at the discretion of the treating physician as a part of routine care. The hematoma was classified on the basis of the location of its major component. Hematoma volume was determined with the length × width × height/2 method at bedside by the neurologist on admission and again 24 h after the initiation of nicardipine. If the patient underwent surgical intervention or died within 24 h, the hematoma volume on CT just prior to the event was used as follow-up data.

Clinical and laboratory assessment

Patient characteristics such as sex, age, height, body weight, BMI, vascular risk factors such as hypertension, diabetes mellitus, dyslipidemia, alcohol intake, histories of ischemic and hemorrhagic stroke, comorbidities such as liver cirrhosis and chronic renal dysfunction on hemodialysis, use of antithrombotic medication, and premorbid modified Rankin Scale (mRS) score were collected. Hypertension was defined as SBP 140 mmHg or more or DBP 90 mmHg or more before stroke onset or in the chronic stage of stroke or the use of antihypertensive medication. Diabetes mellitus was defined as a fasting blood glucose 126 mg/dl or more or the use of oral antidiabetic agents or insulin. Dyslipidemia was defined as a total plasma cholesterol level 220 mg/dl or more, low-density lipoprotein cholesterol level 140 mg/dl, or the use of antihypercholesterolemic medication. Alcohol intake was defined as daily consumption of alcohol 40 g or more. Neurological status was assessed using the National Institutes of Health Stroke Scale (NIHSS) by the treating neurologist just before (as baseline) and at 72 (±12) h after the initiation of nicardipine infusion. Neurological deterioration, including the level of consciousness and new or worsening focal neurological deficits were frequently (at least hourly) monitored by an attending nurse or neurologist for 24 h. Adverse events such as extensive BP lowering, ischemic stroke, transient ischemic attack, recurrent ICH, convulsion, tachycardia, phlebitis, pneumonia, and other adverse events within 72 h were also recorded, regardless of potential causal relationships with nicardipine. Routine laboratory surveillance including activated partial thromboplastin time, INR, a complete blood count, glucose, liver enzymes, and lipid profiles were measured at baseline, 24 and 72 h, respectively. Patients underwent a follow-up evaluation at 3 months after ICH onset to assess mRS score, cardiovascular events including newly developed stroke, and acute coronary syndrome in person or by telephone.

Clinical outcome measures

Clinical outcome measures are summarized in Table 1. Primary outcomes included: neurological deterioration corresponding to a decrease of 2 points or more from the baseline GCS score or an increase of 4 points or more from the baseline NIHSS score at 72 h after the initiation of treatment and serious adverse event (SAE) to stop intravenous nicardipine within 24 h. Patients who received surgical intervention for ICH within the initial 72 h were regarded as having neurological deterioration regardless of GCS or NIHSS scores. Secondary endpoints were as follows: time to reach target SBP range; frequency of time in the target range of SBP, once within the range; ICH volume expansion over 33% from baseline to 24 h; unfavorable outcome corresponding to patients with mRS of 4–6 at 3 months after ICH onset; and death at 3 months of onset. Patients who received surgical intervention for ICH were regarded as having unfavorable outcome regardless of the mRS score.

Safety and feasibility regarding primary outcomes were assessed whether the proportion of outcomes was at least less than the upper limit of the 90% confidence interval (CI) for the predicted proportion based on the weighted average of cited studies in the protocol study for the ATACH [11, 18–23], and main results of the INTERACT [10]. Finally, the weighted average of 588 patients was used for outcome 1 and that of 225 patients were used for the outcome 2. Secondary outcomes (5–7) were assessed whether their proportion was at least less than the upper limit of the 90% CI for the proportion of 445 patients who were registered in the Bleeding with Antithrombotic Therapy (BAT) Retrospective Study and had the same inclusion criteria as the present study [24], and patients in the INTERACT study for the assessment of outcomes 5–7. Finally, the weighted average of 549 patients within 3 h from onset was used for outcome 5, that of 445 patients were used for outcome 6, and that of 849 patients were used for outcome 7. The differences of confounding factors between our study and previous studies are shown in Appendix Table 1, http://links.lww.com/HJH/A200. Patients' background features were generally similar among the studies.

TABLE 1. Clinical endpoints

Endpoints	90% CI of predictive proportion for 211 patients	Present results number [% (95% CI)] (211 patients)
Primary		
Neurological deterioration within 72 h	15.2–25.9%	17 [8.1% (5.1–12.5)]
Serious adverse event to stop intravenous nicardipine within 24 h	1.8–8.9%	2 [0.9% (0.3–3.4)]
Secondary		
Time to reach the target SBP range	N/A	Median 30 min (IQR 15–45)
Frequency of time in the target SBP range	N/A	77.6% (75.3–79.9)
Hematoma expansion (>33%) at 24 h	17.1–28.3%	36 [17.1% (12.6–22.7)]
Modified Rankin Scale 4–6 at 3 months	54.5–67.9%	87 [41.2% (34.8–48.0)]
Death at 3 months	6.0–13.5%	4 [1.9% (0.7–4.8)]

CI, confidence interval; IQR, interquartile range.

Statistical analysis

Data are presented as mean ± SD or median [interquartile range (IQR)]. ICH volumes at baseline and at 24 h, and NIHSS scores at baseline and at 72 h were compared by Wilcoxon's signed rank test. For each primary outcome (1 and 2) and secondary outcomes (5–7), independent predictors were assessed from sex, age, BMI, vascular risk factors, history of stroke, comorbidities, prior antithrombotic medication, onset to treatment time, initial levels of SBP, pulse rate and hematoma volume, hematoma location (putamen versus other sites), and initial NIHSS by backward stepwise logistic regression analysis using $P > 0.10$ of the likelihood ratio test as the exclusion criterion. Outcomes were considered statistically significant if $P < 0.05$.

RESULTS

We enrolled 211 patients (81 women, 65.6 ± 12.0 years old) with acute supratentorial ICH from July 2009 to June 2011. Baseline characteristics are shown in Table 2. Figure 1 shows the trends for SBP, DBP, and pulse rate during the initial 24 h, at 48 and 72 h, respectively. SBP was 201.8 ± 15.7 mmHg at baseline, and steeply lowered to the target SBP range between 120 and 160 mmHg within 1 h for most patients. The median time to reach the target range was 30 min (15–45 min) (Table 1). For seven patients, nicardipine was not strong enough, and additional intravenous antihypertensive drugs (diltiazem in three, nitroglycerin in three, isosorbide nitrate in one) were started at a median of 110 min (97.5–120 min) from the initiation of nicardipine. The proportion of time in the target SBP range once within the range was 77.6% (75.3–79.9%). DBP was 107.9 ± 15.0 mmHg at baseline and was steeply lowered to less than 90 mmHg in most patients within 1 h. Pulse rate was 81.8 ± 16.1/min at baseline and mildly increased up to 90/min until 105 min, and thereafter gradually returned to the initial rate after about 10 h.

TABLE 2. Baseline characteristics

Total, number	211
Women, number (%)	81 (38.4)
Age (year)	65.6 ± 12.0
Body height (cm)	160.4 ± 9.9
Body weight (kg)	61.6 ± 14.9
BMI (kg/m^2)	23.7 ± 4.2
Risk factors, number (%)	
Hypertension	176 (83.4)
Diabetes mellitus	29 (13.7)
Dyslipidemia	87 (41.2)
Alcohol intake	57 (27.0)
Comorbidity	
Liver cirrhosis	10 (4.7)
Renal failure on hemodialysis	23 (10.9)
History of stroke/TIA	26 (12.3)
Ischemic stroke or TIA	19 (9.0)
Hemorrhagic stroke	10 (4.7)
Prior medication, number (%)	
Antiplatelet	22 (10.4)
Anticoagulant	2 (0.9)
SBP (mmHg)	201.8 ± 15.7
DBP (mmHg)	107.9 ± 15.0
Pulse rate (per min)	81.8 ± 16.1
Hematoma volume (ml) median (IQR)	10.2 (5.6–19.2)
Hematoma location, number (%)	
Putamen	112 (53.1)
Thalamus	75 (35.5)
Subcortex	12 (5.7)
Mixed	10 (4.7)
Caudate nucleus	1 (0.5)
Internal capsule	1 (0.5)
Admission NIHSS score, median (IQR)	13 (8–17)

Data are mean ± SD unless otherwise stated. IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale; TIA, transient ischemic attack.

