LR on neurological recovery in patients treated with IV tissue plasminogen activator (IV t-PA).

Methods

Subjects

From April 2005 to March 2011, consecutive acute ischaemic stroke patients who fulfilled the following criteria were prospectively enrolled:

- Developed ischaemic stroke in the anterior circulation
- Had an occluded artery compatible with the neurological symptoms on initial magnetic resonance angiography (MRA); and
- Received IV t-PA therapy within three-hours of onset. All patients underwent IV t-PA therapy according to the published criteria (17). Patients with contraindications to magnetic resonance imaging (MRI) (e.g. cardiac pacemakers, heart valve replacements, or clipping of cranial arteries) and those who received concomitant intra-arterial thrombolysis therapy with IV t-PA were excluded.

This study was approved by the institutional ethics committee. Written informed consent was obtained from all patients or their next of kin.

Clinical background characteristics

The patients' clinical background characteristics, including age, gender, smoking status, and cardiovascular risk factors, were recorded on admission. Cardiovascular risk factors were defined as: (1) hypertension, history of using antihypertensive agents, systolic blood pressure ≥140 mmHg, or diastolic blood pressure ≥90 mmHg before or two-weeks after stroke onset; (2) diabetes mellitus, use of hypoglycaemic agents, random glucose level ≥200 mg/dl, or glycosylated haemoglobin >6·4% on admission; and (3) hyperlipidaemia, use of antihyperlipidaemic agents or a serum total cholesterol level ≥220 mg/dl. Atrial fibrillation was diagnosed on a 12-lead electrocardiogram.

Neurological manifestations were assessed using the National Institutes of Health Stroke Scale (NIHSS) score. Stroke aetiology was determined at hospital discharge using the Trial of ORG 10172 in Acute Stroke Treatment criteria (18). Dramatic improvement was defined as a reduction of ≥8 in the total NIHSS score or complete recovery from initial to 24 h after IV t-PA. Routine blood biochemistry examinations were performed on admission.

Neuroimaging

MRI studies including DWI, fluid attenuated inversion recovery (FLAIR), and MRA were performed four times [on admission, just after (within one-hour) finishing IV t-PA, 24 h after IV t-PA, and seven-days from admission], using a commercially available echo planar instrument operating at 1·5 T (Signa EXCITE XL ver. 11·0, GE Healthcare, Milwaukee, WI, USA). DWI was obtained using the following parameters: TR/TE, 6000/78 ms; *b*-values, 0 and 1000 s/mm^2; field of view, 24 cm; acquisition matrix, 128 × 192; and slice thickness, 6·0 mm, with a 1·0-mm intersection gap. FLAIR parameters were as follows: TR/TE, 8002 ms/109 ms; TI 2000 ms; field of view, 24 cm; acquisition matrix, 256 × 224; and section thickness, 6·0 mm, with a 1·0-mm intersection gap.

Cerebral infarct volume was assessed using DWI on admission (V_0), just after IV t-PA (V_{1h}), at 24 h from IV t-PA, and on FLAIR imaging seven-days after admission with image analysis software (ImageJ 1·38, US National Institutes of Health, Bethesda, MD, USA) by Y. S., who was blinded to clinical information. After the hyperintense lesion on DWI or FLAIR imaging was manually outlined on each slice, it was multiplied by the slice thickness plus intersection gap, resulting in a volume measurement. The LG on DWI is considered to represent infarction of a 'DWI-perfusion weighted imaging (PWI) mismatch' area (4,5,19), and an initial PWI/DWI ratio more than 1·2 was one of the targets for thrombolysis in a recent large prospective trial (20). Therefore, early LG or reduction in this study was defined as more than a 20% increase or decrease of the DWI lesion volume at one-hour after finishing IV t-PA (V_{1h}) compared with initial lesion volume (V_0). The recanalization status was evaluated based on the Thrombolysis in Myocardial Infarction (TIMI) grading system (21). Early recanalization of the initially occluded artery was defined as TIMI grade 2 (partial) or 3 (complete) on MRA just after IV t-PA.

Statistical analysis

All patients were divided into three groups based on early DWI lesion change between initial (V_0) and just after IV t-PA (V_{1h}): LG group ($V_{1h}/V_0 > 1{\cdot}2$); lesion unchanged (LU) group ($0{\cdot}8 \leq V_{1h}/V_0 \leq 1{\cdot}2$); and LR group ($V_{1h}/V_0 < 0{\cdot}8$) (Fig. 1). The three groups' clinical characteristics were first compared. Univariate analyses were performed using the Kruskal–Wallis test, chi-square test, and Fisher's exact test. The data are presented as median values [interquartile range (IQR)] or frequencies (%). Then, multivariate logistic regression analysis was performed to identify independent factors associated with early DWI LR. In addition to the age and gender, all variables identified on univariate analyses with *P*-values <0·1 were entered into the model. The relative risks of LR were expressed as odds ratios (OR) with 95% confidence intervals (CI). Next, the time course of the infarct volume in the three groups was evaluated. Finally, the relationship between early LR on DWI and dramatic improvement was investigated.

All statistical analyses were performed using PASW for Windows version 17·0 software (SPSS Inc, Chicago, IL, USA). Results were considered significant at $P < 0{\cdot}05$.

