

result in relatively few ICH events and affect the statistical analysis, but prior statin use seems to be safe for Japanese patients receiving i.v. rt-PA.

A unique point was that statin use seems to be less prevalent in Japan than in Western countries. Statin users prior to ischemic stroke onset accounted for 13.6–16.5% in Japanese multicenter prospective observational studies [37, 38], as compared to 18–23% in Western studies [15, 30–34]. The major reason for this less prevalence is that Japanese relatively uncommonly have dyslipidemia (21.5% in our study, 21% in the SUMO study [39] from Japan vs. 29–36% in Western studies [15, 30–34]) and coronary artery diseases (12.7% in ours, 12% in the SUMO study [39] vs. 18–32% in Western studies [15, 30–34]) possibly due to the difference in ethnic and dietary habit.

Previous studies showed the lower HDL-C levels and higher triglyceride levels in statin users than non-users [32, 36], and our results were similar. Statin increased HDL-C levels in some reports [40, 41], and did not in another [42]. Thus, the therapeutic effect of statin on HDL-C does not seem to be as clear as that on LDL-C. Another possible reason for lower HDL-C levels in our statin users was that their HDL-C levels prior to statin medication might be too low. Anyway, premorbid statin use could make the association of HDL-C levels to stroke outcomes complicated.

The strengths of this study included that it was a multicenter study with frequent use of MR techniques. On the other hand, it had several limitations. First, this study only included patients treated with rt-PA. Thus, the present results could not be compared with those in patients not receiving rt-PA. Second, this study was a retrospective observational study, and 46 patients were excluded from the analysis because of lack of data on admission

lipid levels or 3-month mRS scores. The excluded patients had different baseline features from included ones to some extent, and this may have caused selection bias. Third, we did not have complete information on doses and duration of prior statin use. Also, the information on initiation and continuation of statin use after stroke onset was incomplete, and we could not assess the effects of them on clinical outcome.

Although HDL-C seems to be a promising outcome predictor after i.v. rt-PA, it is not clear if HDL-C level raising therapy prior to stroke or during the acute stroke improves stroke outcomes. Recently, pharmacotherapy other than statins to increase directly HDL-C levels is developing [43, 44]. The future studies to examine whether increasing HDL-C levels prevent and improve stroke are desired.

Acknowledgment

This study was supported by a grant-in-aid (H20-Junkanki-Ippan-019 and H23-Junkanki-Ippan-010) from the Ministry of Health, Labour and Welfare, Japan, and received research funding from the National Cerebral and Cardiovascular Center (22-4-1).

Disclosure Statement

Dr. Nakagawara receives honoraria from Mitsubishi Tanabe Pharma, Kyowa Hakko Kirin, and Lundbeck. Dr. Okada receives an honorarium from Mitsubishi Tanabe Pharma and a consulting fee from Lundbeck. Dr. Toyoda receives research support from Grants-in-Aid from the Ministry of Health, Labour and Welfare, Japan.

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Early Neurological Deterioration within 24 Hours after Intravenous rt-PA Therapy for Stroke Patients: The Stroke Acute Management with Urgent Risk Factor Assessment and Improvement rt-PA Registry

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Key Words

Acute ischemic stroke · Diabetes mellitus · Hyperglycemia · Intracerebral hemorrhage · Thrombolysis · Tissue plasminogen activator

Abstract

Background: The initial 24 h after thrombolysis are critical for patients' conditions, and continuous neurological assessment and blood pressure measurement are required during this time. The goal of this study was to identify the clinical factors associated with early neurological deterioration (END) within 24 h of stroke patients receiving intravenous recombinant tissue plasminogen activator (rt-PA) therapy and to clarify the effect of END on 3-month outcomes. **Methods:** A retrospective, multicenter, observational study was

conducted in 10 stroke centers in Japan. A total of 566 consecutive stroke patients [211 women, 72 ± 12 years old, the median initial NIH Stroke Scale (NIHSS) score of 13] treated with intravenous rt-PA (0.6 mg/kg alteplase) was studied. END was defined as a 4-point or greater increase in the NIHSS score at 24 h from the NIHSS score just before thrombolysis.

Results: END was present in 56 patients (9.9%, 18 women, 72 ± 10 years old) and was independently associated with higher blood glucose [odds ratio (OR) 1.17, 95% confidence intervals (CI) 1.07–1.28 per 1 mmol/l increase, $p < 0.001$], lower initial NIHSS score (OR 0.92, 95% CI 0.87–0.97 per 1-point increase, $p = 0.002$), and internal carotid artery (ICA) occlusion (OR 5.36, 95% CI 2.60–11.09, $p < 0.001$) on multivariate analysis. Symptomatic intracranial hemorrhage within the initial 36 h from thrombolysis was more common in patients with END than in the other patients (per NINDS/Cochrane

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1015-9770/12/0342-0140\$38.00/0

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protocol, OR 10.75, 95% CI 4.33–26.85, $p < 0.001$, and per SITS-MOST protocol, OR 12.90, 95% CI 2.76–67.41, $p = 0.002$). At 3 months, no patients with END had a modified Rankin Scale (mRS) score of 0–1. END was independently associated with death and dependency (mRS 3–6, OR 20.44, 95% CI 6.96–76.93, $p < 0.001$), as well as death (OR 19.43, 95% CI 7.75–51.44, $p < 0.001$), at 3 months. **Conclusions:** Hyperglycemia, lower baseline NIHSS score, and ICA occlusion were independently associated with END after rt-PA therapy. END was independently associated with poor 3-month stroke outcome after rt-PA therapy.