Figure 2a shows the change in the NIHSS scores during the initial 72 h. The median NIHSS score was 13 (8–17) at baseline and 10 (5–15) at 72 h ($P < 0.0001$). The average absolute change was −2 (−4 to 0). Six patients (2.8%) received surgical intervention for ICH (a hematoma evacuation in five and a ventriculoperitoneal shunting in one) within 72 h. Of the remaining 205 patients, 11 showed a decrease of 2 points or more from the baseline GCS score or an increase of 4 points or more from the baseline NIHSS score at 72 h. In total, neurological deterioration was identified in 17 patients (8.1%), and the proportion was low compared with the lower cutoff (15.2%) of 90% CI for the predicted proportion (Table 1). Crude odds ratios (ORs) of confounding factors to predict neurological deterioration are shown in Appendix Table 2, http://links.lww.com/HJH/A200. On multivariate logistic regression analysis with backward selection, the initial pulse rate (OR 1.47, 95% CI 1.08–2.03 per 10 beat increase) was positively related to neurological deterioration (Table 3).

As another primary outcome, SAEs to stop nicardipine were observed in two patients (0.9%) (Table 1). One experienced extensive SBP lowering to 84 mmHg and the other had tachycardia and heart rhythm change into atrial fibrillation. The proportion was also low compared with the lower cutoff (1.8%) and was too small to perform multivariate analysis. Additionally, five adverse events were identified within 24 h. There was recurrent ICH in two, tachycardia in one, and phlebitis in two. Another 16 events were identified between 24 and 72 h including tachycardia in three, phlebitis in eight, pneumonia in three, epilepsy in one, and elevated total bilirubin in one.

Figure 2b shows the change in the hematoma volume during the initial 24 h. The volume was 10.2 ml [5.6–19.2 (IQR), 14.9 ± 13.2 ml] at baseline and 11.5 ml (6–24.9, 18.1 ± 19.0 ml) at 24 h ($P < 0.0001$). The absolute volume increment and relative volume increment were 0 ml (0–1, 3.2 ± 12.3 ml) and 0% (0–15.6, 22.5 ± 73.5%), respectively. Hematoma expansion greater than 33% at 24 h was found in 36 patients (17.1%), and the proportion was equal to the lower cutoff (17.1%) of 90% CI for predicted proportion (Table 1). Crude ORs of confounding factors to predict hematoma expansion are shown in Appendix Table 2, http://links.lww.com/HJH/A200. On multivariate regression analysis, prior antiplatelet medication (OR 4.69, 95% CI 1.51–14.20), and initial pulse rate (OR 1.36, 95% CI 1.07–1.74, per 10 beat increase) were independently related to hematoma expansion (Table 3).

A 3-month follow-up was completed for all 211 patients. The 3-month mRS score was 3 (2–4) (Fig. 3). Eighty-seven patients (41.2%) had unfavorable outcomes, including

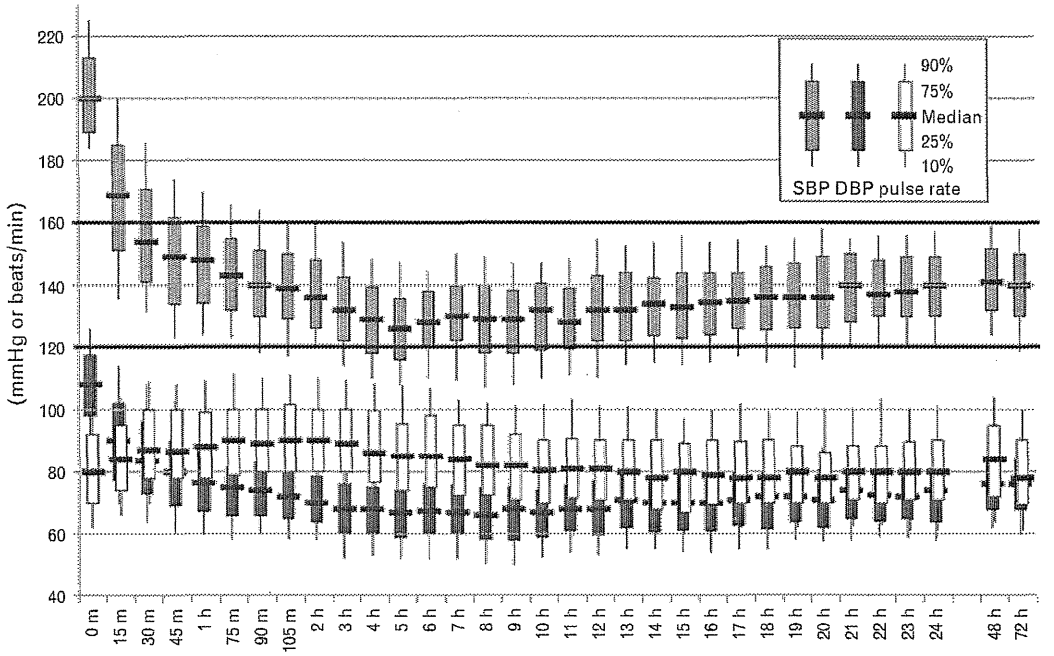

FIGURE 1 Trends of SBP, DBP, and pulse rate after the initiation of intravenous nicardipine.

three patients who received surgical intervention and recovered with an mRS score of 2 or 3. The proportion of unfavorable outcomes was low compared with the lower cutoff (54.5%) of the 90% CI for the predicted proportion (Table 1). Crude ORs of confounding factors to predict unfavorable outcomes are shown in Appendix Table 2, http://links.lww.com/HJH/A200. On multivariate regression analysis, men (OR 2.28, 95% CI 1.15–4.67), advanced age (OR 2.46, 95% CI 1.79–3.52, per 10-year increase), and higher initial NIHSS score (OR 4.45, 95% CI 2.53–8.25, per 10-point increase) were positively associated with unfavorable outcomes (Table 3). Four patients (1.9%) died within 3 months, one from the index ICH, two from pneumonia, and one from hepatoma. The proportion was low as compared with the lower cutoff (6.0%) of the 90% CI for the predicted proportion and was too small to perform multivariate analysis.

DISCUSSION

This study showed the safety and feasibility of major expert opinions in our nationwide survey that SBP should be lowered to 160 mmHg or less using intravenous nicardipine for acute ICH [17]. The first major finding was that neurological deterioration was relatively uncommon as compared with that from previous studies and neurological

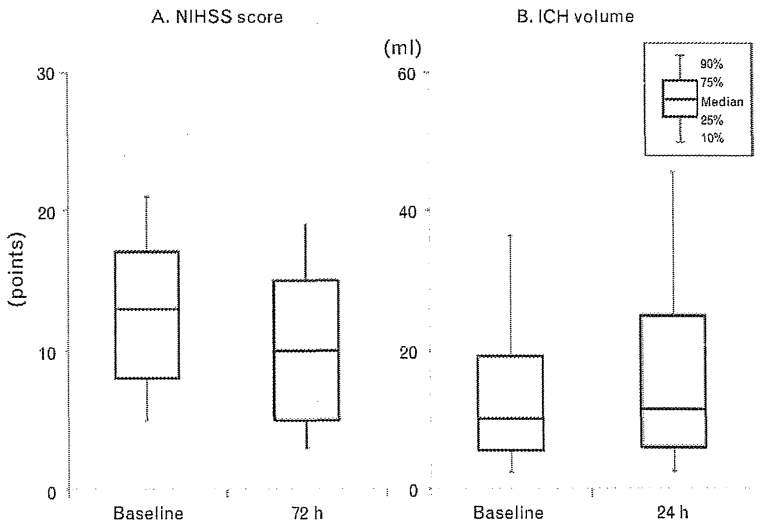

FIGURE 2 Changes in National Institutes of Health Stroke Scale score from baseline to 72 h and intracerebral hematoma volume from baseline to 24 h. ICH, intracerebral hemorrhage; NIHSS, National Institutes of Health Stroke Scale score.