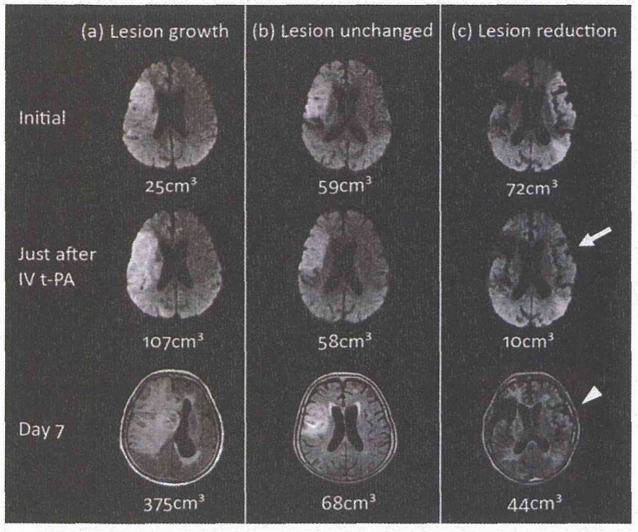

Fig. 1 Representative DWI lesion change in the (a) lesion growth (LG), (b) lesion unchanged (LU), and (c) lesion reduction (LR) groups. Note that the reversed lesion on DWI (arrow) re-appeared seven-days after IV t-PA (arrowhead).

Results

One hundred eighty patients received IV t-PA therapy within three-hours from onset in the study period. Of these, 75 were excluded due to: posterior-circulation stroke in 30 patients; no occluded vessel in 41 patients; and concomitant intra-arterial thrombolytic therapy in four patients. Finally, 105 patients [56 males, median age 77 (IQR 70–83) years, and NIHSS score 16 (10–22)] were enrolled in the present study.

Table 1 shows the clinical characteristics of the included patients. The median onset to needle time was 139 mins, and the median time interval from onset to initial MRI was 85 mins. Of the 105 patients, 25 (24%) had arterial occlusion in the internal carotid artery, 47 (45%) in the middle cerebral artery (MCA) horizontal segment, 32 (30%) in the MCA insular segment, and one (1%) in the anterior cerebral artery. Early LR was observed in seven (7%; 95% CI 1·9 to 11%) patients (LR group), LU was seen in 25 (24%; 95% CI 16 to 32%) (LU group), and LG was seen in 73 (70%; 95% CI 61 to 78%) (LG group). MRI examination was not performed for two (2%) patients at 24 h after IV t-PA and five (5%) subjects after seven-days from onset because of the patient's unstable condition or death. Of the clinical characteristics, initial blood glucose [113 mg/dl (100–125 mg/dl) in the LR group, 124 mg/dl (115–169 mg/dl) in the LU group, and 145 mg/dl (119–181 mg/dl) in the LG group, $P = 0{\cdot}007$], lesion volume on initial DWI (V_0) [28·5 cm³ (6·51–53·0 cm³) in the LR group, 34·3 cm³ (8·03–67·7 cm³) in the LU group, and 5·65 cm³ (1·51–37·3 cm³) in the LG group, $P = 0{\cdot}007$], and the rate of early recanalization (86% in the LR group, 28% in the LU group, and 27% in the LG group, $P = 0{\cdot}006$) were significantly different among the three groups on univariate analysis.

The results of multivariate regression analysis for early LR are presented in Table 2. Glucose level on admission (OR 0·95, 95% CI 0·91 to 0·99, $P = 0{\cdot}045$) and early recanalization (OR 15·7, 95% CI 1·61 to 153, $P = 0{\cdot}018$) were independently related to LR.

Figure 2 shows the time course of infarct volume in the three groups. Although infarct volume decreased just after IV t-PA in the LR group, the lesion increased subsequently [6·0 cm³ (0·4–11·8 cm³) just after IV t-PA vs. 15·9 cm³ (3·0–30·0 cm³) at 24 h from IV t-PA, $P = 0{\cdot}018$]. There was no exacerbation of neurological symptoms or reocclusion of intracranial arteries on MRA at 24 h from IV t-PA in the LR group. The area of DWI hyperintensity was still smaller at 24 h after IV t-PA [15·9 cm³ (3·0–30·0 cm³)] than the initial volume [28·5 cm³ (6·5–53·0 cm³), $P = 0{\cdot}043$], but there was no difference in volume between initial [28·5 cm³ (6·5–53·0 cm³)] and seven-days from onset (28·9 cm³ [10·9–38·8 cm³], $P = 1{\cdot}000$).

At 24 h from IV t-PA, the DWI lesion volume was larger in both the LU [65·0 cm³ (17·3–110 cm³), $P = 0{\cdot}025$] and LG [56·5 cm³ (9·4–146 cm³), $P = 0{\cdot}043$] groups than in the LR group [15·9 cm³ (3·0–30·0 cm³)]. This tendency continued in the LU group [94·4 cm³ (37·4–117 cm³) vs. 28·9 cm³ (10·9–38·8 cm³), $P = 0{\cdot}020$] at seven-days from onset, although not in the LG group [97·5 cm³ (14·3–196 cm³) vs. 28·9 cm³ (10·9–38·8 cm³), $P = 0{\cdot}077$].

Dramatic improvement was more common in the LR group (71%) than in the other groups (21% in LU and 30% in LG group, respectively, $P = 0{\cdot}037$, Table 1).

Discussion

There were four main results in the present study:

- Early LR was observed in 7% of patients treated with IV t-PA
- Early recanalization and initial blood glucose level were independently associated with LR
- The decreased lesion just after IV t-PA increased subsequently; and
- Dramatic improvement was more common in the LR group.