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Introduction

Neurological deterioration within the initial couple of days affects stroke patients' long-term outcomes [1–11]. Neurological deterioration during acute stroke is associated with initial stroke severity [2], large vessel occlusion [3, 4], hypodensity $>33\%$ in the middle cerebral artery territory [5], the hyperdense middle cerebral artery sign on brain CT [5, 6], cerebral edema on early CT [5, 6], diabetes mellitus [4, 5, 7], hyperglycemia [6, 8, 9], high or low blood pressure [7, 8], early recurrent ischemic stroke [10], and symptomatic intracranial hemorrhage (sICH) [6, 11].

Intravenous (IV) thrombolytic therapy with recombinant tissue plasminogen activator (rt-PA) has been shown to improve stroke outcomes [12, 13]. However, about half of the patients were not independent in their activities of daily living or died at 3 months despite IV rt-PA therapy [14]. Since the initial 24 h after thrombolysis are critical for patients' conditions, partly because of the frequent occurrence of intracranial hemorrhage (ICH), continuous neurological assessment and blood pressure measurement are required during this period of time [15]. Changes in the neurological status during this period may decisively affect outcomes after thrombolysis. The aims of this study were to identify the clinical factors that were associated with early neurological deterioration (END) within 24 h after IV rt-PA therapy and to clarify the effect of END on 3-month stroke outcomes.

Patients and Methods

The Stroke Acute Management with Urgent Risk Factor Assessment and Improvement (SAMURAI) rt-PA Registry has a multicenter, hospital-based, retrospective, observational cohort design [16]. Details of this study have been described previously [16–18]. In brief, this study involved 600 consecutive patients with

acute ischemic stroke receiving alteplase from October 2005 through July 2008. All of the patients treated during the study period were registered sequentially. Informed consent was obtained from all study participants. Of these, 34 patients whose 24-hour National Institutes of Health Stroke Scale (NIHSS) scores were not available were excluded from this study. The remaining 566 patients were included. Each local Ethics Committee approved the retrospective collection of clinical data from the database and submission of the data to our central office. Each patient received a single alteplase dose of 0.6 mg/kg (the recommended dose in the Japanese guidelines and the approved labeling) intravenously, with 10% given as a bolus within 3 h of stroke onset, followed by a continuous IV infusion of the remainder over 1 h [19].

The data collected from the database of the SAMURAI rt-PA registers for the present study are listed in table 1. Neurological deficits were assessed using the NIHSS score just before and 24 h after rt-PA, and at discharge [median hospital stay 27 days, interquartile range (IQR) 18–44.5 days]. END was defined as a 4-point or greater increase in the NIHSS score at 24 h from the NIHSS score just before thrombolysis. The ischemic stroke subtype was defined according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) categories [20]. Early ischemic change on CT was quantitatively calculated using the Alberta Stroke Programme Early CT Score (ASPECTS) [21, 22]. To identify arterial occlusion sites, MR angiography, CT angiography, or ultrasound was performed [23].

The outcomes investigated were any ICH and sICH within the initial 24–36 h, NIHSS score at discharge, excellent functional outcome corresponding to modified Rankin Scale (mRS) score 0–1, death and dependency (mRS 3–6), and death at 3 months. Any ICH was defined as CT evidence of a new ICH [24]; it was assessed by at least two experienced vascular neurologists at each stroke center [16]. Symptomatic ICH was defined with neurological deterioration corresponding to an increase of ≥ 1 point from the baseline NIHSS score according to the NINDS/Cochrane protocol [13]. Symptomatic ICH was also defined according to the Safe Implementation of Thrombolysis in Stroke Monitoring Study (SITS-MOST) protocol as parenchymal hemorrhage type II combined with an increase of ≥ 4 points from the baseline NIHSS score [14]. Outcomes at 3 months were assessed by clinical examination at a hospital clinic or by telephone survey for patients whose neurological deficits were too severe to visit the clinic. Mainly study assistance nurses carried out the follow-up survey by telephone. When the patients or their families could not be reached, they called repeatedly till they were successful. Five patients were lost to follow-up at 3 months and for these 5 patients the mRS scores at discharge were used as their 3-month follow-up status.

Statistical analysis was performed using JMP 9.0 statistical software (SAS Institute Inc., Cary, N.C., USA). Patients' baseline characteristics were compared between those with and without END using χ^2 tests, unpaired t tests, and the Mann-Whitney U test, as appropriate. To identify the clinical factors associated with END, multivariate analyses were performed. Sex and age were initially entered, and the other variables listed in table 1 were chosen by a backward selection procedure using the Bayesian information criterion for exclusion. In addition, to identify the association between END and stroke outcomes, multivariate analyses with a backward selection procedure were performed. Statistical significance was established at $p < 0.05$.

