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Voxel-based analysis of apparent diffusion coefficient in perihaematomal oedema: associated factors and outcome predictive value for intracerebral haemorrhage

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ABSTRACT

Objectives: The pathophysiology of perihaematomal oedema (PO) surrounding a primary intracerebral haemorrhage (ICH) is complicated and incompletely understood. We prospectively investigated the components of PO with voxel-based analysis of the apparent diffusion coefficient (ADC) value and assessed its predictive value for functional outcome.

Design: Forty-six patients with ICH who were enrolled for clinical evaluation underwent MRI scans within 24 h after ICH. Based on the ADC value of the ipsilateral voxels divided by the mean ADC value of the contralateral mirror region of interest, the voxels with oedema were classified into three categories: cytotoxic, vasogenic and undetermined. The percentages of cytotoxic and vasogenic oedema were then calculated and correlated with clinical outcome according to the modified Rankin Scale (mRS) at 6 months after ICH. The intraobserver and interobserver reliability of this method were examined using intraclass correlation coefficients.

Results: The intraclass correlation coefficients showed that analysis using the voxel-based method is highly reliable. Among the clinical variables tested, age and serum creatinine levels were positively correlated with percentage of cytotoxic oedema. Age, history of coronary artery disease, National Institutes of Health Stroke Scale score and percentage of cytotoxic oedema were all associated with mRS at 6 months after ICH.

Conclusions: The pathophysiological processes within PO are complicated. Voxel-based analysis of ADC values may help to identify the components of PO and may be beneficial for decision making and predicting outcome.

ARTICLE SUMMARY

Article focus

- Diffusion weighted MRI for characterising the components of perihaematomal oedema
- Voxel-based analysis of the apparent diffusion coefficient as an imaging biomarker for predicting functional outcome in primary intracerebral haemorrhage (ICH)

Key messages

- Several clinical variables, such as age and serum creatinine levels, were correlated with the percentage of cytotoxic oedema in the perihaematomal oedema region.
- Age, history of coronary artery disease, National Institutes of Health Stroke Scale score and percentage of cytotoxic oedema were all associated with modified Rankin Scale score at 6 months after ICH.
- The study results highlight the potential use of this method to evaluate tissue damage in the region affected by oedema and to predict functional outcome.

INTRODUCTION

Perihaematomal oedema (PO) develops within the first few days after primary intracerebral haemorrhage (ICH). Whether or not PO contributes to ICH-induced neurological deficits and patient outcome is still controversial and deserves further investigation.[1 2] The pathophysiological processes within PO are complicated and may provide valuable clues regarding outcome.[2] Diffusion MRI, a technique that can be used to probe tissue microstructures by measuring the molecular diffusion of water, can help characterise the components of oedema. Cytotoxic oedema decreases the apparent diffusion coefficient (ADC), whereas vasogenic oedema increases the ADC.[3 4] Diffusion MRI has been applied to the study of perihaematomal injury in patients with ICH but with inconsistent results.[5–10] In this study, we investigated the components of PO in 46 consecutive patients with ICH using voxel-based analysis of the ADC value.

ARTICLE SUMMARY

Strengths and limitations of this study

- The role of cytotoxic oedema in ICH in term of functional outcome has not been previously evaluated.
- Voxel-based ADC analysis provides relatively unbiased quantitative results compared to the traditional method which only evaluates the region of interest.
- The study population had small haematomas, better initial National Institutes of Health Stroke Scale scores and high Glasgow Coma Scale scores, which may reduce the generalisability of the result.
- The automatically selected mirror region of interest may be contaminated with cerebrospinal fluid space.
- Definite thresholds of cytotoxic and vasogenic oedema established by ADC are not yet validated in a wide population of patients or in animal studies.
- This study did not include MRI data at a later time point (eg, between 10 and 20 days after ICH).

METHODS

Patients

Approval for the study was obtained from the Institutional Review Board of Chang Gung Memorial Hospital, and informed consent was obtained from the patients or their relatives. Forty-six consecutive patients with a first ICH and with no history of any neurological deficits were enrolled. Patients with any contraindication to undergoing MRI, requiring emergent surgery, with a history or imaging findings of previous ICH or other neurological insult, or with evidence of intraventricular haemorrhage or haemorrhage related to a tumour, trauma, coagulopathy or vascular lesion were excluded.