Of the 105 patients in this study, seven (7%) showed early DWI LR. This rate seems to be relatively low compared with previous studies that reported that 86% of patients who received intra-arterial thrombolysis within six-hours of onset (15) and 15% of acute (<24 h from onset) stroke subjects showed DWI LR (8). This small percentage was considered to be due to the difference in the definition of LR. In these past studies, LR was defined as a decrease in DWI lesion volume without any threshold, whereas it was defined as a >20% decrease in the present study. Indeed, Chemmanam *et al.* reported that 10% of thrombolysed patients showed DWI LR when LR was defined as >10% and >10 ml decrease (22), and Campbell *et al.* described that 'true' diffusion reversal was observed in 6·7% of acute stroke patients using co-registration

Table 1 Baseline characteristics

Variables	Total $n = 105$	LR group $n = 7$	LU group $n = 25$	LG group $n = 73$	P
Age, y, median (IQR)	77 (70–83)	79 (75–85)	80 (70–85)	76 (70–82)	0·322
Male gender, n (%)	56 (53)	4 (57)	13 (52)	39 (53)	0·971
Onset to needle time, minutes, median (IQR)	139 (114–164)	120 (93–155)	156 (128–170)	135 (111–159)	0·060
Time interval of repeated MRI, median (IQR)					
From onset to initial, minutes	85 (62–111)	67 (50–85)	109 (71–130)	83 (61–105)	0·052
From initial MRI to MRI just after IV t-PA, minutes	133 (121–146)	124 (120–147)	125 (114–151)	134 (125–145)	0·307
From MRI just after IV t-PA to day 1 MRI, hours	24·9 (23·4–25·9)	24·4 (23·5–25·7)	25·0 (22·4–26·2)	24·9 (23·5–26·2)	0·942
Vascular risk factors, *n* (%)					
Hypertension	66 (63)	4 (67)	15 (60)	47 (64)	0·913
Diabetes mellitus	23 (22)	1 (14)	5 (20)	17 (23)	0·830
Hyperlipidaemia	20 (19)	3 (43)	5 (20)	12 (16)	0·233
Smoking	35 (30)	1 (14)	10 (40)	21 (29)	0·416
Atrial fibrillation, *n* (%)	62 (59)	3 (43)	13 (52)	46 (63)	0·417
Aetiology, *n* (%)					
LAA	10 (10)	0 (0)	4 (16)	6 (8)	0·350
CE	65 (62)	5 (71)	13 (52)	47 (64)	0·473
Others	30 (29)	2 (29)	8 (32)	20 (27)	0·908
Occluded artery, n (%)					
ICA	25 (24)	1 (14)	3 (12)	21 (29)	0·196
M1	47 (45)	3 (43)	13 (52)	30 (41)	0·530
M2	32 (30)	3 (43)	8 (31)	22 (30)	0·785
ACA	1 (1)	0 (0)	1 (4)	0 (0)	0·229
NIHSS score, median (IQR)					
On admission	16 (10–22)	12 (10–20)	12 (9–20)	18 (11–22)	0·422
Day 1	11 (4–19)	8 (0–12)	13 (4–19)	12 (4–19)	0·477
Day 7	7 (2–16)	7 (0–11)	9 (1–19)	7 (2–15)	0·789
Dramatic improvement, n (%)	35 (31)	5 (71)	6 (21)	24 (30)	0·037
Biochemistry sign at admission, median (IQR)					
Leucocyte count, /μl	6600 (5200–8300)	7100 (5900–7700)	6500 (4700–8200)	6400 (5200–8400)	0·784
Haemoglobin, g/dl	13·3 (11·5–14·6)	14·6 (11·3–15·1)	12·9 (11·4–14·4)	13·3 (11·5–14·4)	0·848
Blood glucose, mg/dl	136 (116–174)	113 (100–125)	124 (115–169)	145 (119–181)	0·007
Lesion volume, cm^3, median (IQR)					
On admission (on DWI)	14·0 (2·25–44·1)	28·5 (6·51–53·0)	34·3 (8·03–67·7)	5·65 (1·51–37·3)	0·007
Just after IV t-PA (on DWI)	20·6 (6·27–66·1)	6·01 (0·35–11·8)	36·6 (7·59–65·6)	20·9 (6·39–73·9)	0·041
24 h from IV t-PA (on DWI)	56·4 (9·95–130)	15·9 (3·03–30·0)	65·0 (17·3–109)	64·4 (10·7–164)	0·097
7 days after IV t-PA (on FLAIR)	87·5 (14·6–181)	28·9 (10·9–38·8)	94·8 (37·4–117)	101 (14·5–211)	0·130
Early recanalization immediately after IV t-PA, n (%)	33 (31)	6 (86)	7 (28)	20 (27)	0·006

LR group: patients with DWI lesion reduction >20% from initial to just after IV t-PA.
LU group: patients with 80% ≤DWI lesion ≤120% from initial to just after IV t-PA.
LG group: patients with DWI lesion growth >20% from initial to just after IV t-PA.
MRI, magnetic resonance imaging; IV t-PA, intravenous tissue plasminogen activator; ICA, internal carotid artery; M1, middle cerebral artery horizontal segment; M2, middle cerebral artery insular segment; ACA, anterior cerebral artery; NIHSS, National Institute of Health stroke scale; LAA, large artery atherosclerosis; CE, cardioembolism; FLAIR, fluid-attenuated inversion recovery.

of images and verification with visual inspection (23). IV t-PA can achieve >20% DWI LR in 7% of patients just after finishing the therapy.

Early recanalization and initial blood glucose level were independently associated with early DWI LR. The relationship between recanalization and LR in the present study is compatible with past reports that found that early recanalization could suppress DWI LG (11–13,24) and decrease final infarct volume (22,25). However, studies investigating the correlation between recanalization and early DWI LR are few.

Table 2 Multivariate logistic regression analysis model for early lesion reduction

Variables	OR	95% CI	P
Age (per 10 years)	1·15	0·46–2·85	0·764
Male gender	0·73	0·08–6·43	0·775
Onset to needle time	0·98	0·93–1·03	0·369
Onset to initial MRI	1·01	0·97–1·06	0·620
Glucose level on admission	0·95	0·91–0·99	0·045
Initial lesion volume (per 1 cm^3 increase)	1·00	0·98–1·03	0·885
Early recanalization	15·7	1·61–153	0·018

MRI, magnetic resonance imaging.