TABLE 3. Independent predictors of primary and secondary clinical endpoints

	odds ratio	95% confidence interval	*P*
Neurological deterioration[a]			
Initial pulse rate (per 10 beat)	1.47	1.08–2.03	0.016
Hematoma expansion more than 33%[b]			
Prior antiplatelet medication	4.69	1.51–14.20	0.009
Initial pulse rate (per 10 beat)	1.36	1.07–1.74	0.012
Onset to treatment time (per 10 min)	1.10	0.99–1.23	0.082
Initial NIHSS score (per 10 point)	1.77	0.97–3.29	0.062
Unfavorable outcome at 3 months[c]			
Men	2.28	1.15–4.67	0.018
Age (per 10 year)	2.46	1.79–3.52	<0.0001
Initial NIHSS score (per 10 point)	4.45	2.53–8.25	<0.0001

Items with $P<0.1$ are listed. NIHSS, National Institutes of Health Stroke Scale.
[a]Adjusted for age and prior antiplatelet medication.
[b]Adjusted for age.
[c]Adjusted for prior antiplatelet medication.

severity was rather ameliorated within the initial 72 h, showing an absolute 2-point decrease in the NIHSS score. These results suggest that the present antihypertensive therapy was protective toward the brain from acute insult by ICH. The second major finding was that intravenous nicardipine under tight BP monitoring lowered SBP to the target range within 1 h and kept SBP within the range in most patients with only a small chance of SAEs. Finally, early hematoma expansion, as well as 3-month unfavorable outcome, was relatively uncommon. Death was especially rare, occurring in only four patients in the present sample population.

As early neurological deterioration after ICH is thought to be common due to expansion of hematoma and perihematomal edema, it is impressive that the median NIHSS score was 2 points lower at 72 h than at baseline in the studied patients. A low percentage of hematoma expansion seems to cause neurological improvement, although edema volume was not measured. This improvement seems to contribute to relatively good outcomes at 3 months. One should note, however, that mortality after ICH was reported to be much lower in Japan than in other countries, [25] presumably partly due to the tendency of maintaining intensive therapy even for terminal patients. Thus, the contribution of BP lowering to reduced mortality should be underestimated to some extent. Prior antiplatelet medication and high pulse rate were associated with one or more of the above safety outcomes, as well as the established predictors such as male sex, advanced age, and severe initial neurological disability. Of these, antiplatelet medication was found to be independently related to hematoma expansion and mortality [24,26]. So far, there has been no evidence to show the association between the initial pulse rate and ICH outcomes. High pulse rate may reflect sympathetic hyperactivity, which resists BP lowering. Early hospital visit is a known predictor of hematoma expansion, [27] but late visit was marginally related to hematoma expansion in this study. Earlier initiation of BP lowering might prevent hematoma growth.

Intravenous nicardipine was revealed to be tolerable for the management of acute hypertension in several diseases [12,21,22,28]. The present study showed that nicardipine seldom brought early SAEs and was useful for prompt lowering and maintenance within the scheduled range of SBP. These findings were supportive of safe clinical use of nicardipine for Japanese ICH patients, although such a use was contraindicated in Japan as was explained in our previous study [17]. We submitted our study including the nationwide survey to the Ministry of Health, Labour, and Welfare of Japan, [17] which abolished the description of contraindication for ICH on the official label of nicardipine in June 2011.

The optimal target SBP for hyperacute ICH patients remains uncertain. As stated above, the Japanese guidelines suggested a target SBP of less than 180 mmHg and the recent ASA/AHA guidelines referred to the probable safety

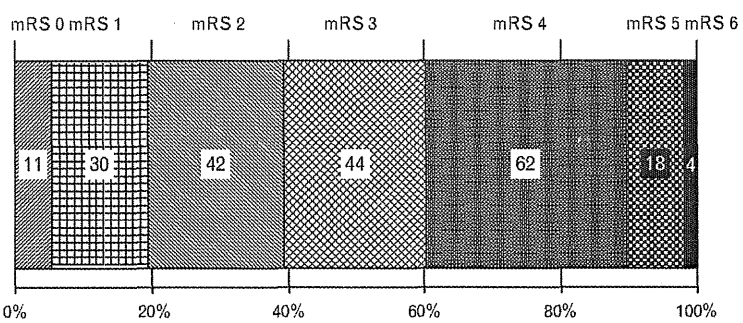

FIGURE 3 The modified Rankin scale at 3 months. Number in the bar indicates patients' number. mRS, modified Rankin scale.

of the target SBP to be less than 140 mmHg without thoroughly describing the efficacy of lowering to this level [13,16]. The European Stroke Initiative advocates the target BP of 160/100 mmHg [29]. The present target of SBP 160 mmHg or less was in the middle of these guideline-based goals. The median SBP levels at 90 min and later were below 140 mmHg, suggesting more than half of our patients were indicative of the intensive treatment arm (SBP lowering to less than 140 mmHg) in the INTERACT 2 and ATACH II [14,15]. Seventeen Japanese institutes, including nine of the present participating ones, began to register patients for the ATACH II in 2012 to clarify and better justify the target SBP goal.

There are some limitations that need to be addressed. First, this was not a randomized trial but an observational study with a comparison to previous studies. The ongoing ATACH II, in which we are involved, will overcome this limitation. Second, hematoma volume in our cohort was relatively small because of the inclusion criterion (<60 ml) and might have caused better outcomes than the predicted ones from historical control studies. At least, the median initial NIHSS score (13) was high compared with those of the INTERACT (9) and the BAT Retrospective Study (12) [10,24].

It is of critical importance and immediate urgency to improve the proportion of favorable outcomes after ICH. As the present study has a similar study design as the ATACH II [15] and some of the authors are also participating in this trial, the present study has the value as a pilot study to ascertain that the ATACH II is feasible in Japan. This study provides some new information and may be used to plan how to proceed to maximize the success of the ongoing ATACH II.

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Conflicts of Interest

There are no conflicts of interest.

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Reviewers' Summary Evaluations

Reviewer 1

Few treatment strategies have been demonstrated to be beneficial for acute intracerebral haemorrhage. In the present prospective study, the authors demonstrated safety and feasibility of nicardipine-based BP lowering treatment with target SBP levels of 120–160 mmHg among Japanese patients with acute intracerebral haemorrhage. This study has provided important information on BP lowering treatment as potentially effective treatment. The strength is its prospective design and well standardized intervention protocol. Although this study does not involve control patients, definite evidence of this treatment strategy will be established by ongoing large-scale randomized controlled trials.

Reviewer 2

The strength of the paper is in being the first demonstration that nicardipine infusion to reduce blood pressure after intracerebral haemorrhage is safe well below 160 mmHg, thereby extending guideline suggestions. Its weakness is in the lack of a control group and in the limitation to small intracerebral haemorrhage with mild disease.

Conjugate Eye Deviation in Acute Intracerebral Hemorrhage

Stroke Acute Management With Urgent Risk-Factor Assessment and Improvement–ICH (SAMURAI-ICH) Study

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Background and Purpose—Conjugate eye deviation (CED) occurs frequently in patients with acute stroke. The purpose of this study was to elucidate the factors that correlate with CED as well as the relationship between CED and outcomes in patients with acute intracerebral hemorrhage.

Methods—A total of 211 patients with acute supratentorial intracerebral hemorrhage were recruited in a multicenter, prospective study. CED was assessed with a National Institutes of Health Stroke Scale "best gaze" subscore of ≥1. Hematoma location and volume were assessed on CT.

Results—Forty-five percent of the patients had CED. On multivariable analysis, right-sided lesion (OR, 2.36; 95% CI, 1.18–4.93), hematoma volume (OR, 1.07; 95% CI, 1.04–1.10 per 1 mL), and baseline Glasgow Coma Scale score (OR, 0.66; 95% CI, 0.53–0.80 per 1 point) were independently associated with CED. After adjusting for sex, age, intraventricular extension of the hematoma, baseline Glasgow Coma Scale score, and hematoma volume, the presence of CED both on admission and 72 hours later was an independent predictor of death or dependency at 3 months poststroke (OR, 5.77; 95% CI, 2.27–16.94). The optimal cutoff volume of hematoma related to CED was ≥13.5 mL for patients with putaminal hemorrhage (sensitivity, 76%; specificity, 72%) and ≥7.7 mL for patients with thalamic hemorrhage (sensitivity, 82%; specificity, 83%).