The following clinical data were recorded within 24 h after ICH: age, sex, blood pressure, blood glucose level, haemoglobin level, white blood cell count, platelet count and creatinine level. The National Institutes of Health Stroke Scale (NIHSS) and Glasgow Coma Scale scores were estimated by two experienced neurosurgeons within 24 h after ICH. The Modified Rankin Scale (mRS) score was estimated by the same neurosurgeons at 6 months after ICH and was defined as patient outcome.

MRI

MRI scans were obtained with a 1.5 T human MRI scanner (Gyroscan Intera; Philips Medical Systems, Best, The Netherlands) within 24 h after symptom onset. Standard sequences included axial T2*-weighted gradient echo images for the location and volume of the haematoma and axial fluid-attenuated inversion recovery (FLAIR) images for PO extension. The area of haematoma was manually segmented on T2*-weighted gradient echo images and the area of oedema was manually segmented on FLAIR images. The volumes of oedema and haematoma were then estimated by the ImageJ processing program (http://rsbweb.nih.gov/ij/). Diffusion-weighted images were acquired using a diffusion-sensitised echo-planar imaging pulse sequence. Diffusion sensitivity (b_1=1000 s/mm^2) was applied sequentially in the x, y and z gradient directions, and

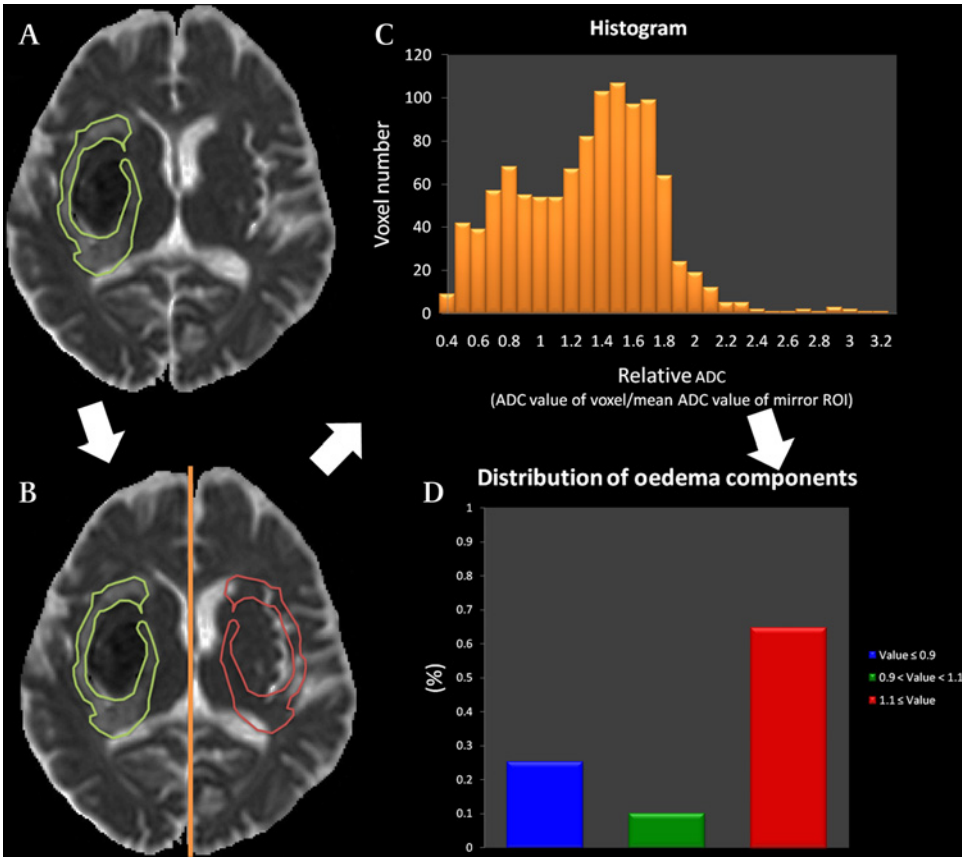

Figure 1 Flow diagram for voxel-based analysis of the apparent diffusion coefficient (ADC). (A) The region of interest, perihematomal edema (PO), was outlined on an ADC map by an experienced neuroradiologist. The PO was marked following inspection of all available imaging data. (B) The mean ADC value of the contralateral mirror region of interest (ROI) was calculated. The relative ADC for each voxel in PO was defined as the ADC value of the ipsilateral voxel divided by the mean ADC value of the contralateral mirror region of interest. (C) Generation of a relative ADC histogram, where the x-axis represents the relative ADC value and the y-axis is scaled with the number of voxels at any relative ADC value. (D) Voxels within PO were stratified into three categories based on the relative ADC value and the percentage of each category was then calculated.

a reference image without diffusion sensitivity ($b_0 \approx 0$ s/mm^2) was acquired. The ADC map was derived directly from these diffusion-weighted images.

Voxel-based analysis of ADC

Voxel-based analysis of ADC values was performed using 'in-house' software developed at MATLAB (Math-Work, Natick, Massachusetts, USA). The analytical process is illustrated in the figure 1.

