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A practical prediction model for early hematoma expansion in spontaneous deep ganglionic intracerebral hemorrhage

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ABSTRACT

Objective: Early hematoma expansion is a known cause of morbidity and mortality in patients with intracerebral hemorrhage (ICH). The goal of this study was to identify clinical predictors of ICH growth in the acute stage.
Materials and methods: We studied 201 patients with acute (<6 h) deep ganglionic ICH. Patients underwent CT scan at baseline and hematoma expansion (>33% or >12.5 ml increase) was determined on the second scan performed within 24 h. Fourteen clinical and neuroimaging variables (age, gender, GCS at admission, hypertension, diabetes mellitus, kidney disease, stroke, hemorrhagic, antiplatelet use, anticoagulant use, hematoma density heterogeneity, hematoma shape irregularity, hematoma volume and presence of IVH) were registered. Additionally, blood pressure was registered at initial systolic BP (i-SBP) and systolic BP 1.5 h after admission (1.5 h-SBP). The discriminant value of the hematoma volume and 1.5 h-SBP for hematoma expansion were determined by the receiver operating characteristic (ROC) curves. Factors associated with hematoma expansion were analyzed with multiple logistic regression.
Results: Early hematoma expansion occurred in 15 patients (7.0%). The cut-off value of hematoma volume and 1.5 h-SBP were determined to be 16 ml and 160 mmHg, respectively. Hematoma volume above 16 ml (HV > 16) ([OR] = 5.05, 95% CI 1.32–21.36, $p = 0.018$), hematoma heterogeneity (HH) ([OR] = 7.81, 95% CI 1.91–40.23, $p = 0.004$) and 1.5 h-SBP above 160 mmHg (1.5 h-SBP > 160) ([OR] = 8.77, 95% CI 2.33–44.56, $p = 0.001$) independently predicted ICH expansion. If those three factors were present, the probability was estimated to be 59%.
Conclusions: The presented model (HV > 16, HH, 1.5 h-SBP > 160) can be a practical tool for prediction of ICH growth in the acute stage. Further prospective studies are warranted to validate the ability of this model to predict clinical outcome.

1. Introduction

Hematoma expansion is known to be a strong predictor of morbidity and mortality in patients with primary intracerebral hemorrhage (ICH) [1]. Early hematoma growth occurs mainly during the first 6 h after ICH [2–5] and precognition and prevention is a key therapeutic target for ultra-acute ICH therapy. Previously, a variety of potential predictors and parameters associated with hematoma expansion have been reported, which included intracerebral [6] and intraventricular [6] hemorrhage volume, occurrence of a "spot sign" in CT angiography [7], hematoma density heterogeneity [8], hematoma shape irregularity [5], short time between onset and first CT [5,6], heavy drinker [5], oral anticoagulant therapy [9,10], reduced platelet activity [11], and elevated interleukin-6 [12]. But few of these predictors has been found positive in more than one of these publications, and the interrelationships among these parameters remain to be elucidated [13]. Additionally, the importance of early intensive lowering of elevated blood pressure is not understood. A recent randomized pilot trial, INTERACT (intensive blood pressure reduction in acute cerebral hemorrhage trial), demonstrated that early intensive BP-lowering treatment (target systolic BP of 140 mmHg) seemed to reduce hematoma expansion in ICH [14]. However, the cut-off value of systolic BP and the time course as early predictors of hematoma expansion remain in dispute [13]. The purpose of this study was to investigate clinical indicators of acute ICH expansion and the effects of intensive BP-lowering treatment.

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2. Materials and methods

2.1. Study population

The medical records of 201 consecutive patients with acute primary basal ganglia ICH (within 6 h of stroke onset) who were transferred to the stroke center at the International Medical Center, Saitama Medical University between April 2007 and May 2009 were retrospectively reviewed. The onset time was defined on the basis of initial symptoms observed by the patient or by a witness. The diagnosis of ICH was based on CT scans in all patients. We excluded those patients with deep coma (Glasgow Coma Scale; GCS = 3), those who underwent urgent surgical hematoma evacuation, and those with underlying pathology (e.g., cerebral aneurysm, vascular malformation, moyamoya disease, or infectious endocarditis). We obtained the following information from all patients at admission: GCS score, systolic and diastolic blood pressure, body temperature, past/present history of medication, as well as routine laboratory tests.

Immediately after admission, efforts were made to reduce systolic BP to a normotensive level (<140 mmHg) with a bolus and/or continuous intravenous administration of a Ca^{2+} channel blocker (Verapamil or Nicardipine). Recording of serial BP readings from arrival to the second CT scan after admission were assessed from the nursing flow sheet. BP was recorded every 10–15 min for several hours either from cuff or from arterial line values, and registered at two points: initial systolic BP on patient arrival (i-SBP), 1.5 h systolic BP after admission (1.5 h-SBP). The difference between BP at the two time points was evaluated (ΔSBP). We chose 1.5 h after admission as the follow-up point for systolic BP because it was a time when acute treatment by emergency medical staff service or emergency room physicians was finished, and patients were transferred to our stroke care unit with stabilized systolic BP in the majority of patients.

