Significance of perihematomal edema in acute intracerebral hemorrhage

The INTERACT trial

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ABSTRACT

Background: Uncertainty surrounds the effects of cerebral edema on outcomes in intracerebral hemorrhage (ICH).

Methods: We used data from the INTERACT trial to determine the predictors and prognostic significance of "perihematomal" edema over 72 hours after ICH. INTERACT included 404 patients with CT-confirmed ICH and elevated systolic blood pressure (BP) (150–220 mm Hg) who had the capacity to commence BP lowering treatment within 6 hours of ICH. Baseline and repeat CT (24 and 72 hours) were performed using standardized techniques, with digital images analyzed centrally. Predictors of growth in edema were determined using generalized estimating equations, and its effects on clinical outcomes were estimated using a logistic regression model.

Results: Overall, 270 patients had 3 sequential CT scans available for analyses. At baseline, there was a highly significant correlation between hematoma and perihematomal edema volumes (r^2 = 0.45). Lower systolic BP and baseline hematoma volume were independently associated with absolute increase in perihematomal edema volume. History of hypertension, baseline hematoma volume, and earlier time from onset to CT were independently associated with relative increase in edema volume. Both absolute and relative increases in perihematomal edema growth were significantly associated with death or dependency at 90 days after adjustment for age, gender, and randomized treatment, but not when additionally adjusted for baseline hematoma volume.

Conclusions: The degree of, and growth in, perihematomal edema are strongly related to the size of the underlying hematoma of acute intracerebral hemorrhage, and do not appear to have a major independent effect in determining the outcome from this condition. ***Neurology*® 2009;73:1963–1968**

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GLOSSARY

AHA = American Heart Association; **BP** = blood pressure; **CI** = confidence interval; **DICOM** = Digital Imaging and Communications in Medicine; **GCS** = Glasgow Coma Scale; **ICH** = intracerebral hemorrhage; **INTERACT** = Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial; **IQR** = interquartile range; **mRS** = modified Rankin scale; **NIHSS** = National Institutes of Health Stroke Scale; **SD** = standard deviation; **SE** = standard error.

Acute intracerebral hemorrhage (ICH) is estimated to affect over 1 million people worldwide each year,[1,2] most of whom either die or are left seriously disabled.[1-3] Brain injury after ICH involves different mechanisms such as physical trauma and mass effect due to hematoma and associated cerebral edema, and secondary adverse effects of coagulation cascade, hemoglobin breakdown products, and inflammation.[4] Among these, hematoma volume is the most important determinant of poor clinical outcomes in ICH.[5] Development of perihematomal edema also leads to an elevation in intracranial pressure or hydrocephalus with subsequent clinical deterioration.[6,7]

There are several potential mechanisms underlying the formation of cerebral edema after ICH.[4] In a very early phase (first few hours) there is the development of hydrostatic pressure and clot

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retraction, with the movement of serum from the hematoma into the surrounding tissue.[8] A second phase (first few days) is related to the coagulation cascade and thrombin production, and the third phase is related to erythrocyte lysis and hemoglobin toxicity. However, the predictors and prognostic significance of growth in cerebral edema after ICH are still controversial and further investigation is needed to help guide treatment of this condition.

The pilot phase of the Intensive Blood Pressure Reduction In Acute Cerebral Haemorrhage Trial (INTERACT) was an international, open, randomized controlled trial which investigated the effects of early intensive blood pressure (BP) lowering in patients with acute spontaneous ICH.[9] In this article, we used data from INTERACT to determine the natural course, predictors, and prognostic significance of perihematomal edema in patients with acute ICH.