PO was manually segmented as the lesion-side region of interest (ROI) on the MRI images by an experienced neuroradiologist. The PO was marked following inspection of all available imaging data including T2-weighted images, fluid-attenuated inversion recovery images and ADC maps. The equation for the straight line of the brain midline was then defined and calculated. The mirror ROI on the contralateral normal hemisphere across the brain midline was then defined automatically according to the coordinates of the lesion-side ROI and the straight line equation. The relative ADC value for each voxel in PO was calculated as the ADC value of the voxel in the lesion-side ROI divided by the mean ADC value of the mirror ROI. The histogram was then calculated to represent the distribution of the relative ADC value. Voxels within PO were stratified into three categories based on the relative ADC value and the percentage of each category was then calculated.

Statistical methods

The values for baseline characteristics were presented as means and SD. Univariate and multiple stepwise linear regression models were used to analyse the correlation between clinical variables and percentages of cytotoxic and vasogenic oedema. Univariate and multiple stepwise linear regression models were used to analyse the relationship of possible predictor variables to continuous clinical outcome (mRS). p Values less than or equal to 0.05 were deemed significant.

To validate the reliability of the voxel-based analytical method in giving the same result on different occasions (intraobserver reliability) or between different neuroradiologists (interobserver reliability), we examined the percentage of cytotoxic oedema measured by a neurologist (Dr Tsai) on different occasions and by two neuroradiologists (Dr Weng and Dr Tsai) with intraclass correlation coefficients (ICC). A one-way ICC with absolute agreement was used to assess intraobserver reliability and a two-way ICC with absolute agreement was used to examine interobserver reliability. All statistical analyses were performed using Stata V.11.0 statistical software (StataCorp).

RESULTS

The baseline characteristics, and clinical and radiological features of the 46 enrolled patients are presented in table 1.

The ICC showed high reliability for measuring the percentage of cytotoxic oedema (ICC=0.978 for intraobserver reliability; ICC=0.933 for interobserver reliability).

Table 1 Baseline characteristics of 46 patients with intracerebral hemorrhage

Age (years)	65.2±12.7
Male (%)	25 (54.3)
Location of haematoma (%)	
Thalamus	17 (37.0)
Basal ganglia	12 (26.1)
Putamen	11 (23.9)
Lobar	5 (10.9)
Cerebellum	1 (2.1)
Medical history (%)	
Hypertension	34 (73.9)
Antihypertensive medication	20 (43.5)
Diabetes	9 (19.6)
Coronary artery disease	3 (6.5)
Smoker	12 (26.1)
Alcoholism	11 (23.9)
Blood pressure (mm Hg)	
Systolic	191.3±22.5
Diastolic	106.3±16.3
Mean arterial	133.6±15.4
Serum glucose (mmol/l)	143.4±59.8
Haemoglobin (g/dl)	14.1±1.5
Platelet count (1000/μl)	193.7±118.1
Creatinine (mg/dl)	1.0±0.4
White blood cell count (1000/μl)	8.1±2.5
NIHSS score within 24 h	10.6±5.3
GCS score within 24 h	13.3±2.6
mRS score at 6 months	2.9±1.7
Haematoma volume (ml)	19.4±14.2
Oedema volume (ml)	14.3±14.2
Percentage of vasogenic oedema (%)	55.7±25.2
Percentage of cytotoxic oedema (%)	15.9±16.7

GCS, Glasgow Coma Scale; mRS, Modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale.

