Patient Selection

We used data contained in the Virtual International Stroke Trials Archive ICH (VISTA-ICH).¹⁰ 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 from the local ethics board; 3) baseline assessment within 24 hours of stroke; 4) baseline assessment of neurologic 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. The VISTA cohort used in this study consisted of patients in the placebo-controlled arm (non-surgical, non-intervention). Only patients presenting with non-contrast computed tomography (CT) proven ICH within 6 hours of symptom onset, and with baseline clinical, radiologic, and laboratory data were selected. All patients had follow-up CT scan at 72 hours, and 90-day modified Rankin Scores (mRS). 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 data obtained on admission included systolic and diastolic blood pressures and coagulation parameters (International Normalized Ratio and partial thromboplastin time). Haematoma volume (HV) and PHE volume were calculated using semi-automated planimetry and were read centrally within each specific trial by a single trial neuroradiologist. Haematoma expansion (HE) was defined as an increase in the absolute baseline HV by either 33% or 12.5 mL of that on the CT at 72 hours.¹¹ PHE expansion rate was calculated by using the formula $(\text{PHE at 72 hours} - \text{PHE at baseline}) / (\text{Time to 72 hour CT scan} - \text{Time to baseline CT scan, in hours})$ and was quantified as mL/hour. Availability of exact timelines for the baseline and 72-hour CT scans in the VISTA database enabled us to accurately calculate the PHE growth rate for each patient.

Outcome Measures

The primary outcome measures were 90-day mortality and poor outcome at 90 days defined as mRS score of 3–6. Secondary outcome measure was predictors of PHE expansion rate over 72 hours.

Statistical Analysis

The Mann-Whitney U test was used for continuous variables because they were not normally distributed. The Pearson Chi square test (Fisher exact test when appropriate) was used for categorical variables. Binary logistic regression was used to assess the relationship between PHE expansion rate and ICH outcome variables. Covariates used for the regression models included age, admission GCS, baseline HV, 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 $p < 0.05$. To study variables associated with PHE expansion, we first performed bivariate linear regression to identify variables with significance of $p < 0.05$. Logarithmic transformations were used when the relationship between the variable and PHE expansion was non-linear. These covariates were then included in the multivariable linear regression. Statistical analyses were performed using Stata (version 14.0, College Station, TX). All analyses were two-tailed, and significance level was determined by $p < 0.05$.

Results

We included a total of 596 ICH patients in the study. At baseline, median haematoma volume was 15.0 mL (interquartile range [IQR]: 7.9–29.2), and the median PHE volume was 8.7 mL (IQR: 4.5–15.5) as shown in Table 1. The median PHE expansion rate was 0.31 mL/hr (IQR: 0.12–0.55). There were 110 deaths (20.9%), and 90-day poor functional outcome occurred in 367 patients (69.6%). PHE expansion rates were 0.51 mL/hr among patients who died (vs. 0.17 mL/hr in those who survived) and 0.35 mL/hr among those with poor functional outcome (vs. 0.12 mL/hr in those with good functional outcome) as seen in Table 2.

In the logistic regression model adjusted for the above mentioned confounders, PHE expansion rate was associated with a higher odds of mortality (OR: 2.63, 95% CI: 1.10–6.25, $p = 0.03$) and higher odds of poor functional outcome (OR: 1.67, 95% CI: 1.28–2.39, $p = 0.01$). In the adjusted linear regression model that assessed factors associated with PHE expansion at 72 hours (Table 3), female sex was associated with lower PHE expansion (beta: -0.09 , $p = 0.01$), while baseline hematoma volume had a direct relationship with PHE expansion (beta: 0.23, $p < 0.001$).