Table 1 Baseline characteristics of patients by perihematomal edema analysis status

	Patients included in edema analysis (n = 270)	Patients excluded from edema analysis (n = 134)
Time from ICH onset to randomization, h, median (IQR)	3.61 (2.86–4.77)	3.75 (2.95–4.99)
Age, y, mean (SD)	63 (12)	61 (13)
Male, n (%)	174 (64)	88 (66)
Country of residence, n (%)		
China	251 (93)	133 (99)
Australia	12 (4)	1 (1)
South Korea	7 (3)	0 (0)
Medical history, n (%)		
Hypertension	199 (74)	101 (75)
Previous ICH	33 (12)	13 (10)
Ischemic stroke	28 (10)	16 (12)
Acute coronary event	6 (2)	8 (6)
Diabetes mellitus	23 (9)	11 (8)
Medication, n (%)		
Antihypertensive therapy	117 (43)	58 (43)
Antiplatelet therapy	24 (9)	8 (6)
Warfarin anticoagulation	3 (1)	1 (1)
Clinical features		
Systolic BP, mm Hg, mean (SD)	181 (18)	181 (18)
Diastolic BP, mm Hg, mean (SD)	102 (14)	104 (16)
Heart rate, beats/min, mean (SD)	79 (14)	79 (14)
Median (IQR) NIHSS score*	9 (5–15)	10 (6–16)
NIHSS score ≥14, n (%)	81 (30)	44 (33)
Median (IQR) GCS score†	14 (13–15)	1 (11–15)
GCS score <9, n (%)	20 (7)	14 (10)
Location of hematoma, n (%)		
Lobar	22 (8)	7 (10)
Basal ganglia or thalamus	228 (84)	58 (80)
Brainstem	10 (4)	2 (3)
Cerebellum	8 (3)	5 (7)
Intraventricular extension	66 (24)	13 (18)

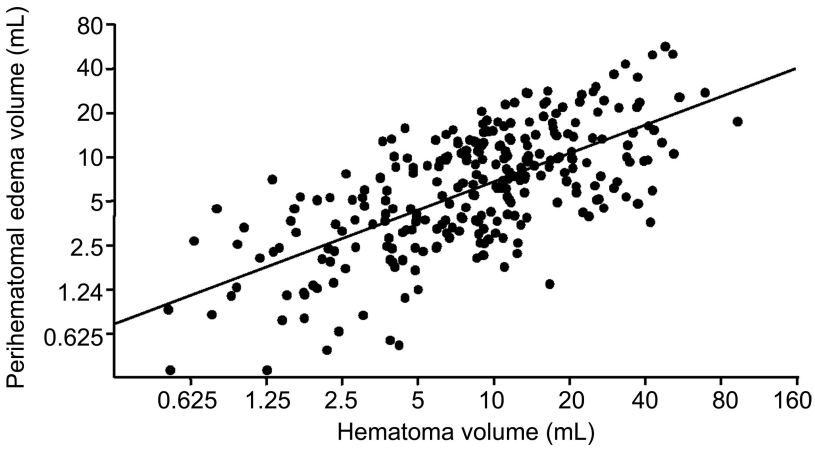
*Scores range from 0 (normal) to 42 (coma with quadriplegia).
†Scores range from 3 (deep coma) to 15 (normal).
ICH = intracerebral hemorrhage; BP = blood pressure; NIHSS = National Institutes of Health Stroke Scale; GCS = Glasgow Coma Scale.

METHODS **Study design and participants.** The design of the INTERACT has been described in detail elsewhere.[9] Briefly, 404 patients were recruited from multiple hospital sites in China, South Korea, and Australia between November 2005 and April 2007. Eligible patients were aged ≥18 years with CT confirmed spontaneous ICH and elevated systolic BP (≥2 measurements of ≥150 mm Hg and ≤220 mm Hg recorded ≥2 minutes apart), with the capacity to commence randomly assigned BP lowering treatment within 6 hours of the onset of ICH in a suitably monitored environment. Exclusion criteria were a clear indication for, or contraindication to, intensive BP lowering; ICH secondary to a structural cerebral abnormality or the use of a thrombolytic agent; a recent ischemic stroke; deep coma; significant prestroke disability or medical illness; and early planned neurosurgical intervention.