Table 2 shows the correlation coefficients of clinical, laboratory and radiological variables in relation to percentages of cytotoxic oedema. As indicated, there were significant positive correlations between both patient age and creatinine level, and percentage of cytotoxic oedema (p=0.003 and p=0.021, respectively). There was also a negative correlation between haemoglobin level and percentage of cytotoxic oedema (p=0.005). In multivariate analysis including variables that were positively associated with the percentage of cytotoxic oedema in univariate analysis, age and creatinine level remained significantly associated with percentage of cytotoxic oedema.

Table 3 shows the correlation coefficients of clinical, laboratory and radiological variables in relation to percentages of vasogenic oedema. There was a significant positive correlation between patient age and percentage of vasogenic oedema (p=0.000) and a negative correlation between haemoglobin level and percentage of vasogenic oedema (p=0.017). In multivariate analysis including variables that were positively associated with the percentage of vasogenic oedema in

Table 2 Correlation between clinical variables and percentage of cytotoxic oedema

	Univariate analysis		Multivariate analysis	
	Coefficient (95% CI)	p Value	Coefficient (95% CI)	p Value
Age	0.572 (0.212 to 0.931)	0.003*	0.534 (0.190 to 0.879)	0.003*
Location of haematoma	−0.904 (−5.444 to 3.636)	0.690		
Medical history (%)				
Hypertension	1.289 (−10.126 to 12.704)	0.821		
Diabetes	1.470 (−11.165 to 14.105)	0.816		
Coronary artery disease	−4.052 (−24.878 to 16.774)	0.697		
Smoker	−7.314 (−21.730 to 7.101)	0.312		
Alcoholism	5.940 (−8.880 to 20.759)	0.423		
Haemoglobin level	−4.595 (−7.764 to −1.426)	0.005*		
Creatinine level	13.320 (2.100 to 24.540)	0.021*	11.822 (1.526 to 22.119)	0.025*
White blood cell count	1.394 (−0.555 to 3.3444)	0.157		
Systolic BP	0.113 (−0.110 to 0.336)	0.314		
Diastolic BP	−0.018 (−0.329 to 0.293)	0.908		
Mean arterial BP	−0.061 (−0.565 to 0.443)	0.804		
Platelet count	−0.008 (−0.051 to 0.035)	0.703		
Serum glucose	−0.018 (−0.103 to 0.066)	0.667		
GCS score	−1.410 (−3.342 to 0.523)	0.149		
NIHSS score	0.788 (−0.136 to 1.713)	0.093		
Haematoma size	0.000 (0.000 to 0.000)	0.555		
Oedema volume	0.000 (−0.000 to 0.001)	0.374		

*Significant differences were defined as those with $p<0.05$.
BP, blood pressure; GCS, Glasgow Coma Scale; NIHSS, National Institutes of Health Stroke Scale.

univariate analysis, age remained significantly associated with the percentage of vasogenic oedema.

Table 4 shows the predictors of functional outcome at 6 months after ICH. The clinical, laboratory and radiological variables that were positively associated with mRS at 6 months in univariate analysis were age (p=0.000), history of coronary artery disease (p=0.025), NIHSS score (p=0.003) and percentage of cytotoxic oedema (p=0.001). Haemoglobin level (p=0.010) and percentage of vasogenic oedema (p=0.041) were negatively correlated with mRS at 6 months. In multivariate analysis including variables that were positively

Table 3 Correlation between clinical variables and percentage of vasogenic oedema