Conclusions—The persistence of CED was a significant predictor of death or dependency after acute supratentorial intracerebral hemorrhage even after adjusting for initial severity and hematoma volume. CED can be evoked by a relatively smaller thalamic hematoma than a putaminal hematoma. **(*Stroke*. 2012;43:2898-2903.)**

Key Words: conjugate eye deviation ■ CT ■ ICH ■ outcomes

Conjugate eye deviation (CED) occurring in association with an acute cerebral lesion is known as a "Prévost sign" or "Vulpian sign."[1–3] The underlying mechanism responsible for the development of CED in supratentorial stroke is thought to be damage to the frontal eye field or subcortical pathways.[1,4,5]

A recent single-center study on acute anterior circulation ischemic stroke showed that CED was an indicator of extended ischemic insult in both the basal ganglia and cortical regions that are also related to spatial attention or gaze.[6] Intracerebral hemorrhage (ICH) can also evoke CED.[7–9] However, the relationships between CED and clinical factors or poststroke outcome in acute ICH have not been fully evaluated. Thus, this issue was investigated using data from a multicenter study on acute supratentorial hemorrhage. The first aim of the present study was to elucidate factors that correlate with CED in acute ICH. The second aim was to elucidate the relationship between CED and outcomes after ICH.

Methods

The patient samples for this study were derived from the Stroke Acute Management With Urgent Risk-Factor Assessment and

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Table 1. Frequency of Conjugate Eye Deviation

	Overall (n=211)	Putamen (n=112)	Thalamus (n=75)	Subcortex (n=12)	*P* Value*
Any CED	96 (45%)	54 (48%)	34 (45%)	3 (25%)	0.307
Forced CED	27 (13%)	15 (13%)	7 (9%)	3 (25%)	0.291
Persistent CED	53 (25%)	29 (26%)	19 (25%)	1 (8%)	0.400

*Among patients with putaminal, thalamic, and subcortical hemorrhages.
CED indicates conjugate eye deviation.

Improvement–ICH (SAMURAI-ICH) study that was a prospective, multicenter, observational study conducted between July 2009 and June 2011 to identify the safety and feasibility of early blood pressure-lowering for acute hypertension in patients with spontaneous ICH. Ten Japanese stroke centers participated in the study. An article with the main results has been submitted elsewhere.

Patients with ICH who met the following criteria were registered: age ≥20 years; total Glasgow Coma Scale (GCS) score[10] ≥5; initial systolic blood pressure >180 mm Hg; CT <2.5 hours of onset demonstrating a supratentorial intraparenchymal hematoma with manual volume measurement <60 mL; absence of extensive intraventricular hemorrhage associated with intraparenchymal hemorrhage; and informed consent was obtained from the patient, legally authorized representative, or next of kin. Titrating of intravenous nicardipine was started within 3 hours of symptom onset and continued for 24 hours to achieve and maintain the target systolic blood pressure level <160 mm Hg and >120 mm Hg. The study was approved by each institutional ethics and hospital management committee.

Neurological status assessments using the GCS and National Institutes of Health Stroke Scale (NIHSS)[11] by the treating stroke specialists were mandatory both on admission and 72 hours after admission. CED was defined as positive when the patient had an NIHSS "#2 best gaze" subscore of ≥1. For the NIHSS item, patients were rated as having normal (subscore of 0), any CED (subscore of 1 or 2), and forced CED (subscore of 2). Patients with any CED both on admission and 72 hours after admission were rated as having persistent CED. Patients underwent follow-up 3 months after ICH onset to assess the modified Rankin Scale (mRS)[12,13] score in person or by telephone. Death was coded as a mRS score of 6. An unfavorable outcome was defined as a mRS score 3 to 6 (death or dependency).

Hematoma volume was determined with the ABC/2 [(length×width×height)/2] method[14] at the bedside by the stroke specialist on admission.

Statistical analysis was performed using JMP 9.0.3 statistical software (SAS Institute Inc, Cary, NC). Frequencies of each CED according to the location of hematoma were tested by χ^2 tests. Baseline clinical characteristics were compared between patients with and without each CED using χ^2 tests and unpaired *t* tests; GCS, NIHSS, and mRS scores were analyzed using the Wilcoxon/Kruskal-Wallis tests. The ORs for associated variables with each CED were determined using multivariable logistic regression analyses by the forced entry method adjusted for sex, age, onset-to-arrival time, right-sided legion, hematoma volume, and baseline GCS score. The ORs for each CED and death or dependency at 3 months were determined using multivariable logistic regression analyses by the forced entry method adjusted for sex, age, and established predictors of poor outcome after supratentorial hemorrhage from previous studies,[15-17] that is, intraventricular extension of the hematoma, baseline GCS score, and hematoma volume. Baseline NIHSS score was not used for the adjustment considering the colinearity both between CED and the NIHSS score and between the GCS score and the NIHSS score. We tested for an interaction between the variables. The tests were accomplished by including all combinations of each 2 variables in the multivariable regression models. To obtain the cutoff hematoma volume, GCS score, and NIHSS score for discriminating between patients with and without each CED, receiver operating characteristic curves were constructed, and the area under the receiver operating characteristic curve was calculated for all patients, for those with putaminal hemorrhage, and those with thalamic hemorrhage, respectively. $P<0.05$ was considered significant.

Results

All Patients

A total of 211 patients were enrolled in the SAMURAI-ICH study (the target sample size was to be 200 patients); all of those were also enrolled in this substudy. Hematomas were in the putamen in 112 patients (53%), thalamus in 75 (35%), subcortex in 12 (6%), caudate nucleus in one, internal capsule in one, and extensively in multiple regions in the remaining 10 (putamen and thalamus in 8, thalamus and caudate nucleus in one, and putamen, thalamus, and subcortex in one). At the time of the emergency visit, 96 patients (45%) had any CED: 69 had partial CED and 27 had forced CED (Table 1). A total of 53 patients (25%) showed persistent CED. The frequency of any CED was lower in patients with subcortical hemorrhage (25%) than in those with putaminal (48%) or thalamic hemorrhages (45%), although the differences were not significant.

The baseline clinical characteristics of the patients are presented in Table 2. Patients with any CED had a larger hematoma volume ($P<0.001$), a lower GCS score ($P<0.001$), and a higher NIHSS score ($P<0.001$) than patients without any CED. These

Table 2. Patients' Baseline Clinical Characteristics

	Total (n=211)	Any CED		*P* Value
		With (n=96)	Without (n=115)	
Male sex (%)	130 (62)	57 (59)	73 (63)	0.542
Age, mean y (SD)	66 (12)	67 (12)	65 (12)	0.184
Previous stroke (%)	26 (12)	10 (10)	16 (14)	0.442
Onset-to-arrival time, median (IQR), min	55 (40–76)	50 (41–65)	58 (40–82)	0.163
Right-sided lesion (%)	110 (52)	54 (56)	56 (49)	0.274
Hematoma volume, median (IQR), mL	10.2 (5.6 to 19.2)	15.6 (9.0 to 30.0)	7.0 (3.4 to 12.1)	<0.001
Intraventricular extension of the hematoma (%)	39 (18)	22 (23)	17 (15)	0.130
Baseline GCS score, median (IQR)	14 (13–15)	13 (11–15)	15 (14–15)	<0.001
Baseline NIHSS score, median (IQR)	13 (8–17)	17 (13–20)	9 (6–13)	<0.001

CED indicates conjugate eye deviation; IQR, interquartile range; GCS, Glasgow Coma Scale; NIHSS, National Institutes of Health Stroke Scale.

Table 3. Multivariable Logistic Regression Analysis for the Presence of Conjugate Eye Deviation

	Any CED			Forced CED			Persistent CED		
	OR	95% CI	*P* Value	OR	95% CI	*P* Value	OR	95% CI	*P* Value
Male sex	0.89	0.45–1.78	0.742	0.77	0.28–2.13	0.614	0.56	0.27–1.15	0.112
Age (per y)	1.02	0.99–1.05	0.237	1.01	0.97–1.05	0.715	1.02	0.99–1.05	0.154
Onset-to-arrival time (per min)	0.99	0.98–1.00	0.236	1.00	0.98–1.02	0.922	1.00	0.98–1.01	0.679
Right-sided legion	2.36	1.18–4.93	0.015	3.01	1.02–10.17	0.046	2.17	1.02–4.84	0.045
Hematoma volume (per mL)	1.07	1.04–1.10	<0.001	1.07	1.04–1.10	<0.001	1.05	1.03–1.08	<0.001
Baseline GCS score (per point)	0.66	0.53–0.80	<0.001	0.67	0.54–0.82	<0.001	0.82	0.69–0.96	0.013

CED indicates conjugate eye devation; GCS, Glasgow Coma Scale.