Table 1. Baseline clinical characteristics

	END (n = 56)	No END (n = 510)	p value
Females, n	18 (32.1)	193 (37.8)	0.468
Age, years	71.5 ± 9.3	72.0 ± 11.9	0.733
Risk factors and comorbidities, n			
Hypertension	35 (62.5)	312 (61.2)	0.886
Diabetes mellitus	18 (32.1)	85 (16.7)	0.010
Dyslipidemia	18 (32.1)	97 (19.0)	0.034
Atrial fibrillation	29 (51.8)	213 (41.8)	0.157
Prior ischemic stroke	10 (17.9)	93 (18.5)	1.000
Prior ischemic heart disease	9 (16.8)	62 (12.2)	0.396
Prior congestive heart failure	2 (3.6)	45 (8.8)	0.300
Prior use of antihypertensives	28 (50.0)	224 (43.9)	0.399
Prior use of hypoglycemic agents	10 (17.9)	36 (7.1)	0.016
Prior use of statins	12 (21.4)	51 (10.0)	0.022
Prior use of antithrombotic therapy	25 (44.6)	185 (36.3)	0.244
Physiological and laboratory data on admission			
Systolic BP, mm Hg	158 ± 20	150 ± 20	0.005
Diastolic BP, mm Hg	84 ± 15	81 ± 15	0.216
Blood glucose, mmol/l	9 ± 3.5	7.4 ± 0.2	<0.001
Hemoglobin A1c, %	6.1 ± 0.9	5.7 ± 1.0	0.021
Initial NIHSS score	11 (7–16)	13 (7–19)	0.076
ASPECTS	9 (8–10)	10 (8–10)	0.277
ICA occlusion, n	20 (35.7)	67 (13.1)	<0.001
Cardioembolism as stroke subtype, n	32 (57.1)	323 (63.3)	0.384
Onset-to-treatment time, min (IQR)	141 (120–170)	145 (121–166)	0.894
IV antihypertensives just before rt-PA, n	18 (32.1)	141 (27.7)	0.531

Values in parentheses represent percentage or range. Total cholesterol ($p = 0.997$), HDL cholesterol ($p = 0.379$), LDL cholesterol ($p = 0.538$), triglycerides ($p = 0.711$), and creatinine ($p = 0.366$) were not significantly different between the two groups.

Results

A total of 566 consecutive stroke patients (211 women, 72.0 ± 11.6 years old) were studied. Of these, 56 patients (9.9%, 18 women, 71.5 ± 9.3 years old) had END (fig. 1).

Risk Factors Associated with END

The baseline clinical characteristics of patients with and without END are presented in table 1. Patients with END more commonly had diabetes mellitus ($p = 0.010$), dyslipidemia ($p = 0.034$), prior use of hypoglycemic agents ($p = 0.016$), prior use of statins ($p = 0.022$), and internal carotid artery (ICA) occlusion ($p < 0.001$) than patients without END. Systolic blood pressure ($p = 0.005$), blood glucose ($p < 0.001$), and hemoglobin A1c levels ($p = 0.021$) were higher in patients with END than in those without. Initial NIHSS scores just before thrombolysis were not significantly different between the two groups ($p = 0.076$).

Multivariate regression analysis to identify the clinical factors associated with END showed that higher blood glucose [odds ratio (OR) 1.17, 95% confidence intervals (CI) 1.07–1.28 per 1 mmol/l increase, $p < 0.001$], lower initial NIHSS score (OR 0.92, 95% CI 0.87–0.97 per 1-point increase, $p = 0.002$), and ICA occlusion (OR 5.36, 95% CI 2.60–11.09, $p < 0.001$) were independently associated with END (table 2).

Association of END with ICH within the Initial 36 Hours

Of the 566 patients, 113 (20.0%) had some ICH, including 22 (3.9%) with sICH per NINDS/Cochrane and 7 (1.2%) with sICH per SITS-MOST. Compared to patients without END, patients with END more often had ICH (42.9 vs. 17.5%, $p < 0.001$), sICH per NINDS/Cochrane (19.6 vs. 2.2%, $p < 0.001$), and sICH per SITS-MOST (7.1 vs. 0.6%, $p = 0.002$). On multivariate regression analysis, END was independently associated with any ICH (OR

Fig. 1. Change in NIHSS score between baseline score before thrombolysis and 24 h after it.

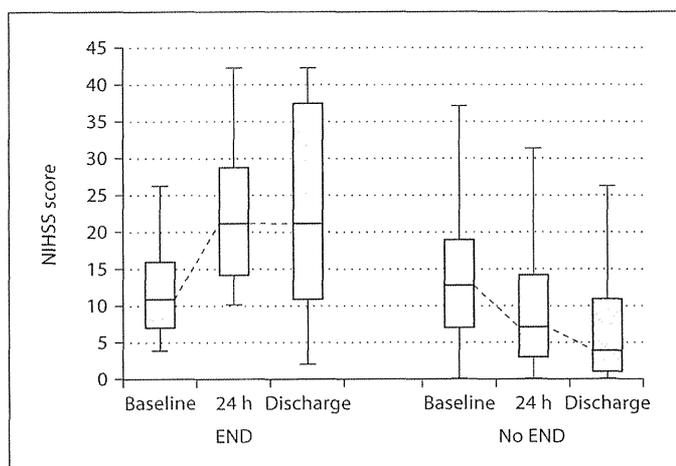
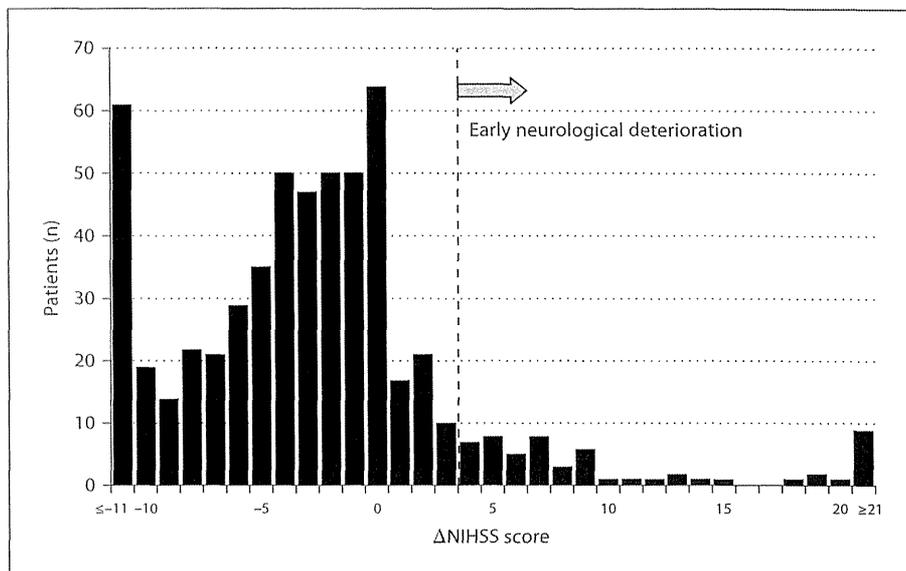