Patients were randomly assigned to receive either an early intensive BP-lowering treatment strategy or the recommended best practice standard of BP lowering at the time, that of the American Heart Association (AHA) guidelines published in 1999.[10] For patients allocated to the intensive group, the goal was to achieve a systolic BP of 140 mm Hg within 1 hour of randomization and subsequently to maintain this target level for the next 7 days. For patients allocated to the guideline group, treatment was recommended to achieve a target systolic BP of 180 mm Hg.

Procedures. Sites were required to perform CT scans on patients according to standardized techniques at baseline and at 24 ± 3 and 72 ± 3 hours after the initial CT. For these analyses, if the 24-hour CT scan was not done within the specified time period, this assessment was replaced by the first available scan between 27 and 48 hours, or by the last available scan between 6 and 24 hours if this was the only CT scan available. Similarly, if the 72-hour CT scan was not done within the specified time period, this assessment was replaced by the first available scan between 75 and 80 hours, or by the last available scan between 48 and 69 hours. For each patient, uncompressed digital images were sought by the analysis laboratory in Digital Imaging and Communications in Medicine (DICOM) format. Hematoma and perihematomal edema volumes were calculated independently by 2 trained neurologists who were blind to clinical data, treatment, and date and sequence of scan, using computer-assisted multislice planimetric and voxel threshold techniques in MIStar software, version 3.2 (Apollo Medical Imaging Technology, Melbourne, Australia).[11] Inter-reader reliability was tested by reanalysis of 10% of CT scans by both readers after 30% and 60% of the scans were completed, to avoid drift (intraclass correlation coefficient 0.97, 95% confidence interval [CI] 0.95–0.98 for hematoma volume; and 0.91, 95% CI 0.87–0.94 for perihematomal edema volume). Perihematomal edema volumes were

Figure Association between hematoma and perihematomal edema volumes at baseline



Linear regression line was estimated using a simple linear regression model. Hematoma and perihematomal edema volumes were log-transformed to remove skewness. Log of edema volume (mL) = 0.446 + 0.642 × log of hematoma volume (mL). $r^2 = 0.45$.

not estimated in the small number of CT scans which were received as digital images or plain films.

Clinical assessments were performed on enrollment, at 24 and 72 hours, and at 7, 28, and 90 days after randomization. These clinical assessments included the NIH Stroke Scale (NIHSS)[12] and the modified Rankin scale (mRS).[13] The clinical outcome in the present analysis was the combination of death and dependency (defined by a mRS score of 3–5) at the end of follow-up at 90 days.

Standard protocol approvals, registrations, and patient consents. The trial was conducted in compliance with the principles outlined in the World Medical Association's Declaration of Helsinki. The study protocol was approved by the appropriate ethics committee at each participating site. Written informed consent was obtained from each patient or legal surrogate in situations where the patient were unable to do so. This study was registered with ClinicalTrials.gov (NCT002226096).

Statistical analysis. Hematoma and perihematomal edema volumes were log-transformed to remove skewness for all analyses. Geometrical means of perihematomal edema volumes were reported with 95% CI obtained by back-transformation. The association between log-transformed hematoma and perihematomal edema volumes was evaluated using a simple linear regression model. Predictors of absolute and relative increase in perihematomal edema over 72 hours were ascertained by generalized estimating equations using increases in volumes as repeat measures. Relative changes in perihematomal edema volumes were calculated as ([edema volume at 24 or 72 hours/baseline edema volume] − 1) and then log-transformed to remove skewness after addition of the value 1.1 to eliminate negative values, thus achieving approximate normality for these analyses. Effects of absolute and relative increase in perihematomal edema volume on clinical outcomes were estimated using univariate and multivariate logistic regression models. A standard level of significance ($p < 0.05$) was used and the data were reported with 95% CI. Analyses were performed using SAS statistical software (version 9.1).