3 variables were also significantly different between patients with and without forced CED ($P<0.001$ for all) and between patients with and without persistent CED ($P<0.001$ for all).

Table 3 shows the results of the multivariable analysis to identify variables significantly associated with the presence of CED. Right-sided lesion (OR, 2.36; 95% CI, 1.18–4.93), hematoma volume (OR, 1.07; 95% CI, 1.04–1.10 per 1 mL), and baseline GCS score (OR, 0.66; 95% CI, 0.53–0.80 per 1 point) were independently associated with any CED. These 3 variables were also independently associated with both forced CED and persistent CED. In models using interaction terms, these 3 variables were still independently associated with any CED, forced CED, and persistent CED. For predicting any CED, the optimal cutoff hematoma volume was ≥8.1 mL, the optimal cutoff GCS score was ≥14, and the optimal cutoff NIHSS score was ≥12 (Table 4).

Finally, the association of CED with the clinical outcome at 3 months was examined. The median mRS score was higher in patients with any CED than in those without (4 [interquartile range, 2–4] versus 2, [1–4]; $P<0.001$; Figure); the score was also higher in patients with forced CED than in those without ($P<0.001$) and in patients with persistent CED than in those without ($P<0.001$). Dead or dependent patients, corresponding to mRS scores of 3 to 6, accounted for 74% of those with any CED, 78% of those with forced CED, and 89% of those with persistent CED, whereas they accounted for 50% of those without any CED. Both any CED and persistent CED were independently associated with death or dependency after adjusting for sex, age, and intraventricular extension of the

Table 4. The Optimal Cutoff Hematoma Volume to Predict Conjugate Eye Deviation

	Cutoff Volume, mL	Sensitivity, %	Specificity, %	PPV, %	NPV, %	AUC
Hematoma volume						
Overall						
Any CED	8.1	90	57	63	87	0.777
Forced CED	9.2	96	53	23	99	0.809
Persistent CED	8.1	94	46	37	96	0.739
Putamen: any CED	13.5	76	72	72	76	0.802
Thalamus: any CED	7.7	82	83	80	85	0.855
Glasgow Coma Scale						
Overall						
Any CED	14	75	66	65	76	0.742
Forced CED	13	67	71	25	94	0.719
Persistent CED	13	57	74	42	84	0.680
Putamen: any CED	14	74	69	69	74	0.738
Thalamus: any CED	13	59	93	87	73	0.811
NIHSS						
Overall						
Any CED	12	83	71	71	84	0.854
Forced CED	15	89	67	28	98	0.843
Persistent CED	15	81	73	51	92	0.832
Putamen: any CED	12	85	72	74	84	0.843
Thalamus: any CED	11	91	68	70	90	0.867

CED indicates conjugate eye deviation; PPV, positive predictive value; NPV, negative predictive value; AUC, area under the receiver operating characteristic curve; NIHSS, National Institutes of Health Stroke Scale.

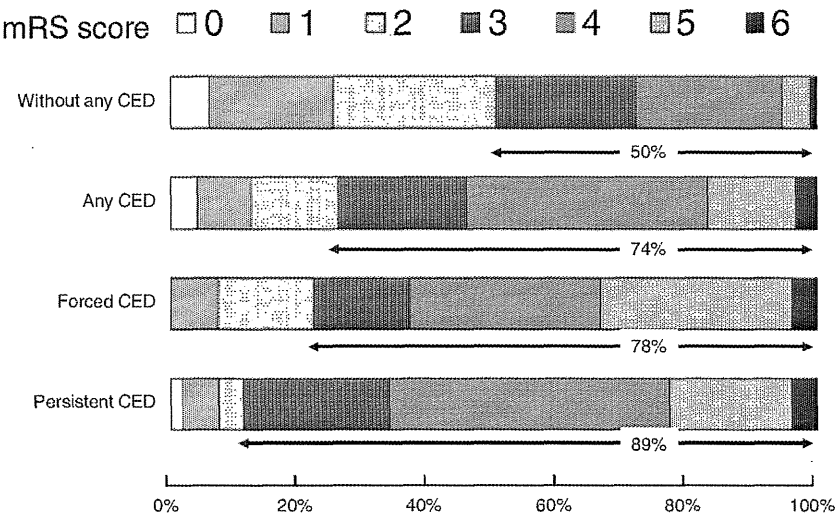

Figure. Distribution of the mRS score at 3 months. CED indicates conjugate eye deviation; mRS, modified Rankin Scale.

hematoma (OR, 2.70; 95% CI, 1.46–5.08 and OR, 8.38; 95% CI, 3.46–23.82, respectively) and after further adjusting for the baseline GCS score (OR, 2.23; 95% CI, 1.15–4.41 and OR, 7.41; 95% CI, 3.01–21.28, respectively; Table 5). Persistent CED remained significantly predictive of death or dependency after adjusting for sex, age, intraventricular extension of the hematoma, baseline GCS score, and hematoma volume (OR, 5.77; 95% CI, 2.27–16.94).

Patients With Putaminal Hemorrhage

One hundred twelve patients (69 men, 62±13 years old) had putaminal hemorrhages (median volume, 13.6 mL). At the time of the emergency visit, 54 patients (48%) had CED: 39 had partial CED and 15 had forced CED (Table 1). A total of 29 patients (26%) showed persistent CED. Of the baseline clinical characteristics of patients, age (65±12 years versus 60±13 years, P=0.020), median hematoma volume (19.4 mL versus 8.8 mL, P<0.001), GCS score (13 versus 15, P<0.001), and NIHSS score (17 versus 10, P<0.001) were significantly different between patients with and without any CED. Multivariable analysis indicated that age (OR, 1.04; 95% CI, 1.00–1.09 per 1 year; P=0.028) and hematoma volume (OR, 1.10; 95% CI, 1.05–1.17 per 1 mL; P<0.001) were independently associated with any CED. For predicting any CED, the optimal cutoff hematoma volume was ≥13.5 mL, the optimal cutoff GCS score was ≥14, and the optimal cutoff NIHSS score was ≥12 (Table 4).

At 3 months, the median mRS score was higher (3 [interquartile range, 2–4 versus 2 interquartile range, 1–3]; P=0.006) and death or dependency was more common (67% versus 38%; P=0.002) in patients with any CED than in those without. After adjusting for sex, age, and intraventricular extension of the hematoma, any CED was independently associated with death or dependency (OR, 2.73; 95% CI, 1.22–6.25; Table 5); the independent association did not remain after further adjustment for baseline GCS score or hematoma volume.

Patients With Thalamic Hemorrhage

Seventy-five patients (47 men, 69±10 years old) had thalamic hemorrhages (median volume, 6.8 mL). These patients were older than those with putaminal hemorrhages (P<0.001). At the time of the emergency visit, 34 patients (45%) had CED: 27 had partial CED and 7 had forced CED (Table 1). A total of 19 patients (25%) showed persistent CED. Of the patients'

Table 5. Association Between Conjugate Eye Deviation and Death or Dependency at 3 Mo

	Crude			Multivariable-Adjusted: Model 1			Multivariable-Adjusted: Model 2			Multivariable-Adjusted: Model 3		
	OR	95% CI	*P* Value	OR	95% CI	*P* Value	OR	95% CI	*P* Value	OR	95% CI	*P* Value
Overall (211 patients)												
Any CED	2.89	1.63–5.24	<0.001	2.70	1.46–5.08	0.001	2.23	1.15–4.41	0.018	1.56	0.75–3.24	0.235
Forced CED	2.52	1.03–7.13	0.044	2.53	0.98–7.40	0.054	1.96	0.72–5.98	0.194	0.94	0.30–3.14	0.921
Persistent CED	7.45	3.23–20.32	<0.001	8.38	3.46–23.82	<0.001	7.41	3.01–21.28	<0.001	5.77	2.27–16.94	<0.001
Putamen (112 patients): any CED	3.27	1.53–7.23	0.002	2.73	1.22–6.25	0.015	1.89	0.77–4.63	0.165	1.00	0.35–2.78	0.993
Thalamus (75 patients): any CED	5.87	1.89–22.48	0.002	7.91	2.14–38.69	0.001	3.49	0.72–21.01	0.123	1.49	0.23–11.13	0.680

CED indicates conjugate eye deviation; GCS, Glasgow Coma Scale.