Fig. 2. Course of the NIHSS score during hospitalization. The horizontal line in the box is the median, the bottom and top of the box are the 25th and 75th percentile, respectively, and the ends of the whiskers are the minimum and maximum values.

3.38, 95% CI 1.87–6.06, $p < 0.001$), sICH per NINDS/Cochrane (OR 10.75, 95% CI 4.33–26.85, $p < 0.001$), and sICH per SITS-MOST (OR 12.90, 95% CI 2.76–67.41, $p = 0.002$).

Association of END with 3-Month Outcomes

The median NIHSS score at discharge of the 566 patients was 4 (IQR 1–13). The discharge NIHSS score of patients with END was different from that of patients

Table 2. Multivariate logistic regression analysis for END

	Adjusted OR	95% CI	p value
Female	0.81	0.41–1.55	0.529
Age (per 10 years)	1.02	0.78–1.35	0.911
Blood glucose (per 1 mmol/l)	1.17	1.07–1.28	<0.001
Initial NIHSS score (per 1 point)	0.92	0.87–0.97	0.002
ICA occlusion	5.36	2.60–11.09	<0.001

These variables were chosen by a backward selection procedure using the Bayesian information criterion for exclusion.

without END [21 (IQR 11–37.5) vs. 3 (1–11), $p < 0.001$] (fig. 2).

Five patients were lost to follow-up at 3 months, and their mRS score at discharge was used as the 3-month mRS score. None of these 5 patients showed END; at hospital discharge, 1 had mRS of 2, 2 had mRS of 4, and 2 had mRS of 5. Of the 566 patients, 190 (33.6%) had an excellent functional outcome (mRS 0–1), 295 (52.1%) had death and dependency (mRS 3–6), and 38 (6.7%) had died by 3 months. No patients with END were independent while 37.3% of patients without END were independent ($p < 0.001$, fig. 3). Patients with END had poorer stroke outcomes than those without END at 3 months (death and dependency: 91.1 vs. 47.8%, $p < 0.001$; death: 25.0 vs. 4.7%, $p < 0.001$).

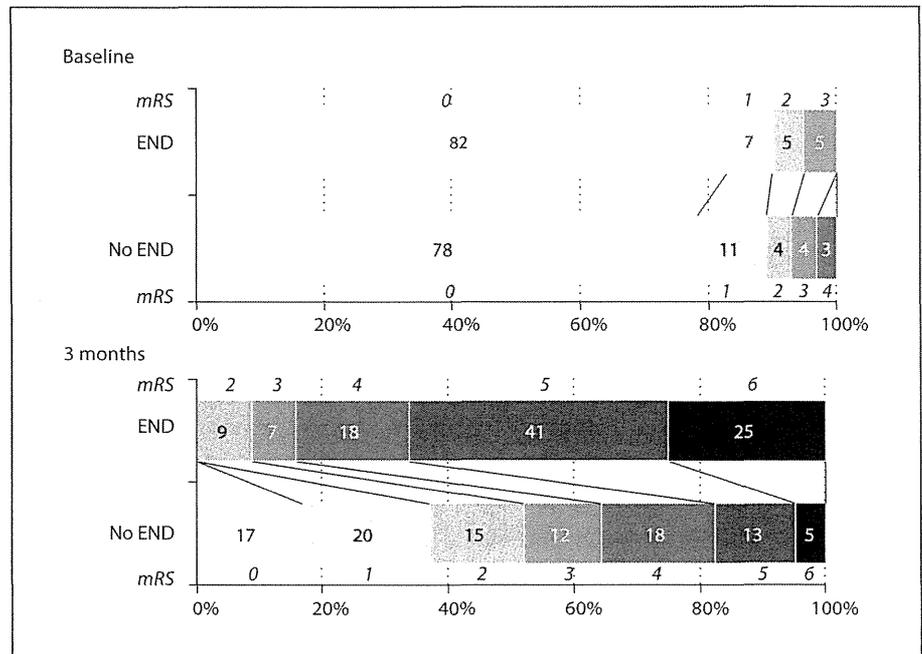


Fig. 3. mRS score at baseline and at 3 months.

Table 3. Association of END with each outcome parameter

	OR	95% CI	p value
Any ICH	3.38	1.87–6.06	<0.001
sICH (NINDS/Cochrane protocol)	10.75	4.33–26.85	<0.001
sICH (SITS-MOST protocol)	12.90	2.76–67.41	0.002
Death and dependency at 3 months (mRS score 3–6)	20.44	6.96–76.93	<0.001
Death at 3 months	19.43	7.75–51.44	<0.001

These variables were chosen by a backward selection procedure using the Bayesian information criterion for exclusion.