	Univariate analysis		Multivariate analysis	
	Coefficient (95% CI)	p Value	Coefficient (95% CI)	p Value
Age	−0.990 (−1.513 to −0.466)	0.000*	−0.990 (−1.513 to −0.466)	0.000*
Location of haematoma	2.155 (−4.692 to 9.001)	0.529		
Medical history (%)				
Hypertension	−3.754 (−20.987 to 13.479)	0.663		
Diabetes	2.176 (−16.929 to 21.282)	0.819		
Coronary artery disease	8.069 (−22.548 to 38.686)	0.598		
Smoker	10.359 (−6.622 to 27.341)	0.225		
Alcoholism	−1.713 (−19.485 to 16.068)	0.847		
Haemoglobin level	6.031 (1.126 to 10.935)	0.017*		
Creatinine level	−6.386 (−24.317 to 11.546)	0.477		
White blood cell count	−1.518 (−4.500 to 1.463)	0.310		
Systolic BP	−0.076 (−0.416 to 0.265)	0.657		
Diastolic BP	0.304 (−0.156 to 0.765)	0.190		
Mean arterial BP	0.237 (−0.464 to 0.937)	0.492		
Platelet count	0.022 (−0.043 to 0.086)	0.502		
Serum glucose	0.080 (−0.046 to 0.206)	0.206		
GCS score	1.028 (−1.949 to 4.004)	0.490		
NIHSS score	−0.656 (−2.086 to 0.775)	0.361		
Haematoma size	0.000 (0.000 to 0.001)	0.343		
Oedema volume	0.000 (0.000 to 0.001)	0.691		

*Significant differences were defined as those with $p<0.05$.
BP, blood pressure; GCS, Glasgow Coma Scale; NIHSS, National Institutes of Health Stroke Scale.

Table 4 Predictors of functional outcome at 6 months after intracerebral hemorrhage

	Univariate analysis		Multivariate analysis	
	Coefficient (95% CI)	p Value	Coefficient (95% CI)	p Value
Age	0.065 (0.031 to 0.100)	0.000*	0.043 (0.013 to 0.074)	0.007*
Location of haematoma	−0.246 (−0.690 to 0.206)	0.206		
Medical history (%)				
Hypertension	0.475 (−0.655 to 1.606)	0.401		
Diabetes	0.910 (−0.321 to 2.141)	0.143		
Coronary artery disease	2.209 (0.297 to 4.122)	0.025*	2.339 (0.931 to 3.747)	0.002*
Smoker	−0.363 (−1.497 to 0.772)	0.523		
Alcoholism	−0.751 (−1.902 to 0.400)	0.195		
Haemoglobin level	−0.427 (−0.747 to −0.107)	0.010*		
Creatinine level	0.856 (−0.305 to 2.017)	0.145		
White blood cell count	0.133 (−0.062 to 0.328)	0.175		
Systolic BP	−0.009 (−0.031 to 0.013)	0.424		
Diastolic BP	−0.019 (−0.050 to 0.011)	0.205		
Mean arterial BP	−0.027 (−0.074 to 0.019)	0.236		
Platelet count	0.004 (−0.001 to 0.008)	0.096		
Serum glucose	0.004 (−0.004 to 0.013)	0.270		
GCS score	−0.126 (−0.320 to 0.068)	0.198		
NIHSS score	0.135 (0.049 to 0.221)	0.003*	0.116 (0.048 to 0.184)	0.001*
Haematoma size	0.000 (−0.000 to 0.000)	0.566		
Oedema volume	0.000 (−0.000 to 0.000)	0.232		
Cytotoxic oedema	0.047 (0.021 to 0.074)	0.001*	0.026 (0.002 to 0.050)	0.037*
Vasogenic oedema	−0.020 (−0.039 to −0.001)	0.041*		

*Significant differences were defined as those with p≤0.05.
BP, blood pressure; GCS, Glasgow Coma Scale; mRS, Modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale.

associated with mRS at 6 months in univariate analysis, age, history of coronary artery disease, NIHSS score and percentage of cytotoxic oedema remained significantly associated with mRS at 6 months.

DISCUSSION

Diffusion MRI has been used to study perihaematomal injury in patients with ICH, but with inconsistent results.[5–14] In general, the mean ADC values in the perihaematomal regions relative to contralateral, homologous brain regions may be elevated early during the acute stage with peak increases noted 2–3 days after ICH. Nevertheless, decreased relative mean ADC values can be observed in some patients and have been reported to be associated with poor clinical outcome.[4 8 13 14] However, the overall mean ADC value within ROI, as used in most studies of PO, may be the result of reduced ADC due to cytotoxic oedema or ischaemia being cancelled out by the effect of vasogenic oedema which would elevate the ADC value, thus decreasing the sensitivity and specificity for predicting outcome.[11] This may be the reason why the results of the different diffusion MRI studies were controversial and inconsistent.