RESULTS Among the 404 patients recruited into INTERACT, a total of 296 (73%) patients had all 3 CT scans (baseline, 24 and 72 hours) available for analyses and perihematomal edema volume could be determined in 270 (67%) patients with CT scans available in DICOM format. Table 1 shows that patients with and without perihematomal edema analysis had broadly similar baseline characteristics except

Table 2 Predictors of absolute increase in perihematomal edema volume over 72 hours

	Univariate analysis			Multivariate analysis		
	Beta	SE	*p* Value	Beta	SE	*p* Value
Age (per 10 years)	−0.750	0.683	0.27	−0.504	0.525	0.34
Sex (male vs female)	−1.227	1.607	0.45	−1.409	1.226	0.25
Hypertension (yes vs no)	1.948	1.604	0.22	1.052	1.181	0.37
Previous ICH (yes vs no)	−1.529	3.172	0.63	0.662	3.072	0.83
Previous ischemic stroke (yes vs no)	−0.996	2.302	0.67	−2.947	2.543	0.25
Diabetes mellitus (yes vs no)	−4.236	1.472	0.004	0.500	1.521	0.74
Antiplatelet therapy (yes vs no)	6.484	5.398	0.23	2.836	4.236	0.50
Warfarin anticoagulation (yes vs no)	29.924	24.891	0.23	27.903	20.600	0.18
Systolic BP (per 20 mm Hg)	−1.340	0.736	0.07	−1.196	0.522	0.02
Heart rate (per 10 beats/min)	−0.666	0.505	0.19	−0.580	0.389	0.14
NIHSS score (≥14 vs <14)	6.647	1.807	0.0002	1.971	1.494	0.19
Location of hematoma (lobar vs others)	4.092	4.062	0.31	−3.277	2.938	0.26
Log of baseline hematoma volume (per 1)	6.250	0.929	<0.0001	5.664	0.819	<0.0001
Time from ICH onset to CT (per 1 hour)	−1.497	0.715	0.04	−1.007	0.696	0.15
Randomized treatment (intensive vs standard)	−1.659	1.546	0.28	−2.129	1.443	0.14

Values were calculated by generalized estimating equations.
ICH = intracerebral hemorrhage; BP = blood pressure; NIHSS = National Institutes of Health Stroke Scale; SE = standard error.

Table 3 Predictors of relative increase in perihematomal edema volume over 72 hours*

	Univariate analysis			Multivariate analysis		
	Beta	SE	p Value	Beta	SE	p Value
Age (per 10 years)	−0.048	0.023	0.04	−0.043	0.024	0.07
Sex (male vs female)	−0.010	0.059	0.87	−0.008	0.054	0.88
Hypertension (yes vs no)	0.121	0.062	0.05	0.116	0.057	0.04
Previous ICH (yes vs no)	−0.160	0.106	0.13	−0.122	0.111	0.27
Previous ischemic stroke (yes vs no)	−0.083	0.092	0.37	−0.118	0.090	0.19
Diabetes mellitus (yes vs no)	−0.096	0.118	0.41	0.033	0.130	0.80
Antiplatelet therapy (yes vs no)	0.119	0.114	0.30	−0.015	0.112	0.89
Warfarin anticoagulation (yes vs no)	0.561	0.322	0.08	0.456	0.251	0.07
Systolic BP (per 20 mm Hg)	−0.042	0.032	0.19	−0.042	0.030	0.17
Heart rate (per 10 beats/min)	−0.037	0.021	0.08	−0.036	0.019	0.06
NIHSS score (≥14 vs <14)	0.075	0.063	0.24	−0.101	0.062	0.10
Location of hematoma (lobar vs others)	0.087	0.215	0.69	−0.069	0.183	0.71
Log of baseline hematoma volume (per 1)	0.181	0.038	<0.0001	0.184	0.037	<0.0001
Time from ICH onset to CT (per 1 hour)	−0.075	0.028	0.008	−0.067	0.029	0.02
Randomized treatment (intensive vs standard)	0.022	0.059	0.72	0.019	0.057	0.74

Values were calculated by generalized estimating equations.
*Relative increase in perihematomal edema volume was log-transformed to remove skewness after addition of the value 1.1 to eliminate negative values.
ICH = intracerebral hemorrhage; BP = blood pressure; NIHSS = National Institutes of Health Stroke Scale; SE = standard error.

for country of residence (China 93% with and 99% without edema analysis; $p = 0.02$).