Multivariate regression analysis indicated that END was independently associated with death and dependency (OR 20.44, 95% CI 6.96–76.93, $p < 0.001$), as well as death (OR 19.43, 95% CI 7.75–51.44, $p < 0.001$, table 3), at 3 months.

Discussion

In this observational study, the clinical factors associated with END within 24 h after IV rt-PA therapy and the effect of END on stroke outcomes were determined. The first major finding was that END was independently associated with higher blood glucose, lower baseline NIHSS score and ICA occlusion. The second major finding was

that END was independently associated with early ICH after IV rt-PA. The third major finding was that none of the patients with END had an excellent outcome (mRS 0–1) at 3-month follow-up; they were more often dependent or had a fatal outcome (mRS 3–6) at 3 months after multivariate adjustment.

END was present in one tenth of the patients in our study. Previous studies indicated that END was present in 14–38% of patients after IV rt-PA [5, 6] and in 13–40% of patients who did not receive thrombolysis [2–4, 7, 8]. However, it is important to note that the definition of END differed among the studies. The time interval to assess deterioration differs greatly among studies, including the initial 24 h [5, 6, 9, 11], 36 h [7], 48–72 h [1, 2, 4, 8, 10], and 7 days after stroke onset [3]. As an indicator for

neurological deterioration, the Scandinavian Neurological Stroke scale [5, 7], the Canadian Neurological Scale [8], and different cutoff scores of the NIHSS (increase of more than 1 [4], 3 [2], and 4 points [1, 6, 9–11]) were used. Thus, a direct comparison of the results among these studies is difficult.

In the present study, higher blood glucose was associated with END. Hyperglycemia is known to be a risk factor for poor outcome of stroke patients even after early recanalization following thrombolysis [9, 25, 26]. Hyperglycemia is also known to be a risk factor for thrombolysis-associated sICH [27]. Possible mechanisms of hyperglycemia-associated neurological deterioration include endothelial damage, deteriorating tissue acidosis, and worsening of blood-brain barrier breakdown [9, 25, 26]. ICA occlusion was inversely correlated with early improvement (≥ 8 -point decrease in the NIHSS score) 24 h after IV rt-PA in our single-center cohort [28]. The present results may be the reverse side of the same coin. A reduction in local cerebral perfusion pressure after ICA occlusion with poor leptomeningeal collaterals could be a reason for END [1]. It was paradoxical that the lower baseline NIHSS score was associated with END in the present study, the opposite of what was found in previous studies [2, 3, 5–7]. These unusual results may be due to a ceiling effect, preventing the high score from increasing further. Prior use of antithrombotic therapy and history of congestive heart failure may influence early neurological states after thrombolysis via growth of ICH [27, 29], although they were not associated with END in the present study.

Symptomatic ICH often occurs within several hours after thrombolysis and is the most common cause of END [6]. In our cohort, sICH was more than 10 times as frequent in END patients as in other patients. In addition, acute arterial reocclusion [6], acute recurrent stroke [10, 11], edema progression [1, 30], and noncerebral accidents including infections and cardiovascular events are less common causes of END, although these possible mechanisms of END were not assessed in the present study. Of these, large swelling edema and edema with ICH were reported to show a strong association with a poor 3-month outcome [30].

The clear messages from the present study are that END within 24 h excludes independence and is associated with a very high risk of death and dependency (OR 20.44) at 3 months. These findings are similar to those from previous trials on IV rt-PA [5, 6]. Thus, careful stroke care to avoid END could lead to better 3-month outcomes.

Certain limitations need to be considered prior to interpretation of the present results. First, patients who did not receive rt-PA were not included in this study. Second, early recanalization of the occluded cerebral artery, which greatly affects early neurological status, was not assessed. Third, END was evaluated at 24 h and sICH was assessed within the initial 24–36 h. Fourth, biochemical variables were modified by onset of stroke and they might not reflect patients' characteristics before stroke onset. Finally, the present results based on low-dose rt-PA therapy (0.6 mg/kg) may not be applicable to the regular dose therapy (0.9 mg/kg).

Hyperglycemia, lower baseline NIHSS score, and ICA occlusion were independently associated with END after rt-PA therapy. The present study clearly indicates that END within 24 h after thrombolysis has an important association with poor 3-month outcomes.

Acknowledgment

This study was supported in part by Grants-in-Aid (H20-Junkanki-Ippan-019 and H23-Junkanki-Ippan-010, chief investigator: Kazunori Toyoda) from the Ministry of Health, Labor and Welfare, Japan.

Disclosure Statement

Yasushi Okada received an honorarium from Mitsubishi Tanabe Pharma and a consulting fee from Lundbeck. Jyoji Nakagawa received honoraria from Mitsubishi Tanabe Pharma, Kyowa Hakko Kirin, and Lundbeck. Masatoshi Koga received research support from the Japan Cardiovascular Research Foundation (the Bayer Scholarship for Cardiovascular Research). Kazuo Mine-matsu received research support from the Ministry of Health, Labour and Welfare, Japan, and research grants for Cardiovascular Diseases, Grants-in-Aid, the Foundation for Biomedical Research and Innovation, Mitsubishi Tanabe Pharma Corporation, and Kyowa Hakko Kirin Pharma, Inc., and Hitachi Medical Corporation. Kazunori Toyoda received research support from Grants-in-Aid from the Ministry of Health, Labour and Welfare, Japan and Mitsubishi-Tanabe Pharma Corporation.