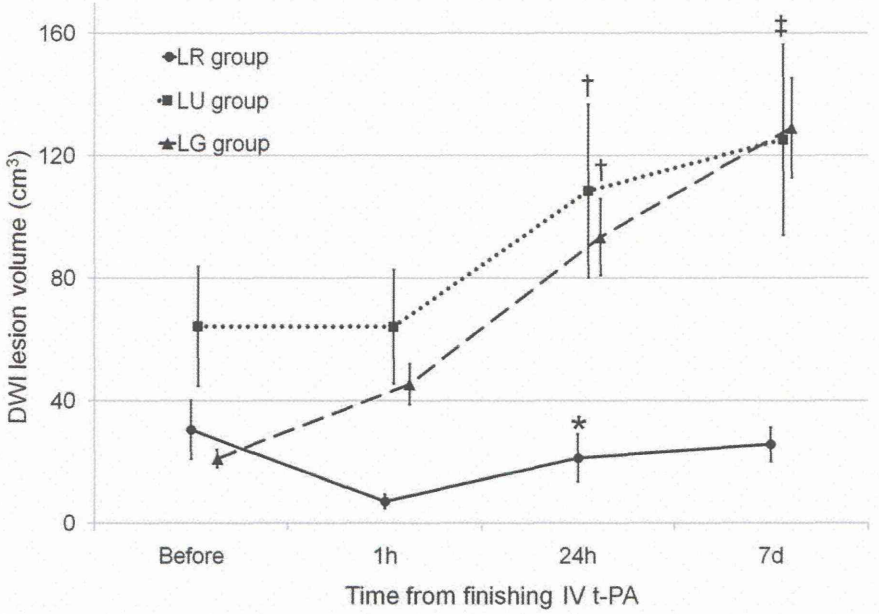

Fig. 2 Time course of the mean ± standard error of the infarct volume in the three groups. Solid line indicates the LR group, dotted line indicates the LU group, and broken line indicates the LG group. The decreased lesion volume just after IV t-PA in the LR group subsequently increases. At seven-days after IV t-PA, the median lesion volume reaches the level of infarct volume on admission. At 24 h from IV t-PA, the DWI lesion volume is larger in the LU and LG groups than in the LR group. This tendency continues in the LU group seven-days from onset, although not in the LG group. *$P < 0{\cdot}05$, DWI lesion 24 h after IV t-PA versus initial in the LR group; †$P < 0{\cdot}05$, LU and LG group versus LR group at 24 h after IV t-PA; ‡$P < 0{\cdot}05$, LU group versus LR group at seven-days after IV t-PA.

DWI hyperintensity represents a restricted apparent diffusion coefficient (ADC) (26), and restricted ADC due to ischaemia recovers when the occluded artery is recanalized (27). Therefore, it appears that early recanalization can decrease DWI lesion volume through restoration of restricted ADC.

Some investigations demonstrated that a high blood glucose level was related to DWI LG (28) or an increase in the final infarct volume (29), and the present findings are in line with these studies. Parsons *et al.* found that a broader DWI-PWI mismatch area developed infarction in patients with hyperglycaemia than in subjects without hyperglycaemia (29). An initial high glucose level can preclude DWI LR because a wider penumbral area becomes infarcted.

The decreased DWI lesion just after IV t-PA subsequently increased. This result is comparable to that of a previous study that showed increased DWI lesion volume that had been initially reduced by successful intra-arterial thrombolysis (15). Because there was no reoccluded artery on MRA or exacerbation of neurological symptoms, the enlargement of DWI hyperintensity seemed not to be caused by recurrence of ischaemic stroke. Two factors may account for this finding. First, restored ADC by early recanalization may again decrease, therefore increasing the DWI lesion. This 'secondary ADC decline' has been reported in several studies (15,30), in which the secondary ADC decline was asymptomatic, as in the present cases. Second, the early 'T2 shine-through phenomenon' may occur with early recanalization. Burdette *et al.* reported that DWI hyperintensity reflects not only ADC decline but also T2 prolongation (31). They referred to a spill-over effect of T2 on the DWI as the 'T2 shine-through phenomenon'. Although T2 prolongation usually becomes the most influential component of DWI hyperintensity after seven-days from stroke onset (31), early recanalization by IV t-PA has a potential to cause an early T2 shine-through phenomenon (16). The decreased DWI lesion following IV t-PA in the hyperacute phase subsequently increases, and seven-days later, it reaches the initial volume. When evaluating DWI LR, the timing of follow-up MRI seems to be an essential information.

Early DWI lesion change was associated with good neurological recovery. This result was partly compatible with previous reports that demonstrated that DWI LG from baseline to day 5 (8) or LR from initial DWI to 90-day FLAIR (9) affected clinical outcome. However, the effect of DWI lesion change in the hyperacute phase on clinical outcome has not been well documented. DWI lesion change, even in the hyperacute phase, may relate to clinical outcome.

This study had some limitations. First, in this study, we could not perform PWI, and the ADC value was unavailable. The DWI lesion volume was measured by one single investigator using manual trace, not derived from ADC value quantitatively. With this method, every voxel inside the outline of the DWI hyperintensity was regarded as 'DWI positive', which might overestimate the DWI lesion volume. Moreover, because co-registration of the images was not conducted in this study, infarct growth in some regions could offset reversal in other areas. Second, tracing the outside of the hyperintensity on seven-day FLAIR might also contribute to overestimate

the infarct volume due to oedema formation, although FLAIR volume at seven-days of onset had proven to correlate with final infarct volume and clinical prognosis (32). The difference in lesion volume, especially increase in infarct volume, could consist of oedema formation rather than true infarct growth. Third, the sample size was relatively small, particularly in the LR group. The present findings should be confirmed with a large cohort and multiple MRI parameters.

In conclusion, early DWI LR of >20% was observed in 7% of patients treated with IV t-PA. Early recanalization and initial blood glucose level were independently associated with LR. The decreased lesion increased subsequently, and seven-days later, it returned to the initial volume.