Model 1: adjusted for sex, age, and intraventricular extension of the hematoma; Model 2: adjusted for sex, age, intraventricular extension of the hematoma, and baseline GCS score; Model 3: adjusted for sex, age, intraventricular extension of the hematoma, baseline GCS score, and hematoma volume.

baseline clinical characteristics, median hematoma volume (9.5 mL versus 4.5 mL, $P<0.001$), GCS score (13 versus 15, $P<0.001$), and NIHSS score (16 versus 8, $P<0.001$) were significantly different between patients with and without any CED. Multivariable analysis indicated that hematoma volume (OR, 1.21; 95% CI, 1.05–1.44 per 1 mL; $P=0.006$) and baseline GCS score (OR, 0.54; 95% CI, 0.29–0.86 per 1 point; $P=0.008$) were independently associated with any CED. For predicting any CED, the optimal cutoff hematoma volume was ≥7.7 mL, the optimal cutoff GCS score was ≥13, and the optimal cutoff NIHSS score was ≥11 (Table 4).

At 3 months, the median mRS score was higher (4 [interquartile range, 3–4] versus 3 [interquartile range, 2–4]; $P<0.001$) and death or dependency was more common (88% versus 56%; $P=0.003$) in patients with any CED than in those without. After adjusting for sex, age, and intraventricular extension of the hematoma, any CED was independently associated with death or dependency (OR, 7.91; 95% CI, 2.14–38.69; Table 5); the independent association did not remain after further adjustment for baseline GCS score or hematoma volume.

Discussion

This study had 4 major findings: (1) CED was observed in 45% of patients with supratentorial hemorrhage at the time of the emergency visit and lasted for 72 hours in half of them; (2) right-sided lesion, hematoma volume, and baseline GCS score were independently associated with CED; (3) the presence of CED, especially CED lasting for 72 hours, was an independent predictor of death or dependency at 3 months poststroke; and (4) a relatively smaller hematoma evoked CED in thalamic than in putaminal hemorrhages, and the optimal cutoff volume of the hematoma related to CED was ≥7.7 mL for thalamic and ≥13.5 mL for putaminal hemorrhages.

CED occurs more frequently after ICH than after cerebral infarction.[1,18] Its frequency was 14% to 33% in patients with supratentorial infarction,[6,19] 33% in 215 patients with striate–capsular hemorrhage,[9] and 32% in 100 patients with thalamic hemorrhage.[7] The percentage of detection of CED in the present patients with ICH (45%) was relatively higher than in previous studies, probably partly due to the short time interval between stroke onset and the initial neurological examination (<3 hours). CED was reported to subside in 57% of patients within 48 hours after hemispheric ischemic or hemorrhagic stroke,[20] and it subsided in 43 of 96 patients (45%) in the present study. CED in patients with subcortical hemorrhage has not been adequately studied. In the present cohort, CED after subcortical hemorrhage was half as common as that after deeper hemorrhage, although the sample size was not large enough for the difference to be significant.

The present results are unique in that right-sided hematoma was associated with any, forced, or persistent CED. CED attributable to right hemispheric stroke was reported to be more common and to persist longer than CED with a left-sided stroke.[6,19,21–24] An imbalance between the left and right cortical inputs on the superior colliculus and premotor reticular formations[4] as well as an association between CED and unilateral neglect[24,25] is a major possible reason for this difference.

Baseline GCS score, hematoma volume, and intraventricular extension are established predictors for poor outcome after supratentorial hemorrhage on multivariable analyses.[15–17] In contrast, CED was reported to be associated with poor outcome on univariate analysis but not on multivariable analysis,[22,26] partly because CED has a strong association with the previously established predictors, as shown in Table 3. In the present results, any CED on admission was independently related to death or dependency at 3 months even after adjustment for GCS, and persistent CED 72 hours after admission was independently related after adjustment for GCS and hematoma volume. This positive statistical result suggests the strengths of the present study: the relatively larger sample size than previous studies and accurate documentation of the severity and duration of CED. Another possible explanation for this result was that the statistical power of hematoma volume might be weakened because patients with huge hematomas (>60 mL) were excluded. Bedside assessment of CED twice is easy, not time-consuming, and appears to provide valuable information related to chronic outcomes.

A smaller cutoff volume causes CED in thalamic than in putaminal hematomas, and this may be due to the dense neurological structures of the thalamus. The volume of the healthy human thalamus is generally less than 6.5 mm^3[27,28] smaller than the present cutoff volume of thalamic hematoma causing CED (≥7.7 mL). Thus, a thalamic hematoma ≥7.7 mL would impair the anterior and posterior limbs of the internal capsule surrounding the thalamus; these are critical structures responsible for CED.[1,3,5,23] A case series demonstrated that a thalamic hematoma >2 cm in diameter, >4 mL in volume, or with lateral extension was associated with CED.[7] The same situation can happen regarding extinction/inattention (neglect), another NIHSS subscore that has relationships with CED. Extinction/inattention (subscore ≥1) was similarly positive between thalamic patients (53%) and putaminal patients (59%, not described in "Results"), although hematoma volume was very different between the 2 regions.

A strength of this study was that emergency brain imaging was done right after the hospital visit and almost at the same time as the initial examination for CED, within 2.5 hours after symptom onset. Because both CED and hematoma volume can change during hyperacute ICH, it is necessary to evaluate CT and neurological examinations in a unified manner without a time delay in the emergency setting to accurately identify hematoma location and cutoff volume for CED. The present association between CED and hematoma volume appears to be highly reliable, whereas previous studies did not do close volumetric analysis of hematoma.[7–9]

The present study had some limitations. First, the study is a retrospective analysis of a prospectively collected sample and implications for bias introduction. Second, analyses only for patients with thalamic ICH and those only for patients with putaminal ICH might not have strong statistical power due to small sample size. Third, data on the detailed hematoma location in the thalamus or putamen were not available in the present database, although the finding might be associated with both presences of CED and stroke outcomes. Fourth, data on the direction of CED were not available for

all patients. Most patients had ipsilateral CED to the hematoma, but some patients, especially those with thalamic hemorrhage, might have contralateral CED.[29,30] Fifth, all patients were treated with intravenous nicardipine to maintain certain levels of blood pressure under the unified protocol of the SAMURAI-ICH study. The antihypertensive intervention might affect the duration of CED or the outcome at 3 months.

Conclusions

Persistence of CED was a significant predictor of death or dependency after acute supratentorial hemorrhage even after adjusting for initial neurological severity and hematoma volume. A relatively smaller hematoma could elicit CED in thalamic than in putaminal lesions among patients with acute ICH.

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Disclosures

None.

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World Stroke Congress（2012年10月、ブラジリア）

IS SYSTOLIC BLOOD PRESSURE LOWERING TO ≤160 MMHG FOR ACUTE INTRACEREBRAL HEMORRHAGE SAFE? - THE SAMURAI-ICH STUDY

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Background and aims: The incidence of intracerebral hemorrhage (ICH) in Asian people is about twice higher than in people of other ethnic origins. Although elevated blood pressure (BP) is often observed in acute ICH, optimal BP control remains controversial. We aimed to reveal the current status of acute BP management for acute ICH in Japan and to determine the effects of the major BP management strategy.

Methods: Using a nationwide questionnaire, we investigated the target systolic BP, first choice antihypertensive drug and others for acute ICH in Japan. Thereafter we conducted a prospective, multicenter, observational study to assess whether the major strategy is safe.

Results: Systolic BP (SBP) lowering to ≤160 mmHg using intravenous nicardipine was a major strategy in Japan. In the prospective study, the primary endpoints with neurological deterioration and serious adverse event to stopping nicardipine and the secondary endpoints with hematoma expansion, modified Rankin scale ≥4 and death at 3 months of onset were equal or below the estimated 90% confidence intervals based on previous similar reports.

Conclusions: SBP lowering to ≤160 mmHg using intravenous nicardipine appeared to be safe. As a next step to establish optimal BP control, we have just started to enroll patients to the Antihypertensive Treatment of Acute Cerebral Hemorrhage (ATACH) II, which is the randomized trial to compare the guideline-based control (<180mmHg) and strict control (<140mmHg), from Japan on February 2012.