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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

Received June 3, 2012; final revision received July 20, 2012; accepted August 9, 2012.

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DOI: 10.1161/STROKEAHA.112.666750

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) score¹⁰ ≥ 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 \times width \times height)/2] method¹⁴ 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 lesion, 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	PValue	OR	95% CI	PValue	OR	95% CI	PValue
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 lesion	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 deviation; 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.

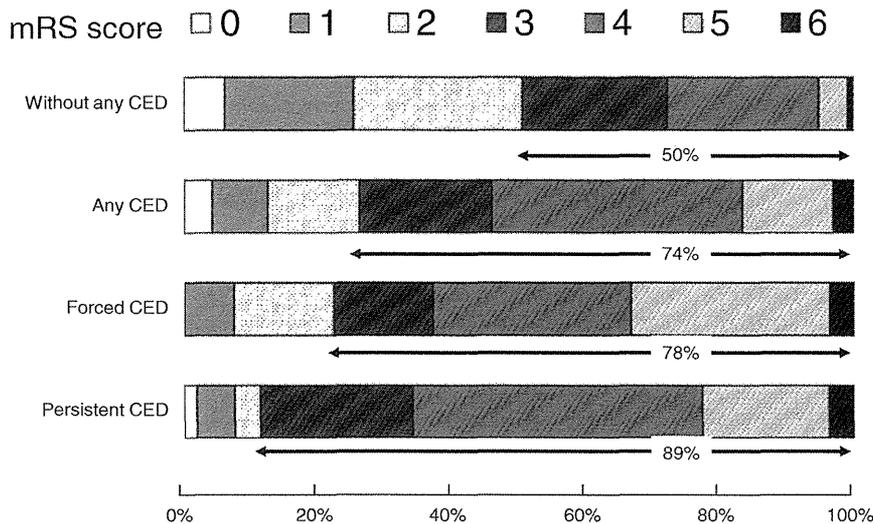


Figure. Distribution of the mRS score at 3 months. CED indicates conjugate eye deviation; mRS, modified Rankin Scale.

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	<i>P</i> Value	OR	95% CI	<i>P</i> Value	OR	95% CI	<i>P</i> Value	OR	95% CI	<i>P</i> 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 formations⁴ 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 mm³,^{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.

Acknowledgments

We thank Akiko Kada, MPH, for advice on the statistical analyses.

Sources of Funding

This study was supported in part by Grants-in-Aid (H20-Junkanki-Ippan-019 and H23-Junkanki-Ippan-010, chief investigator: Dr Toyoda) from the Ministry of Health, Labor and Welfare, Japan.

Disclosures

None.

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Common Carotid Artery Dissection Caused by a Frontal Thrust in Kendo (Japanese Swordsmanship)

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A 66-year-old right-handed man suddenly developed left hemiplegia after an opponent thrust at his neck with a bamboo sword during a practice game of Kendo (Japanese swordsmanship; Figure 1). Fifty minutes later, he visited our emergency service. His blood pressure was 77/55 mm Hg in the left arm but could not be measured in the right arm; his right radial artery was initially pulseless but became palpable 1 hour later. He was somnolent and had left unilateral spatial neglect, left complete hemiplegia, and left-sided sensory disturbance. Enhanced computed tomography (CT) showed an occlusion 15 mm distal to the origin of the right common carotid artery (CCA) without any abnormal findings at the aorta and innominate and right subclavian arteries. On emergent carotid ultrasonography, an intraluminal filling defect occupied the right CCA and swung back and forth with pulsation. He was diagnosed as having ischemic stroke, possibly caused by traumatic CCA dissection, although an infarct was not identified on brain CT.

On the second day, fresh infarcts were identified in the right hemisphere on diffusion-weighted MRI, and the right internal carotid, middle cerebral, and posterior cerebral arteries were poorly demonstrated on magnetic resonance angiography (Figure 2). On the fourth day, the right CCA was recanalized, and the intimal flap was identified on ultrasonography (Figure 3 and Movie I in the online-only Data Supplement). A mobile thrombus was identified within the true lumen, but its shape changed on the follow-up ultrasonography 9 hours later. The false lumen diminished, and the thrombus disappeared with a mild aneurysmal change after day 30. The patient was diagnosed as having a definite dissection of the CCA. These dynamic changes were also identified on CT angiography (Figure 4). The right distal CCA was severely stenotic on the fourth day. The stenosis became milder with aneurysmal change on day 10. The intimal flap and double lumens in the right CCA were detected on axial CT scans. The small false lumen was also identified in the distal

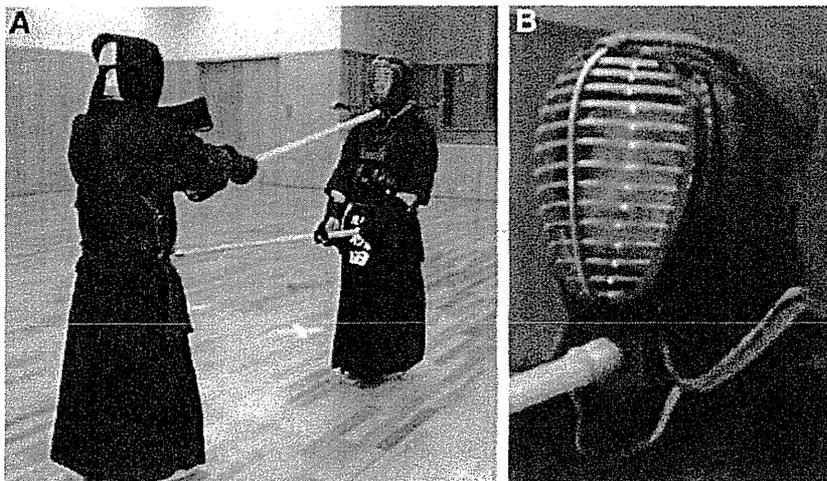


Figure 1. A, A performance of tsuki in Kendo. B, A bamboo sword is thrust at the partner's throat armor.