We then constructed regression models to assess the odds of poor outcome with other previously validated methods of measuring PHE (Table 4). These included absolute PHE volume at baseline, absolute PHE volume at 72 hours, interval increase in absolute PHE volume over 72 hours, and relative PHE volume at baseline. Of these measures, interval increase in absolute PHE volume over 72 hours was associated with poor functional outcomes (OR: 1.78, 95% CI: 1.12–2.64, $p = 0.01$), and with mortality (OR: 1.08, 95% CI: 1.03–1.18, $p = 0.02$). Higher absolute PHE at 72 hours had greater odds of poor functional outcomes (OR: 1.02, 95% CI: 1.01–1.04, $p = 0.03$), but not with mortality (OR: 1.02, 95% CI: 0.98–1.04, $p = 0.09$). The other PHE measures were not associated with ICH outcomes. Additionally, we plotted the receiver operator curves for PHE growth rate and interval increase in PHE volume over 72 hours (Figures 1 and 2). We found no statistically significant difference between the two measures for mortality, with the area under the curve

for PHE growth rate being 0.692 and that for interval increase in PHE 0.727 (p value=0.690). Similarly, there was no difference for poor functional outcome either (p value=0.783).

Discussion

In this large prospective pooled multicenter international trials cohort, PHE expansion rate was independently associated with poor outcome following ICH. PHE growth rate was three times higher in patients with poor outcomes. In comparison with previously studied PHE measures, PHE growth rate and absolute PHE increase over 72 hours were the only two measures that were associated with both mortality and poor functional outcome.

A recent pooled analysis of the Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial (INTERACT) - 1 and 2 trials showed a significant association between PHE and functional outcomes but not with mortality.⁵ The use of interval increase in PHE volumes over a shorter time frame of 24 hours may have led to these results. A smaller prospective study measured absolute PHE volume at baseline and found similar results, but this study used a shorter timeline for outcome assessment (hospital discharge).⁴ We believe that because rate of PHE growth is fastest in the first 72 hours⁶, using a slightly delayed timeframe for PHE measurement allowed us to capture PHE expansion more accurately, thereby accounting for the significant association with mortality. In our secondary analyses, while interval increase in absolute PHE volume at 72 hours correlated with both mortality and poor functional outcomes, absolute PHE volume at 72 hours alone was associated with disability but not with mortality. This suggests that dynamic changes in PHE appear to influence ICH outcomes rather than the absolute PHE volume at a given time point. However, there was no difference between the two dynamic measures of PHE- rate of growth and interval expansion over 72 hours.

Baseline HV, in our study, was independently associated with PHE expansion, which corroborates results from prior studies.^{4,12,13} However, a noteworthy observation was that female patients had significantly lower PHE expansion compared to male patients. Previously Wagner et al. reported similar findings and suggested a possible neuroprotective effect of estrogen.¹⁴ In addition, more-effective autoregulatory mechanisms in women may have contributed to lower PHE growth.¹⁴ From a pathophysiologic standpoint, the underlying mechanism of development of PHE has not been elucidated fully, although animal data suggest the role of inflammation. Data from experimental ICH models have shown cytokines, matrix metalloproteinases, reactive oxygen species and thrombin play a role in secondary injury.¹ However, there is a paucity of similar data in humans. In our study, PHE growth rate was almost three times faster in ICH patients with poor outcome compared with those with good outcome. With recent evidence exploring PHE expansion rate as a potential biomarker for the inflammatory response², one may speculate whether higher rates of PHE growth may be attributed to a more severe inflammatory process.

The use of an ICH cohort with well-defined inclusion criteria and pre-established time points for data collection and CTs are inherent strengths of this study. Moreover, assessment of PHE up to 72 hours is well beyond the timeline used in prior studies. Exclusion of