International Stroke Conference （2013年2月、ホノルル）

Conjugate Eye Deviation in Acute Intracerebral Hemorrhage: Stroke Acute Management With Urgent Risk-factor Assessment and Improvement (SAMURAI) -ICH Study

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Background and Purpose: Conjugate eye deviation (CED) occurs frequently in patients with acute stroke. The purpose of this study was to elucidate the factors that correlate with CED, as well as the relationship between CED and outcomes, in patients with acute intracerebral hemorrhage (ICH).

Methods: A total of 211 patients with acute supratentorial ICH were recruited in a multicenter, prospective study. Both on admission and 72 hours later, CED was assessed with an NIH Stroke Scale "best gaze" subscore of ≥1. Hematoma location and volume were assessed on CT within 2.5 hours of onset.

Results: Ninety-six (45%) patients had CED on admission. On multivariable analysis, right-sided lesion (OR 2.36, 95% CI 1.18-4.93), hematoma volume (OR 1.07, 95% CI 1.04-1.10 per 1 mL), and baseline GCS score (OR 0.66, 95% CI 0.53-0.80 per 1 point) were independently associated with CED. After adjusting for sex, age, intraventricular extension of the hematoma, baseline GCS score, and hematoma volume, the presence of CED both on admission and 72 hours later was an independent predictor of death or dependency at 3 months post-stroke (OR 5.77, 95% CI 2.27-16.94). The optimal cutoff volume of hematoma related to CED was ≥13.5 mL for patients with putaminal hemorrhage (sensitivity, 76%; specificity, 72%) and ≥7.7 mL for patients with thalamic hemorrhage (sensitivity, 82%; specificity, 83%).

Conclusions: The persistence of CED was a significant predictor of death or dependency after acute supratentorial ICH even after adjusting for initial severity and hematoma volume. CED can be evoked by a relatively smaller thalamic hematoma than a putaminal hematoma. Bedside assessment of CED appears to provide valuable information related to chronic outcomes of patients with ICH.

International Stroke Conference （2013年2月、ホノルル）

Reduced estimated glomerular filtration rate and outcomes of intracerebral hemorrhage: the SAMURAI-ICH study

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Key words: kidney dysfunction, acute stroke, intracerebral hemorrhage, antihypertensive treatment

Background and Purpose:

The association between chronic kidney disease and clinical outcomes in acute intracerebral hemorrhage (ICH) remains uncertain. We aimed to assess associations of renal dysfunction and outcomes in acute ICH patients treated with intensive BP lowering.

Methods:

The SAMURAI-ICH study was a prospective, multicenter, observational study. A total of 211 patients with acute supratentorial ICH were recruited. BP was targeted between 120 mmHg and 160 mmHg during initial 24 h using intravenous nicardipine. Glomerular filtration rate (eGFR) was calculated using admission serum creatinine. After 23 patients on maintenance hemodialysis were excluded, the remaining 188 were divided into 3 groups as follows: Group 1, eGFR of <60; Group 2, 60 to 75; and Group 3, ≥75 mL/min/1.73m^2. Clinical outcomes were hematoma expansion of ≥33% at 24 h, neurological deterioration within 72 h (GCS decrement ≥2 points or NIHSS increment ≥4 points), and favorable (modified Rankin Scale [mRS] ≤2) and unfavorable (mRS ≥5) outcomes at 3 months.

Results:

Of 188 patients, 35 (18 women) were allocated to Group 1, 58 (20) to Group 2, and 95 (33) to Group 3. Significant differences among 3 groups were found in age (73.1±13.6, 63.3±13.2, 63.8±9.8 yo; p <0.001) and initial systolic BP (208.9±18.1, 201.2±15.6, 200.2±14.8 mmHg; p=0.018). Initial hematoma volume (14.9±11.9, 15.5±14.9, 14.3±12.3 mL) and initial median NIHSS score (14, 11, 13) were similar among 3 groups. For outcomes, significant differences among 3 groups were found in favorable outcome (17.7%, 51.7%, 41.3%; p=0.004) and unfavorable outcome (22.9%, 10.3%, 5.3%; p=0.021), but not in hematoma expansion (17.1%, 10.3%, 22.1%) and neurological deterioration (11.4%, 8.6%, 7.4%). After adjustment with initial hematoma volume, initial systolic BP and initial NIHSS score, eGFR <60 ml/min/1.73m^2 was inversely associated with favorable outcome (OR 0.20, 95% CI 0.07-0.54) and positively associated with unfavorable outcome (4.27, 1.36-13.53).

Conclusions:

Although decreased eGFR on admission was not associated with initial hematoma volume or initial NIHSS score, it was associated with poor outcomes at 3 months of ICH onset.

脳出血最新治療事情：SAMURAI-ICH研究とATACH II 試験

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話題：日本発の脳卒中大規模臨床研究

脳出血最新治療事情：SAMURAI-ICH研究とATACH II 試験*

豊田一則**

Key Words：acute stroke, antihypertensive therapy, hypertension, international clinical trial, intracerebral hemorrhage

はじめに：日本人は脳出血好発民族

今回の特集では急性期脳梗塞の最新治療法や治療環境を中心に，さまざまな切り口から解説を行った．血栓溶解療法を含めた広義の抗血栓療法の進歩や，各種血管内治療デバイスの開発が，脳梗塞治療を後押ししている状況がわかる．一方で脳出血は，脳梗塞，特にラクナ梗塞と同じ脳の細小動脈病変を基盤に，異なった表現型として発現する．もともとアジア人は脳卒中の発症率が高いが，その中でも脳出血はこの民族差が目立ち，最近のメタ解析ではアジア人の脳出血発症率が白人の2倍を超えている(図1)[1]．国内多施設登録調査を集計した脳卒中データバンク2009[2]では，脳出血患者は新規脳卒中発症者の17％を占めている．同じ動脈硬化を素地として出血性疾患がこれほど高率に虚血性疾患と併在する臓器は脳だけであり，脳血管障害の治療が単純な抗血栓療法の強化では成り立たない理由である．

脳梗塞治療の進歩と比べて，脳出血治療法の開発は出遅れた感がある．大規模臨床試験で急性期外科手術の内科治療に対する優位を証明できず[3]，脳梗塞再開通治療に匹敵するような内科治療法も開発されていない．そのような中で，脳出血急性期の血圧高値が概して患者の転帰不良と結びつくことが知られ(図2)，急性期降圧療法の確立が望まれている．ここでは，筆者が主宰する厚生労働科学研究費による多施設共同研究Stroke Acute Management with Urgent Risk-factor Assessment and Improvement(SAMURAI)研究班が行った全国アンケート調査や観察研究と[4-6]，わが国を含めた国際臨床試験Antihypertensive Treatment of Acute Cerebral Hemorrhage(ATACH) II[7]の紹介を軸に，降圧療法への国内外の取り組みを解説する．

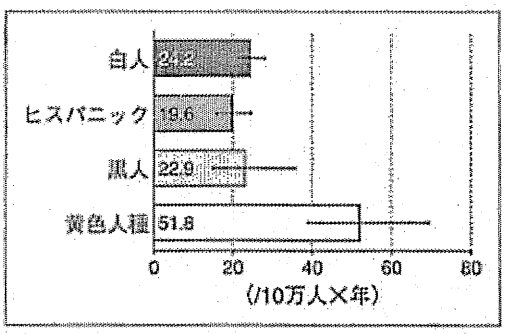

図1　人種差と脳出血発症率
1983～2006年に発表された36編の研究を用いたメタ解析を示す．東アジアないし東南アジア人は白人と比べて，脳出血発症率が2.1倍(95％CI 1.6～2.9)高かった．
(文献[1]より改変引用)

わが国の急性期降圧治療の現状

近年の国内外の治療指針は収縮期血圧180mmHg以上または平均血圧130mmHg以上を降圧開始の目安とし，また降圧目標値としてわが国の指針は降圧開始の目安値を下回ることを，米国の指

* The SAMURAI-ICH Study and ATACH II trial for acute blood pressure lowering in intracerebral hemorrhage.