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The online-only Data Supplement is available with this article at <http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIRCULATIONAHA.111.066472/-/DC1>.

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(*Circulation*. 2012;125:e617-e619.)

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Circulation is available at <http://circ.ahajournals.org>

DOI: 10.1161/CIRCULATIONAHA.111.066472

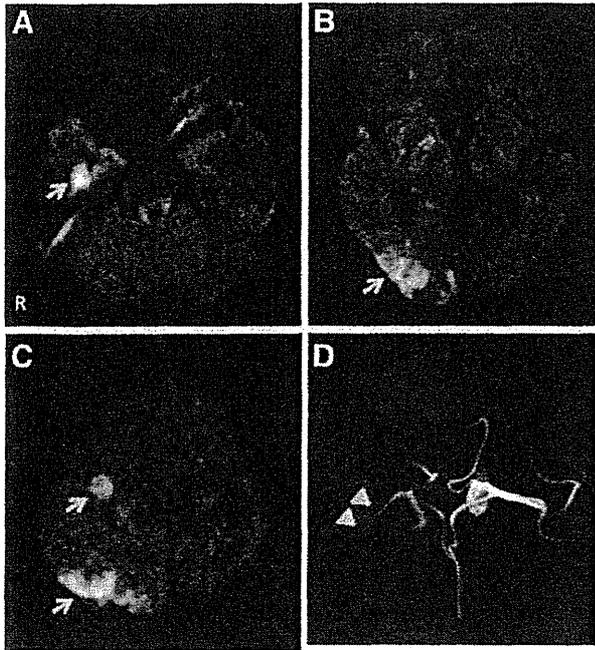


Figure 2. Brain magnetic resonance (MR) images on day 2. **A** through **C**, Diffusion-weighted MR imaging studies demonstrating fresh and scattered infarcts in the right middle and posterior cerebral artery areas (arrows). **D**, MR angiography demonstrating poor visualization of the right internal carotid, middle cerebral (arrowhead), and posterior cerebral arteries.

innominate artery, indicating the existence of the reversible innominate dissection that had caused pulselessness at the time of the initial examination. At hospital discharge on day 49, the patient still had severe hemiplegia. He did not develop recurrent stroke.

A frontal thrust of Kendo can cause cervical artery dissection and stroke,¹ although it has rarely been reported.² The strength of this report is that dynamic changes in the morphology of the dissected CCA were clarified through the use of both ultrasonography and CT angiography examinations.

Sources of Funding

The present study was supported by the Intramural Research Fund (23-6-4) for Cardiovascular Diseases of the National Cerebral and Cardiovascular Center, and the Grants-in-Aid (H23-Junkanki-Ippan-010) from the Ministry of Health, Labour and Welfare, Japan.

Disclosures

None.

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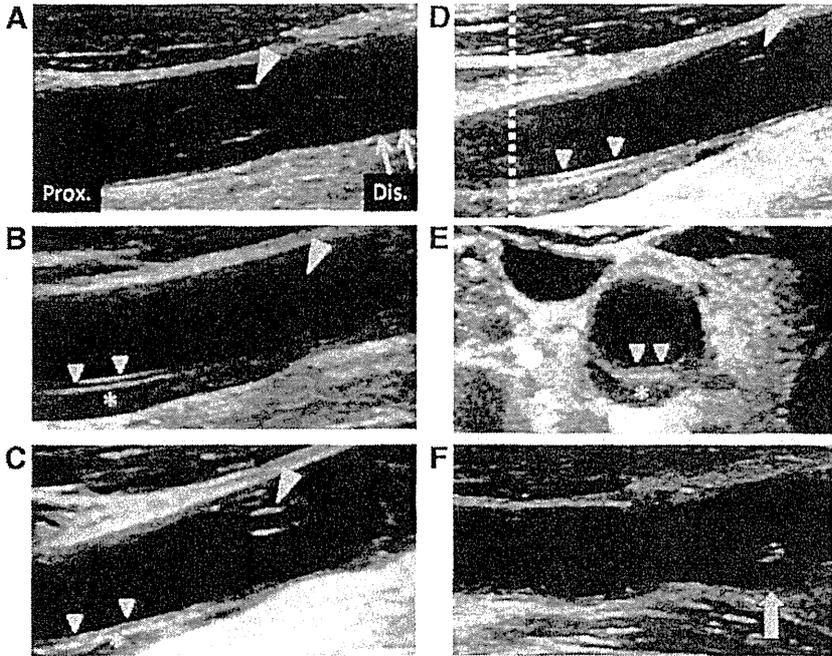


Figure 3. Changes in a B-mode image of the right common carotid artery (CCA). **A**, On day 2, the distal CCA is occluded with a thrombosed false lumen (arrows). A mobile thrombus is identified proximal (Prox.) to the occlusion site (arrowhead). **B through E**, Longitudinal (**B-D**) and axial (**E**) B-mode images on day 4 at 10 AM (**B**), 7 PM (**C**), and 9 PM (**D** and **E**). **E**, Axial image of a dotted line on **D**. The distal (Dis.) CCA is recanalized. The mobile thrombus gradually changes in shape (arrowhead) and a thrombosed false lumen (asterisk) are seen at the proximal CCA. **F**, On day 48, the mobile thrombus and the thrombosed false lumen disappear completely. Aneurysmal formation is seen (filled arrow).