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Clinical Investigative Study

Two Different Days of Transcranial Doppler Examinations Should Be Performed for Detection of Right-to-Left Shunt in Acute Stroke Patients

Junya Aoki, MD, Kazumi Kimura, MD, PhD, Yasuyuki Iguchi, MD, PhD, Kenichiro Sakai, MD, Yuki Sakamoto, Yuka Terasawa, MD, Kensaku Shibazaki, MD, PhD, Kazuto Kobayashi, MD, PhD

From the Department of Stroke Medicine, Kawasaki Medical School, Kurashiki-City, Okayama, Japan.

ABSTRACT

BACKGROUND

We investigated how many contrast-transcranial Doppler (c-TCD) examinations should be performed on different days in patients with acute stroke.

METHODS

Consecutive acute stroke patients within 24 hours of onset were enrolled. Presence of RLS was examined using c-TCD examinations on days 1, 7, and 14. Each c-TCD examination used one test without Valsalva maneuver (VM) and three tests with VM. Patients were diagnosed with RLS when TCD detected ≥1 microembolic signal on ≥1 c-TCD examination on any of the days 1, 7, or 14.

RESULTS

One hundred seventy patients (105 men [62%]; median age, 74 [IQR, 66–81] years) were enrolled. RLS was diagnosed in 45 patients (26%). RLS was identified on day 1 in 30 patients (18%), on day 7 in 28 patients (16%), and on day 14 in 23 patients (14%; $P = .143$). Detection rate of RLS by combining day 1 and 7 examinations was significantly higher than that of day 1 alone (25% vs 18%, $P < .001$). However, the rate did not increase when results of day 14 were added (25% vs 26%, $P = .250$).

CONCLUSIONS

c-TCD examinations should be performed on at least two different days to assess the prevalence of RLS.

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Correspondence: Address correspondence to Junya Aoki, MD, Department of Stroke Medicine, Kawasaki Medical School, 577 Matsushima, Kurashiki City, Okayama 701-0192, Japan. E-mail: aojyun@med.kawasaki-m.ac.jp.

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Introduction

Right-to-left shunt (RLS), such as patent foramen ovale and pulmonary arteriovenous fistula, represents an important component of paradoxical brain embolism.[1] Transcranial Doppler ultrasonography (TCD) has been widely used as a sensitive and specific method to diagnose the presence of RLS.[2] A consensus meeting has recommended three standard approaches: (1) use of agitated saline/air mixture;[3] (2) repeated testing;[4] and (3) appropriate Valsalva method (VM).[5]

However, how many times TCD examination should be performed remains uncertain. We hypothesized that not only the frequency of TCD examination, but also examinations on different days are important to accurately assess the prevalence of RLS. As some patients with acute stroke cannot perform adequate VM because of disturbance of consciousness, the rate of RLS detection might be underestimated.

We evaluated rates of RLS detection using TCD on days 1, 7, and 14, and investigated how many TCD examinations should be performed on different days to accurately detect the presence of RLS in acute stroke patients.

Methods

Population

We prospectively enrolled consecutive acute ischemic stroke patients who had been admitted to Kawasaki Medical School Hospital (Kurashiki City, Okayama, Japan) within 24 hours of onset between May 2008 and July 2009. Only patients who satisfied the following criteria were included: (1) presence of neurological deficit; and (2) findings of an acute ischemic lesion on diffusion-weighted imaging (DWI) on admission. This study was conducted in accordance with the Declaration of Helsinki and all protocols were approved by Ethics Committee of Kawasaki Medical School Hospital.

Clinical Backgrounds

The following information including age, gender, patient history, and past medication were obtained on admission. Cardiovascular risk factors were identified as follows: (1) hypertension, a history of using antihypertensive agents, systolic blood pressure ≥140 mmHg, or diastolic blood pressure ≥90 mmHg at

hospital discharge; (2) diabetes mellitus, use of hypoglycemics, random glucose level ≥200 mg/dL, or glycosylated hemoglobin >6.4% on admission; (3) hyperlipidemia, use of antihyperlipidemic agents or serum total cholesterol level >220 mg/dL; and (4) smoking, any lifetime experience of cigarette use. Past history included ischemic stroke, cerebral hemorrhage, transient ischemic attack, ischemic heart disease, and atrial fibrillation. Body mass index was calculated as weight in kilograms divided by height in meters squared.[6] Arterial blood pressure was measured from the arm with the patient in a supine position on admission. Stroke neurologists assessed neurological symptoms using the National Institute of Health Stroke Scale (NIHSS) score on days 1 and 7.[7] Clinical deterioration was defined as a ≥4-point increase in total NIHSS score. Global disability was assessed using the modified Rankin Scale (mRS) score before stroke onset and at discharge.[8] Stroke etiology was determined at hospital discharge using the Trial of ORG 10172 in Acute Stroke Treatment criteria: (1) small-vessel occlusion; (2) large-artery atherosclerosis; (3) cardioembolism; and (4) other or undetermined etiology of stroke.[9]

Contrast-TCD Examination for RLS

Intracranial arteries were evaluated with a 2-MHz handheld transducer (Pioneer TC 8080; Nicolet Vascular, Madison, WI) using a standard scanning protocol, as previously reported.[10] Middle cerebral arteries (MCAs) were insonated from the temporal window at a depth of 50–55 mm. After identifying the MCA, continuous monitoring of both MCA flow signals was performed. When no suitable temporal window was present, the right siphon portion of the internal carotid artery (S-ICA) was isonated through the orbital window at a depth of 60–65 mm for as short a time as possible.