patients who underwent surgery is also a strength of this analysis, since decompression alters oedema volume measurements and often obscures the association of oedema and poor outcome². However, this exclusion limits the results of the present study to ICH patients who do not have surgical intervention. This study has some important limitations. First, the ICH severity (based on GCS scores and haematoma volumes) in the VISTA patients is lower compared to those in the general population since these patients were selected from clinical trials, which affects the generalizability. Second, we assessed PHE growth for only the first 72 hours, although PHE evolves beyond this timeframe. Third, our method of PHE measurement assumes a uniform rate of PHE growth, which is unlikely to be the case. From a practical standpoint, obtaining multiple CT scans during the hospitalizations was not feasible. Hence pre-established timed assessments of PHE volumes at 0 and 72 hours ensured homogeneity. Data on body temperature or the use of osmotherapy, both known modifiers of PHE volume¹⁵¹⁶, were also not available. Finally, the VISTA database did not provide information on blood pressure control, which could potentially affect PHE volumes, although randomized studies have suggested evidence to the contrary.¹⁷¹⁸

In conclusion, our study supports other work that dynamic change in PHE volume over time, whether PHE growth rate or absolute expansion in volume, is associated with poor outcomes after ICH. Further prospective confirmation with larger haematoma volumes would be useful. Targeting PHE growth appears to be an exciting avenue for new therapies for patients with ICH.

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Appendix

VISTA-ICH Steering Committee

D. F. Hanley (Chair), K. Butcher, S. Davis, B. Gregson, K.R. Lees, P. Lyden, S. Mayer, K. Muir and T. Steiner.

Figure 1.
Receiver operator curves for mortality
Area under the curve for each measure
PHE growth rate: 0.692
iPHE: 0.727
Abbreviations: PHE: Perihæmatomal oedema

Figure 2.
Receiver operator curves for mRS 3–6
Area under the curve for each measure
PHE growth rate: 0.668
iPHE: 0.679
Abbreviations: PHE: Perihæmatomal oedema

Table 1

Baseline demographics and ICH characteristics of patients with intracerebral haemorrhage.

Demographic Characteristics	ICH cases N= 596 (%)
Age in years, median (IQR)	66.0 (56.0–75.0)
Sex	
Males	388 (65.1)
Females	208 (34.9)
Race	
Caucasians	476 (80.3)
African Americans	27 (4.6)
Asians	78 (13.2)
Others	12 (2.0)
Diabetes mellitus	110 (18.5)
Hypertension	486 (81.5)
Hyperlipidemia	55 (9.2)
Atrial fibrillation	39 (6.5)
Antiplatelet Use	85 (14.3)
Warfarin Use	19 (3.2)
Admission HbA1C	6.8 (5.8–8.4)
ICH Characteristics	
Admission GCS, median (IQR)	14 (13–15)
GCS <9	116 (19.5)
Median Baseline NIHSS (IQR)	14.0 (9.0–18.0)
Haematoma volume at baseline (mL), median (IQR)	15.0 (7.9–29.2)
Haematoma Volume at 72 hours (mL), median (IQR)	22.6 (10.1–44.5)
PHE at baseline (mL), median (IQR)	8.7 (4.5–15.5)
PHE at 72 hours (mL), median (IQR)	26.4 (12.8–48.5)
Median rate of PHE growth (mL/hour, IQR)	0.31 (0.12–0.55)
Lobar Location of ICH	176 (29.6)
Basal Ganglia ICH	400 (67.2)
Infratentorial ICH	20 (3.2)

Demographic Characteristics	ICH cases N= 596 (%)
Intraventricular Haemorrhage	178 (29.8)
Hydrocephalus	384 (64.4)
Median Time to Initial CT scan (in hours, IQR)	1.9 (1.5–2.5)
Median Time to 72-hour CT scan (in hours, IQR)	70.5 (65.2–75.8)
Admission Systolic Blood Pressure (mm Hg), median (IQR)	174.0 (154.0–194.0)
Admission Diastolic Blood Pressure (mm Hg), median (IQR)	91.0 (80.0–105.0)
Admission INR, median (IQR)	1.0 (0.9–1.1)
Admission aPTT in seconds, median (IQR)	26.8 (23.6–31.6)

Abbreviations: aPTT: Partial Thromboplastin Time, CT: Computerized Tomography, GCS: Glasgow Coma Scale, ICH: Intracerebral Haemorrhage, INR: International Normalized Ratio, IQR: Inter Quartile Range, mL: milliliters, PHE: Perihematoma Oedema

Table 2

Multivariable analysis of rate of perihæmatomal oedema growth on outcomes in intracerebral hæmorrhage.