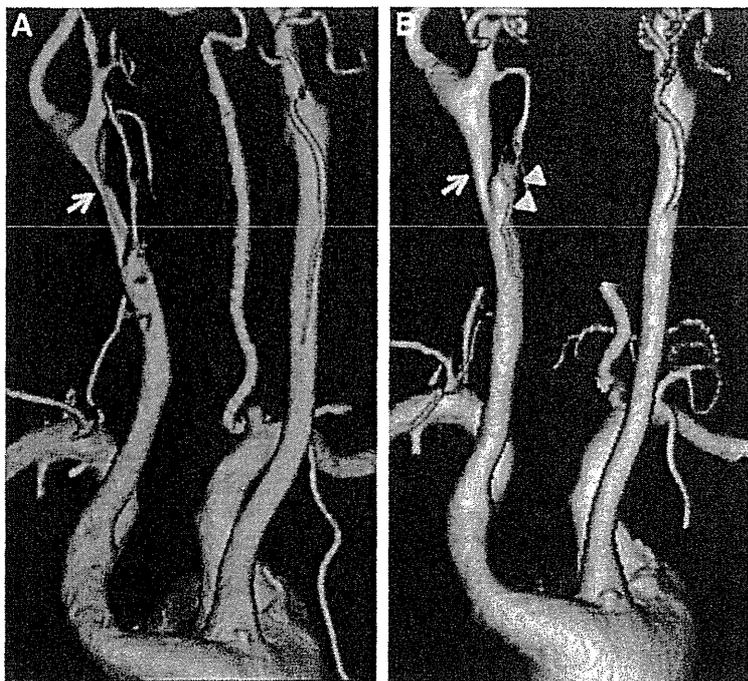


Figure 4. Cervical computed tomography angiography. **A**, On day 4, the right distal common carotid artery (CCA) is stenotic (arrow). **B**, On day 23, the stenotic CCA becomes wider (arrow), and aneurysmal formation is evident (arrowhead).

Dabigatran and Factor Xa Inhibitors for Stroke Prevention in Patients with Nonvalvular Atrial Fibrillation

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Stroke is a major health problem worldwide, and is often fatal or associated with poor long-term outcomes. Atrial fibrillation (AF) is responsible for up to 20% of all strokes; and the risk of stroke in patients with AF increases with age. Although warfarin is well established for the prevention of stroke in patients with AF, it has some limitations, particularly a narrow therapeutic window, variable/unpredictable pharmacokinetic/pharmacodynamic properties, the restriction of vitamin K intake, and the need for regular coagulation monitoring. Therefore, warfarin is underused for stroke prevention in patients with AF. Several anticoagulants that inhibit thrombin or factor Xa have been developed. Dabigatran is a direct thrombin (factor IIa) inhibitor that overcomes many of the limitations associated with warfarin. The recent Randomized Evaluation of Long Term Anticoagulant Therapy study showed the noninferiority of 110 mg and 150 mg dabigatran twice daily, and the superiority of 150 mg dabigatran twice daily versus adjusted-dose warfarin in the prevention of stroke or systemic embolism in patients with nonvalvular AF. In addition, the rate of intracranial hemorrhage was much lower with both doses of dabigatran than with warfarin. Dabigatran was recently approved in Japan for the prevention of ischemic stroke and systemic embolism in patients with nonvalvular AF. Therefore, in this review, we discuss the properties of dabigatran and its clinical efficacy, safety, and positioning in the prevention of stroke. We also discuss precautions for the use of dabigatran and future perspectives with

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Received January 16, 2012; accepted January 22, 2012.

Dr. Uchiyama has received consulting fees and support for travel to meetings, and his institution has received grants from Boehringer Ingelheim, Bayer, and Daiichi-Sankyo. Dr. Ibayashi has received consulting fees and support for travel to meetings from Boehringer Ingelheim and Bayer. Dr. Matsumoto has received consulting fees, and his institution has received grants from Bayer, Boehringer Ingel-

heim, Daiichi-Sankyo, and Pfizer. Dr. Nagao has received consulting fees and support for travel to meetings, and his institution has received grants from Boehringer Ingelheim, Bayer, and Daiichi-Sankyo. Dr. Nakagawara has received honoraria from Boehringer Ingelheim and Bayer. Dr. Tanahashi has received payment for development of educational presentations from Pfizer Japan, Boehringer Ingelheim, Bayer, and Daiichi-Sankyo. Dr. Tanaka has received consulting fees and support for travel to meetings, and his institution has received grants from Boehringer Ingelheim. Dr. Toyoda and his institution have received grants from Boehringer Ingelheim. Dr. Yasaka and his institution have received grants from Boehringer Ingelheim. Dr. Nagata has no potential conflicts of interest to declare.

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1052-3057/\$ - see front matter

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doi:10.1016/j.jstrokecerebrovasdis.2012.01.011