After TCD was positioned, contrast-TCD (c-TCD) examination was conducted to assess the presence of RLS. Patients underwent c-TCD examination three times during hospitalization, on days 1, 7, and 14. Each c-TCD examination included one test without VM and three tests with VM. Tests were performed as follows (Fig 1). An indwelling catheter was placed in the right anterior cubital vein. After 9 mL of saline solution and 1 mL of air was agitated between two 10-mL syringes connected via a three-way stopcock to produce microbubbles (MBs), saline containing MBs was injected with or without VM. MCA or S-ICA flow was monitored 30 seconds after injection. Doppler audio signals on TCD examination were recorded onto a hard disc.

Assessment of the Presence of RLS

On each day, RLS was diagnosed if ≥1 microembolic signal (MES) was detected in any of the four tests (one test without VM and three tests with VM).[11–12] Patients were finally diagnosed with RLS if MESs were identified on ≥1 c-TCD examination on day 1, 7, or 14.

Assessment of the Number of MESs

We calculated the total number of MESs for the 3 days of examination. When we were unable to count the correct number of MESs in the case of a "shower" of MESs on each test, the maximum number was defined as 20 in each test.

Neuroimaging

Patients were examined using commercially available echo planar instrumentation on a 1.5-T magnetic resonance imaging unit (Signa EXCITE XL ver. 11.0; GE Healthcare, Milwaukee, WI) with DWI sequences. DWI was obtained using the following parameters: repetition time, 6,000 ms; echo time, 78 ms; *b* values, 0 and 1,000 s/mm^2; field of view, 24 cm; acquisition matrix, 128 × 192; and slice thickness, 6.0 mm with 1.0-mm intersection gap.

Statistical Analysis

First, all patients were divided into two groups: (1) RLS group, comprising patients with RLS; and (2) Non-RLS group, comprising patient without RLS. Baseline and clinical characteristics were compared between the groups. Data are presented as median values (interquartile range [IQR]) or frequencies. Fisher's exact test was used to analyze differences in categorical variables. The Mann–Whitney U and Kruskal–Wallis test were used to analyze differences in continuous variables. Second, we compared detection rates of RLS among the three c-TCD examinations on days 1, 7, and 14. Third, we assessed total number of MESs among the following three groups: (1) patients with RLS who were diagnosed from only 1 day of the 3 days of c-TCD examination; (2) patients with RLS found on 2 days; and (3) patients with RLS found on all 3 days. Next, we investigated clinical factors contributing to different results among 3 days of examinations. Finally, we evaluated how many c-TCD examinations should be performed on different day to assess the presence of RLS. The rate of RLS detection was compared between day 1 and the combination of days 1 and 7 (1/7), and the combination of days 1, 7, and 14 (1/7/14). Results were considered significant for values of $P < .05$ using McNemar's test. All statistical analyses were performed using SPSS for Windows version 11.0.1 J software (SPSS, Chicago, IL).

Results

From May 2008 and July 2009, a total of 208 acute ischemic stroke patients who satisfied the inclusion criteria were admitted to our hospital. Of these, 38 patients (18%) were excluded because of death, early discharge, or insufficient cooperation. There was not any adverse event related to serial c-TCD examinations. As a result, 170 patients (82%; 105 men [62%]; median age, 74 years; IQR, 66–81 years) were enrolled into this study. Median NIHSS score on admission was 6.0 (IQR, 2.0–14.0).

Forty-five of the 170 patients (26%) were finally allocated to the RLS group and the remaining 125 patients (74%) made up the non-RLS group. Median total number of MESs in the RLS group was 4 (IQR, 1–22). The largest number of MESs in one test was 1–20 in 35 (78%) of the 45 patients and over 20 in 10 (22%). Table 1 shows background and baseline clinical characteristics for the RLS and non-RLS groups.

Rate of RLS detection among the examinations on days 1, 7, and 14 are shown in Figure 2. RLS was identified on day 1 in 30 of 170 patients (18%), on day 7 in 28 patients (16%), and on day 14 in 23 patients (14%). Rate of RLS detection did not differ significantly between the three days. Among the 30 patients with RLS on day 1, 14 (47%) did not

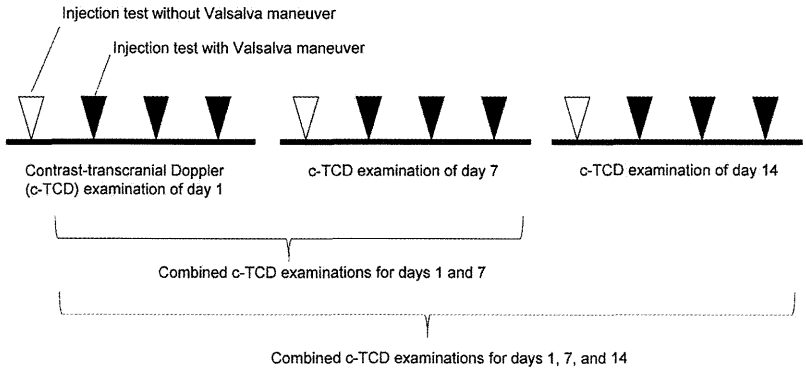

Fig 1. Study design. All patients were examined using contrast-transcranial Doppler (c-TCD) examination on days 1, 7, and 14. Each c-TCD examination included one injection test without Valsalva maneuver (VM) and three injection tests with VM.