The first aim of this study was to clarify the factors associated with cytotoxic oedema formation in the perihaematomal zone. Based on previous studies of ischaemic stroke, a 10% or greater reduction in ADC value is evidence of cytotoxic oedema and ischaemic injury.[3] For ICH, the possible mechanisms of decreased perihaematomal ADC values are cytotoxic oedema and neuronal injury which may result from ICH mass effect, inflammation or toxin injury from blood breakdown products such as thrombin or iron.[4 5 8 11] In our study, we found that the percentage of cytotoxic oedema is associated with patient age and creatinine level. Age has been reported to be an independent contributor to outcome after ICH[14] and was positively correlated with the percentage of cytotoxic oedema. Older age may contribute to a weaker systemic response to acute ICH and result in more ischaemic and neuronal injury. Older rats with ICH were found to have severe brain swelling and greater perihaematomal induction of stress proteins but a weaker astrocytic reaction to haematoma.[15] Serum creatinine level has been reported to be associated with haematoma growth.[16] Creatinine is a recognised marker of long-standing hypertension with accumulated vascular injury and increased fragility of small vessels. This condition may lead to more ischaemic injury after ICH owing to poor vascular auto-regulation.

The second aim of our work was to identify the outcome prediction value of this voxel-based analytical method. We found that the percentage of cytotoxic oedema is positively correlated with mRS at 6 months after ICH. Decreased relative mean ADC values have been reported to be associated with poor clinical outcome.[8] Cytotoxic oedema is due to the derangement in cellular metabolism which results in inadequate functioning of the sodium-potassium pump in the glial cell membrane. As a result, cell swelling, cell lysis,

necrosis and irreversible cell death all occur. Vasogenic oedema, on the other hand, is due to penetration of intravascular proteins and fluid into the cerebral parenchymal extracellular space after a breakdown of tight endothelial junctions which make up the blood–brain barrier. Vasogenic oedema is often recognised as a reversible injury. The results of this study may help to clarify the debate on whether there is a perihaematomal ischaemic penumbra.[4 5 11 17] Cytotoxic and vasogenic oedema coexist in the perihaematomal area. Perihaematomal regions with cytotoxic oedema may develop irreversible neural injury. The outcome for oedematous brain tissue and its effects upon patient prognosis depend not only on the mass effect but also on the underlying neural damage, such as cytotoxic and vasogenic oedema.

There are several limitations to this study. First, we excluded patients with extensive haemorrhage that required emergent surgical evacuation. Haematoma volumes in this study ranged between 1.5 and 65.9 ml (mean 19.4 ml; SD 14.2), which were relatively small, and may explain why haematoma and oedema size were not related to functional outcome in this study. Second, our results were derived from a small sample size and further group analysis of different haematoma locations could not be carried out. Third, the automatically selected mirror ROI may have included cerebrospinal fluid space. Therefore, ADC values calculated in this area could have been affected by methodological imprecision. Furthermore, the definite thresholds of cytotoxic and vasogenic oedema established by ADC have not yet been validated in a wide population of patients or in animal studies. Finally, because PO peaks between 10 and 20 days after ICH in humans,[2 18] an additional MRI scan at this time point may have provided more information regarding diffusional and pathological changes within the oedema zone.

CONCLUSION

The pathophysiological processes within PO are complicated. Voxel-based analysis of ADC appears promising based on this study. It can help identify the components of PO and may be useful for decision-making and predicting outcome. Further research should be carried out to determine how the factors which contribute to PO affect the ADC and how this analytical method can be used for predicting the result of treatment and providing individualised therapy.

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Competing interests None.

Ethics approval The Institutional Review Board of Chang Gung Memorial Hospital approved this study.

Contributors The authors' responsibilities were as follows: T-YH: study design, MRI data collection and analysis, and manuscript production; H-LM, W-HH: analysis and interpretation of data; L-CP: study design and editing of the manuscript; L-MH, Y-JT: clinical data collection and discussion. All authors were responsible for critical revisions and final approval of the manuscript.

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