Geometric mean values of perihematomal edema volumes were 6.1 mL (95% CI 5.5–6.9 mL) at baseline, 9.8 mL (95% CI 8.7–11.0 mL) at 24 hours, and 12.7 mL (95% CI 11.2–14.3 mL) at 72 hours. The figure shows that there was a highly significant correlation between hematoma and perihematomal edema volumes at baseline ($r^2 = 0.45$). Similarly high levels of correlation were seen between the respective volumes at 24 hours ($r^2 = 0.55$) and at 72 hours ($r^2 = 0.60$).

Table 2 shows the predictors of absolute increase in perihematomal edema volume over 72 hours. The baseline variables that were associated with absolute growth of volumes in univariate analysis were no known diabetes mellitus, higher NIHSS score, baseline hematoma volume, and earlier time from onset to CT. In multivariate analysis, lower systolic BP and baseline hematoma volume were independently associated with absolute increase in perihematomal edema volume. Absolute increase in hematoma volume from baseline to 24 hours was associated with absolute growth in perihematomal edema volume (beta = 0.397, SE = 0.198, $p = 0.04$), but this association was not significant after adjustment for other predictors.

Table 3 shows the predictors of relative increase in perihematomal edema volume over 72 hours. The baseline variables that were associated with relative growth of volumes in univariate analysis were younger age, history of hypertension, baseline hematoma volume, and earlier time from onset to CT. In multivariate analysis, history of hypertension, baseline hematoma volume, and earlier time from onset to CT were independently associated with relative increase in perihematomal edema volume.

Table 4 shows the effects of absolute and relative growth in perihematomal edema volume on clinical outcomes at 90 days by which time 15 patients were dead and 104 were dependent. Both absolute and relative growth in perihematomal edema volume were associated with death or dependency at 90 days (OR 1.68 [95% CI 1.21–2.32] for increase of 1 SD in absolute growth of edema volume; OR 1.38 [95% CI 1.07–1.78] for increase of 1 SD in log-transformed relative growth of edema volume). These associations remained significant after adjustment for age, gender, and randomized treatment, but not when additionally adjusted for baseline hematoma volume. There were no significant interactions between absolute growth of perihematomal edema volume and hematoma volume or between relative growth of perihematomal edema volume and hematoma volume. Finally, absolute and relative growth in perihematomal edema volumes were clearly associated with neither death at 90 days nor dependency at 90 days after adjustment for baseline hematoma volume.

Table 4 Effects of absolute and relative growth in perihematomal edema volume on clinical outcomes at 90 days

	Univariate analysis		Multivariate analysis 1*		Multivariate analysis 2*	
	Odds ratio (95% CI)†	*p* Value	Odds ratio (95% CI)†	*p* Value	Odds ratio (95% CI)†	*p* Value
Death or dependency						
Absolute increase in edema volume from baseline to 72 h, mL	1.68 (1.21–2.32)	0.002	1.85 (1.30–2.65)	0.001	1.05 (0.73–1.51)	0.78
Relative increase in edema volume from baseline to 72 h, mL‡	1.38 (1.07–1.78)	0.01	1.48 (1.13–1.94)	0.004	1.26 (0.94–1.70)	0.13
Death						
Absolute increase in edema volume from baseline to 72 h, mL	1.43 (1.02–1.99)	0.04	1.44 (1.02–2.02)	0.04	1.00 (0.64–1.56)	0.99
Relative increase in edema volume from baseline to 72 h, mL‡	1.43 (0.85–2.42)	0.18	1.49 (0.88–2.54)	0.14	1.18 (0.65–2.14)	0.59
Dependency						
Absolute increase in edema volume from baseline to 72 h, mL	1.68 (1.19–2.36)	0.003	1.87 (1.28–2.73)	0.001	1.09 (0.74–1.61)	0.66
Relative increase in edema volume from baseline to 72 h, mL‡	1.37 (1.05–1.79)	0.02	1.46 (1.10–1.95)	0.009	1.27 (0.93–1.74)	0.14

Values were calculated by logistic regression analysis.
*In multivariate analysis 1, adjustments were made for age, sex, and randomized treatment. In multivariate analysis 2, adjustments were made for age, sex, randomized treatment, and log of baseline hematoma volume.
†Odds ratios and 95% CI for variables represent a difference of 1 SD.
‡Relative increase in perihematomal edema volume was log-transformed to remove skewness after addition of the value 1.1 to eliminate negative values.
95% CI = 95% confidence interval.