Table 1. Backgrounds and Characteristics of RLS and Non-RLS Groups

Variables	RLS Group $n = 45$	Non-RLS Group $n = 125$	P
Age, y, median (IQR)	73 (66–81)	74 (67–81)	.724
Male sex, *n* (%)	24 (53)	81 (65)	.211
Height, cm, median (IQR)	159.0 (151.3–164.5)	160.0 (150.4–166.0)	.629
Body weight, median (IQR)	60.0 (48.2–65.6)	56.0 (49.6–64.3)	.469
Body mass index, median (IQR)	22.6 (20.6–24.3)	22.6 (20.0–24.7)	.719
NIHSS score on admission, median (IQR)	4 (3–11)	6 (2–15)	.453
Modified Rankin scale score			
Before stroke onset	0 (0–0)	0 (0–3)	.032
At discharge	3 (0–3)	3 (0–4)	.365
Clinical deterioration	5 (11)	14 (11)	1.000
TOAST classification			
Small-vessel occlusiomn	3 (7)	17 (14)	.286
Large-artery atherosclerosis	4 (9)	16 (13)	.597
Cadrioembolism	15 (33)	43 (34)	1.000
Others	23 (51)	49 (39)	.218
Vascular risk factor, *n* (%)			
Hypertension	29 (64)	87 (70)	.577
Diabetes mellitus	6 (13)	25 (20)	.375
Hyperlipidemia	8 (18)	31 (25)	.411
Smoking	20 (44)	61 (49)	.728
Past history, *n* (%)			
Ischemic stroke	6 (13)	24 (19)	.495
Intracerebral hemorrhage	0 (0)	4 (3)	.574
Transient ischemic attack	1 (2)	5 (4)	1.000
Ischemic heart disease	3 (7)	9 (7)	1.000
Atrial fibrillation	9 (20)	26 (21)	1.000

RLS group = group with right-to-left shunt; Non-RLS group = group without left-to-right shunt; IQR = interquartile range; NIHSS score = National Institutes of Health Stroke Scale score; Clinical deterioration = 4-points increase in the total NIHSS score; TOAST = Trial of Org 10172 in Acute Stroke Treatment.

show RLS on day 7 (RLS 1+/7–). Conversely, among 140 patients without RLS on day 1, 12 patients (9%) showed RLS on day 7 (RLS 1–/7+). Similarly, 12 of 30 patients (40%) with RLS on day 1 did not show RLS on day 14 (RLS 1+/14–). Five of 140 patients (4%) without RLS on day 1 showed RLS on day 14 (RLS 1–/14+).

Figure 3 shows the total number of MESs in patients diagnosed as having RLS on only 1 of the 3 different days of c-TCD examination, on 2 of 3 days, and on all 3 days. A total of 69 MESs (IQR, 19–127) were detected in 15 patients with RLS who were diagnosed with RLS on all 3 days. Four MESs (IQR, 2–8) were detected in 6 patients with RLS who were diagnosed on 2 of 3 days, and 1 (IQR, 1–3) MES was detected in 24 patients with RLS diagnosed on only 1 of the 3 days.

Total number of MESs and clinical severity were associated with serial changes in RLS detection rate. Median total number of MESs was higher in RLS 1+/7+ than in RLS 1+/7– (66 [16–126] vs 1 [1–4], $P < .001$). Similarly, median total number of MESs was higher in RLS 1+/14+ than in RLS 1+/14– (50 [7–125] vs 1 [1–4], $P < .001$). Among the 14 patients with RLS 1+/7–, 3 patients (21%) showed clinical deterioration at day 7. Conversely, among 16 patients with RLS 1+/7+, no patients (0%) complained of clinical deterioration by day 7 ($P = .090$). Although NIHSS score on day 1 did not differ between RLS

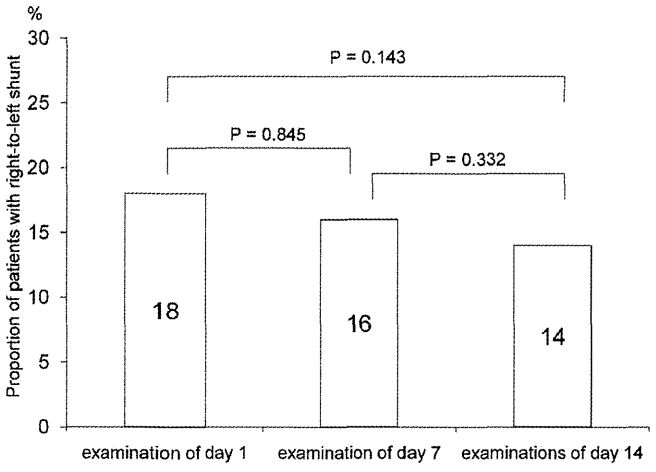

Fig 2. Rates of right-to-left shunt detection among the three examinations of days 1, 7, and 14.

1+/14– and RLS 1+/14+ (8 [3–12] vs 3 [2–9], $P = .113$), mRS at discharge was higher in RLS 1+/14– than in RLS 1+/14+ (3 [2–5] vs 1 [0–3], $P = .039$).

Figure 4 shows detection rates of RLS for combinations of different days of c-TCD examination. The proportion of patients with RLS diagnosed by combined examinations for day 1/7 was significantly higher than that identified from single examination on day 1 (25% vs 18%, $P < .001$). However, no significant differences were seen in rate of RLS detection between combined examinations for day 1/7 and 1/7/14 (25% vs 26%, $P = .250$).

Discussion

Our study demonstrated three major findings. First, c-TCD examinations should be performed on at least two different days

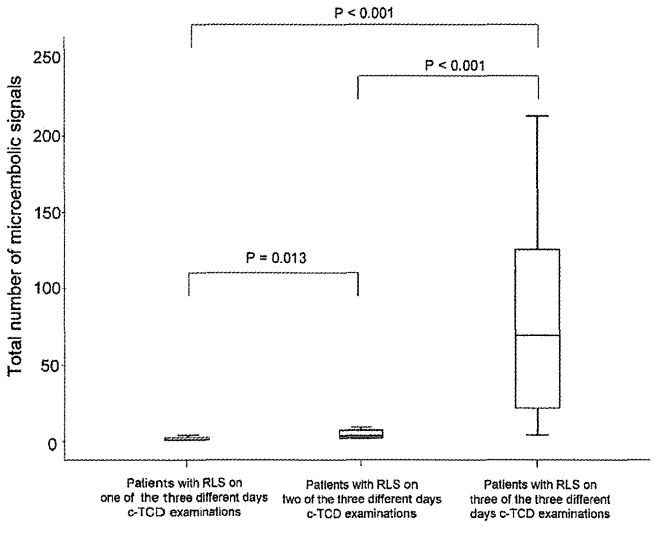

Fig 3. Total number of microembolic signals in patients with right-to-left shunt diagnosed on one of three different days of contrast-transcranial Doppler (c-TCD) examination, in those with RLS on two different days, and in those with RLS on all three examinations.