Outcome Variables	N (%)	PHE Expansion Rate (mL/Hour)	Adj. OR (95% CI)	p value
Mortality at 90 days	110 (20.9)	0.51 (vs. 0.17 in survivors)	2.63 (1.10–6.25)	0.03
Death or Disability at 90 days (mRS 3–6)	367 (69.6)	0.35 (vs. 0.12 in mRS 0–2)	1.67 (1.28–2.39)	0.01

Models adjusted for age, admission GCS, baseline hæmatoma volume, lobar location, infratentorial location, intraventricular extension, warfarin use, and time to baseline CT scan.

Abbreviations: Adj: adjusted, CI: Confidence Interval, ICH: Intracerebral Haemorrhage, mL: milliliters, mRS: modified Rankin Scale, OR: Odds Ratio, PHE: Perihæmatomal Oedema

Table 3

Linear Regression showing factors associated with perihematoma edema expansion at 72 hours

Modifier of PHE	Unadjusted Analysis		Adjusted Analysis	
	Beta (SE)	p value	Beta (SE)	p value
Age	−0.06 (0.08)	0.91	-	
Female	−0.10 (2.06)	0.02	−0.09 (1.93)	0.01
Race	−0.03 (1.34)	0.53	-	
Log admission systolic blood pressure	0.07 (0.03)	0.11	-	
Log admission diastolic blood pressure	0.05 (0.25)	0.78	-	
Admission hemoglobin A1C	0.12 (0.36)	0.007	0.04 (0.32)	0.37
Prior statin use	−0.04 (2.31)	0.44	-	
Prior warfarin use	0.05 (3.27)	0.23	-	
Log admission GCS	−0.19 (0.53)	<0.001	−0.04 (0.52)	0.32
Log baseline haematoma volume	0.50 (0.04)	<0.001	0.23 (0.09)	<0.001
Log time to baseline CT scan	0.05 (1.08)	0.22	-	
Log time to 72 hour CT scan	0.08 (0.20)	0.24	-	

Only variables significant in the bivariate unadjusted analysis were included in the multivariable analysis.

Abbreviations: CT: Computerized Tomography, GCS: Glasgow Coma Scale, Logarithm to base 10.

Table 4

Multivariable analysis of rate of perihaematomal oedema volume using different perihaematomal oedema expansion definitions, on clinical outcomes in intracerebral haemorrhage.

PHE definition	Adj. OR (95% CI)	p value
Mortality at 90 days		
Interval increase in absolute PHE over 72 hours	1.08 (1.03–1.18)	0.02
Absolute PHE at baseline	1.03 (0.98–1.07)	0.09
Absolute PHE at 72 hours	1.02 (0.98–1.04)	0.09
Relative PHE at baseline	0.72 (0.36–1.44)	0.35
Death or Disability at 90 days (mRS 3–6)		
Interval increase in absolute PHE over 72 hours	1.78 (1.12–2.64)	0.01
Absolute PHE at baseline	1.01 (0.97–1.06)	0.63
Absolute PHE at 72 hours	1.02 (1.01–1.04)	0.03
Relative PHE at baseline	0.85 (0.57–1.28)	0.44

Models adjusted for age, admission GCS, baseline haematoma volume, lobar location, infratentorial location, intraventricular extension, warfarin use, and time to baseline CT scan.

Abbreviations: Adj: adjusted, CI: Confidence Interval, ICH: Intracerebral Haemorrhage, mL: milliliters, mRS: modified Rankin Scale, OR: Odds Ratio, PHE: Perihaematomal Oedema