DISCUSSION The present analysis of the INTERACT study demonstrates the natural course, predictors, and prognostic significance of growth in perihematomal edema of ICH. The volume of cerebral edema increased from baseline to 72 hours, and was closely and significantly correlated with the volumes of underlying hematoma. Baseline hematoma volume also independently predicted both absolute and relative growth of perihematomal edema volume. Perihematomal edema growth was associated with increased risks of death or dependency at 90 days after adjustment for age, gender, and randomized treatment, but not when additionally adjusted for baseline hematoma volume.

INTERACT included a large number of patients with CT-confirmed ICH who were assessed within 6 hours of onset, and followed systematically and with standardized measures to show that edema volume increased from baseline to 72 hours after the initial CT. This finding is consistent with results obtained from previous observational studies suggesting that perihematomal edema develops within 3 hours after onset of ICH and peaks several, perhaps between 10 and 20, days later.[6,7,14,15]

In cross-sectional analyses, there were highly significant correlations between hematoma and perihematomal edema volumes at baseline and at 24 and 72 hours. Longitudinal analyses demonstrated that the baseline variables that were independently associated with absolute growth of edema volumes were lower systolic BP and baseline hematoma volume, and those independently associated with relative growth of edema were history of hypertension, baseline hematoma volume, and earlier time from onset to CT. Of these variables, however, baseline hematoma volume was the only factor that independently predicted both absolute and relative growth of perihematomal edema. Our results confirm an observational study which showed that perihematomal edema volume was directly related to hematoma volume.[16] These data suggest that hematoma volume is the key determinant of perihematomal edema volume and its growth among patients with ICH.

Conflicting results on the association of perihematomal edema on clinical outcomes have been reported. Some observational studies have suggested that the development of perihematomal edema could lead to elevated intracranial pressure or hydrocephalus with subsequent clinical deterioration,[6,7] but one other study found no clear associations between perihematomal edema volume and death or functional outcomes.[17] In the present analysis, both absolute and relative growth in edema volumes were each associated with death or dependency at 90 days after adjustment for age, gender, and randomized treatment, but not when additionally adjusted for baseline hematoma volume. Although nonsignificant associations between perihematomal edema growth and clinical outcomes after adjustment for hematoma volume may be due to the relatively small num-

ber of clinical events observed, these findings suggest that hematoma volume is the most important predictor of poor clinical outcomes among patients with acute ICH.

Strengths of this study include the large sample size of patients assessed early after the onset of ICH, the prospective design, and the quantitative assessment of cerebral tissue volumes. Limitations of the study include the relatively small number of clinical events recorded and consequent wide 95% CI in the predictive models. Another limitation is that we have evaluated edema growth only up to 72 hours after ICH onset, yet edema is known to expand beyond this time point and may reach a maximum point of growth at 2–3 weeks in some patients.[6,7,14,15] Therefore, we may have underestimated the effects of perihematomal edema growth on clinical outcomes. We also recognize difficulty in delineating the border of cerebral edema on CT among a certain proportion of patients. Measurement error could have led to reduction in statistical power to detect predictors and prognostic significance of perihematomal edema growth. However, as the intraclass correlation coefficient for edema volume was as high as 0.91, any misclassification bias is unlikely to invalidate the findings.

AUTHOR CONTRIBUTIONS

Statistical analysis was conducted by Dr. H. Arima, Q. Li, and Dr. S. Su.

DISCLOSURE

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