2.2. CT imaging and measurement

CT scans with a 5-mm-thick slice were obtained at admission. All patients underwent a follow-up CT scan at 24 h after the symptom onset. Two cerebrovascular surgeons who were blind to the clinical data evaluated all CT scans. Hematoma volumes were measured on the baseline and follow-up CT scans using the previously validated ABC/2 method [15]. The longest diameter (A) on the perpendicular line (B) of the hematoma was calculated in the slice with the largest area of ICH. The height of the hematoma (C) was calculated by the number of 5-mm interval slices. The volume of intraventricular hematoma was excluded.

Regularity of shape and heterogeneity of density on the initial CT images were registered as established neuro-imaging characteristics [8]. Hematoma expansion was defined as a >33% or >12.5 ml increase compared to the baseline ICH volume, similar to prior studies [6,14].

2.3. Statistical analysis

The unpaired *t*-test, the Mann–Whitney's *U* test, and the chi-square test were employed to compare 16 variables, including BP and the neuroimaging characteristics mentioned above, in patient groups with and without hematoma expansion. Values of $p < 0.05$ were considered statistically significant. Receiver operating characteristic (ROC) analyses were performed to evaluate predictivity of hematoma volume and 1.5 h-SBP after admission for significant hematoma expansion. Using the ROC analyses, we determined cut-off values that gave the highest Youden index [16]. To correlate HV, HH, and SBP1.5 h with significant hematoma expansion, we applied multiple logistic regression analyses with stepwise variable selection. All analyses were performed using SAS JMP 9.0.3 (SAS Institute Inc., NC, USA) and MedCalc for Windows 12.1.4 (MedCalc Software, Mariakerke, Belgium).

2.4. Ethics comittee

The IRB at Saitama Medical University International Medical Center approved all aspects of this study (the application number 12-038).

3. Results

Significant (>33% or >12.5 ml increase in baseline ICH) hematoma expansion occurred in 15 patients (7.0%) between baseline and follow-up CT scan. Table 1 illustrates the statistical relationship between hematoma expansion and clinical variables. At baseline, each patient with hematoma expansion had significantly lower measures for GCS at admission compared to patients without expansion (median (IQR): 11 (10–14) versus 14 (13–15), $p = 0.005$). There were no significant differences in gender, age, past history, or oral antithrombotic therapy.

Concerning the topography of the ICH, baseline median ICH volume was significantly greater in patients with expanding hematomas (median (IQR): 25.0 (11.0–38.0) versus 8.0 (4.0–15.0) ml, $p = 0.002$). The area under the curve (AUC) was calculated as 0.75, and the predictive cutoff value of hematoma volume was set at 16 ml (sensitivity 66.7, 95% CI 38.4–88.2, specificity 82.8, 95% CI 76.6–87.9, +LR 3.88, 95% CI 2.4–6.2, −LR 0.40, 95% CI 0.2–0.8). In addition, hematoma irregularity (HI) and hematoma heterogeneity (HH) on baseline CT were significantly associated with expansion. HH showed powerful significance (HI; $p = 0.018$, HH; $p < 0.001$). On the other hand, presence of intraventricular hematoma did not influence the probability of hematoma expansion.

There was no significance in iSBP on admission between patients with and without expansion (204 ± 37 versus 201 ± 33 mmHg, $p = 0.792$). However, 1.5 h-SBP was significantly higher in patients with hematoma expansion (182 ± 38 versus 154 ± 23 mmHg, respectively, $p = 0.001$). In addition, the cutoff point of SBP1.5 h for significant hematoma expansion was determined to be 160 mmHg (sensitivity 80.0, 95% CI 51.9–95.7, specificity 63.9, 95% CI 56.4–70.9, +LR 2.22, 95% CI 1.6–3.0, −LR 0.31, 95% CI 0.1–0.9) by ROC curve analyses (AUC = 0.79).

Table 1
Clinical characteristics of patients with and without hematoma expansion.

Variable	Patients with hematoma expansion ($n = 15$)	Patients without hematoma expansion ($n = 186$)	*P* value
Age (years), mean, SD	62.3 ± 10.0	65.2 ± 11.1	0.331
Gender, male, *n* (%)	5(33)	67(36)	0.835
GCS at admission, median (IQR)	11 (10–14)	14 (13–15)	**0.005**
Hypertension, *n* (%)	9 (60)	124 (66)	0.599
Diabetes mellitus, *n* (%)	1(6.7)	21 (11.3)	0.581
Kidney disease, *n* (%)	2 (13)	7 (3.8)	0.085
Stroke, *n* (%)	1 (6.7)	23(12)	0.513
Hemorrhagic, *n* (%)	3 (20)	9 (4.8)	0.069
Antiplatelet use, *n* (%)	3(20)	26(14)	0.798
Anticoagulant use, *n* (%)	1 (6.7)	7 (3.8)	0.894
Density heterogeneity, *n* (%)	12 (80)	39(21)	**<0.001**
Hematoma irregularity, *n* (%)	13(87)	96 (52)	**0.018**
Hematoma volume (cm^3), median (IQR)	25.0 (11.0–38.0)	8.0(4.0–15.0)	**0.002**
Presence of IVH, *n* (%)	9 (60)	70 (38)	0.088
Initial SBP (mmHg), mean, SD	204 ± 37	201 ± 33	0.792
1.5h-SBP (mmHg), mean, SD	182 ± 38	154 ± 23	**0.001**

GCS, Glasgow Coma Scale; SBP, systolic blood pressure; IQR, interquartile range.