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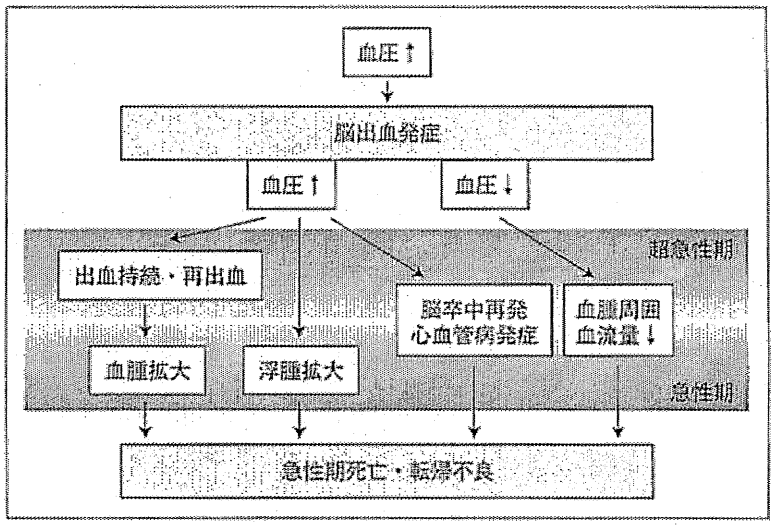

図2 脳出血急性期の血圧と患者転帰
脳出血は脳の細小動脈が破綻して生じ，その最大の原因は高血圧症である．また，脳出血の急性期には概して血圧が上昇し，血腫や浮腫の増大などを介して転帰を増悪させる．一方，急性期降圧によって血腫周囲の血流量が低下し虚血を招くことが懸念されるが，総じて急性期血圧高値は転帰不良と考えられる．

針は平均血圧110mmHgまたは血圧160/90mmHgを例示している[8][9]（表1）．ただし，これらの目標数値は十分なエビデンスに基づいていない．筆者らが2施設共同で行った観察研究では，入院直後の24時間に収縮期血圧平均値が138mmHg未満であった群の転帰が良好であり[10]，筆者の施設ではガイドラインの推奨値よりも低い降圧開始の目安値や降圧目標値を，経験的に選ぶことが多い．

国内の治療の実情を知るため，前述したSAMURAI班で2008年に全国ウェブアンケート調査を行った．降圧開始の目安とする収縮期血圧は180mmHg以上，160mmHg以上との回答が多く，到達目標値は140mmHg以下，150mmHg以下，160mmHg以下との回答が84％を占めた（図3）[9]．急性期の静注降圧薬として，ニカルジピンが第一選択の57.1％，第二選択の26.5％，合わせて83.5％を占め，同薬を選ぶ主たる理由は強い降圧効果であった（96.2％）．ただし，この段階では国内でのニカルジピン静注薬の添付文書には，「頭蓋内出血で止血が完成していないと推定される患者」や「脳卒中急性期で頭蓋内圧が亢進している患者」への使用は禁忌とされ，その理論的根拠も明確でなかった．添付文書と現場の経験的判断の乖離が著しい実例であろう．本アンケート結果などを参考資料として，2009年に日本脳卒中学会，日本脳神経外科学会，日本高血圧学会が厚生労働省へ見直しを要望し，2011年6月に上記2項目は慎重投与項目へ変更された．

表1 脳出血急性期の血圧管理指針：脳卒中治療ガイドライン2009より

1. 脳出血急性期の血圧は，収縮期血圧が180mmHg未満または平均血圧が130mmHg未満を維持することを目標に管理する
2. 外科治療を施行する場合は，より積極的な降圧が推奨される
3. 降圧薬の種類としては特に推奨できるものはないが，脳血管を拡張する可能性のある薬剤は脳圧亢進をひき起こすため慎重な投与が望まれる

※上記の3項目は，すべてグレードC1（行うことを考慮しても良いが，十分な科学的根拠がない）と評価されている．（文献[9]より引用）

SAMURAI-ICH研究

添付文書見直し要望の提出と前後して，アンケートで示された国内治療実態の妥当性を確かめる目的で，SAMURAI班参加施設で共同して2009～2011年に前向き観察研究を行った（表2）[5][6]．本研究の目的は，急性期脳出血症例に対してア

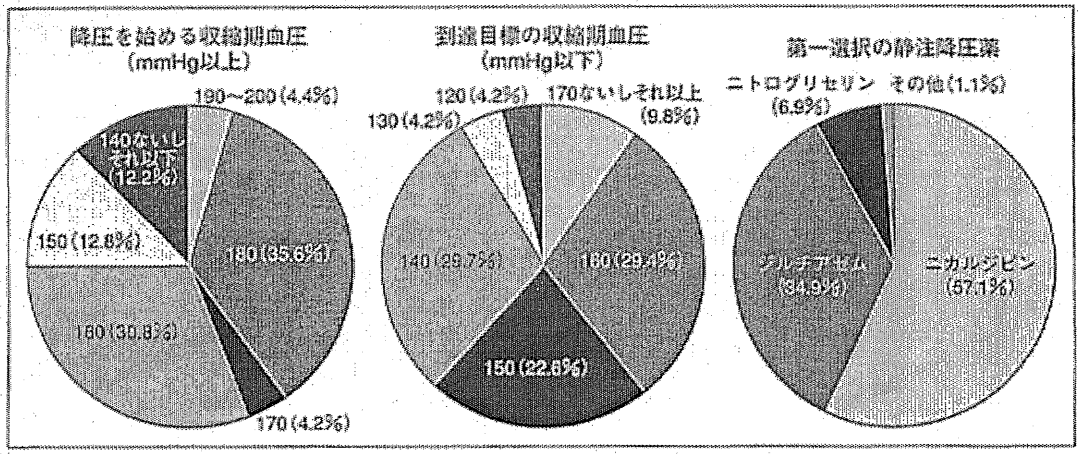

図3　超急性期脳出血患者への降圧治療に関する全国アンケート
2008年に国内1,424専門施設にアンケートへの協力を依頼し，600施設(42.1%)から回答を得た．(文献9より改変引用)

ンケートでの多数意見であったニカルジピン静注を用いて収縮期血圧160mmHg以下に降圧することの安全性を確かめることである．その研究方法と結果を概説する．

患者の選択基準は，ATACH II 試験[7]やそのパイロット試験であるATACH I 試験[11]の基準を参考に，来院時の収縮期血圧が180mmHgを超える，発症3時間以内の天幕上脳出血患者(血腫量60ml以下)とし，200例の登録を目標とした．ニカルジピン持続静注によって治療開始後24時間の収縮期血圧が120～160mmHgを維持するように調整した．ニカルジピンの用量調整法もATACH I, II での方法に倣った．主要評価項目を「治療開始から72時間後の症状進行」と「24時間以内のニカルジピン投与中断を要する副作用発現」とし，副次評価項目を「24時間以内の血腫拡大」，「3か月後の死亡」，「3か月後の転帰不良(脳卒中患者の自立度を示すmodified Rankin Scale[mRS]で4～6)」などとした．これらの項目の安全性を評価する基準として，国内外の既出論文での成績を加重平均して予測値を算出し，その90%信頼区間の上限値を上回らないこととした．

2年間で211例(女性81例，年齢66±12歳)を登録した．評価項目の詳しい数値を記載することをここでは控えるが，いずれの項目も予測値の90%信頼区間の上限値を大きく下回り，予測値自体よりも低率であった．このことより，アンケートで示されたわが国の臨床医家の多数意見が，安全に行える治療であろうと結論できた．前述したニカルジピン添付文書改訂が適切な対応であったことの証明にもなった．また，この研究を遂行したことは，ATACH II に多数の国内施設が参加するための良い契機ともなった．

ATACH II 試験

脳出血急性期の降圧療法確立に向けた介入試験が近年いくつか動き始めた．豪中韓の3国で行われたIntensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial (INTERACT)[12]では，登録時の収縮期血圧値が150～220mmHgを示す発症6時間以内の脳出血患者404例(このうち95%が中国人)を，異なる降圧目標値(180mmHg程度，および140mmHg程度)の2群に分けて比べた結果，24時間後の血腫量拡大率はより厳しい降圧の患者群で低く，130～140mmHgを目指した降圧での血腫量拡大抑制が強く期待できる反面で[13]，浮腫拡大や慢性期予後に有意な差を認めなかった[14]．この結果に基づいて，米国の指針にも「収縮期血圧140mmHgへの急性期降圧はおそらく安全であろう」との記載が加わった(Class IIb, Level of Evidence B)[3]．現在2,800例を目標にした本試験INTERACT2[15]の登録が始まっている．

一方，米国で行われた多施設共同非盲検パイロット試験であるATACH試験では，ニカルジピン静注により収縮期血圧目標値を200～170mmHg，170