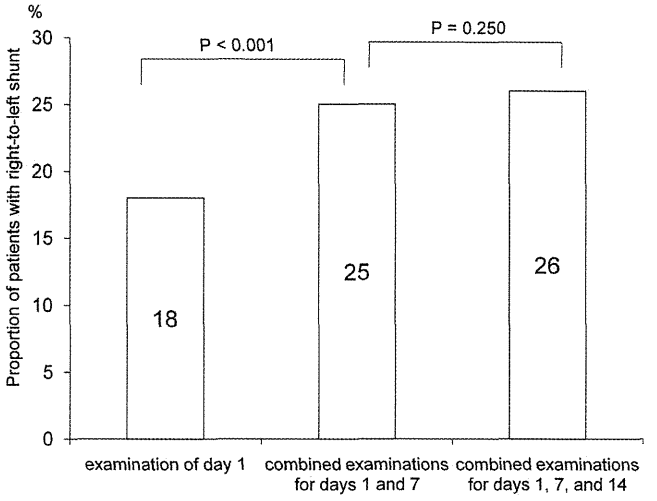

Fig 4. Combined contrast-transcranial Doppler (c-TCD) examinations for days 1 and 7 (1/7) detect a significantly higher rate of RLS than c-TCD examination on day 1 (25% vs 18%, $P < .001$). No significant difference existed between rates of RLS detection in combined c-TCD examinations for day 1/7, and days 1, 7, and 14 (1/7/14; 25% vs 26%, $P = .250$).

to diagnose the presence of RLS. Second, the rate of RLS detection tended to decrease with increasing time interval between stroke onset and c-TCD assessment. Finally, prevalence of patients with RLS was 26% among acute stroke patients.

Two different days of c-TCD examinations should be performed to detect RLS. Although repeated injection tests on the same day reportedly increase the detection rate of RLS,[13] how many days c-TCD examination should be performed on has not been well investigated. In our study, examination on day 1 showed the highest rate of RLS detection. Early examination on day 1 should thus be performed to assess the presence of RLS. However, examination on 1 day is insufficient to diagnose the presence of RLS. We recommended that c-TCD examination should be conducted for 2 days, including day 1, to diagnose the presence of RLS.

Although no significant difference was identified, the rate of RLS detection tended to be higher in the early days after stroke onset. Three hypotheses were suggested to explain our results. First, clinical deterioration may decrease the rate of RLS detection, especially regarding small RLS. Indeed, in our study, clinical deterioration at day 7 and severe mRS score at discharge were associated with decrements in RLS detection rate. In addition, most of the detected RLS were marginally small. Although we did not evaluate the degree of VM, deterioration may make it difficult to perform adequate VM. Second, some acute stroke patients may complain of pulmonary embolism, which elevates right atrial pressure. Detection of RLS may thus become higher in the acute phase.[14] Another explanation is that some MESs recorded on TCD may be derived not only from injected MBs, but also from other embolic sources, carotid stenosis, and/or aortic plaque. MES from arterial lesion is known to be more frequently found in the acute phase than in the chronic phase.[15]

We demonstrated a 26% prevalence of patients with RLS. This result is not in line with previous larger studies.[16-18] Those

studies have shown higher rates of RLS detection at 30–50%. Patients in previous reports were younger than in this study, and older patients may have been excluded from those reports. The incidence of RLS has been reported to decrease with age.[19] We considered this difference was attributable to sampling bias.

This study shows several limitations. First, although we showed the utility of c-TCD examination on two different days, no data is available to confirm that the combination of days 1 and 7 is superior to other combinations. Second, we did not assess the effects of contrast materials other than agitated saline. Contrast materials can elevate the rate of RLS diagnosis.[3] Further information may be obtained with the use of contrast materials. Second, our c-TCD study did not evaluate the presence of RLS comparing transesophageal echocardiography (TEE). TEE was used to assess the presence of RLS as golden standard.[20] Third, we did not classify the size of RLS using International Consensus Criteria or Spencer Logarithmic Scale because some of the enrolled patients did not have temporal window.[21] Analysis on the basis of these criteria will be needed in the future trial. Finally, because we enrolled consecutive stroke patients, our finding will be adapted in clinical practice. However, most of the RLS was relatively small in this study. Our finding may be close to the sensitivity of the TCD technique. Larger TCD study based on the size of the RLS may be needed to establish the utility of serial TCD examinations.[22]

In conclusion, c-TCD examinations on two different days is recommended to evaluate the presence of RLS.

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Maintenance Hemodialysis Independently Increases the Risk of Early Death after Acute Intracerebral Hemorrhage

Takashi Shimoyama Kazumi Kimura Kensaku Shibazaki Shinji Yamashita
Yasuyuki Iguchi

Department of Stroke Medicine, Kawasaki Medical School, Kurashiki City, Japan

Key Words
Maintenance hemodialysis · Intracranial hemorrhage · Early death

Abstract
Background: It is unknown whether the clinical features and outcomes of intracerebral hemorrhage (ICH) patients who undergo maintenance hemodialysis (HD) at the time of ICH are similar to those of general ICH patients. ***Methods:*** We retrospectively examined the medical records of ICH patients admitted to the Stroke Center of Kawasaki Medical School Hospital within 7 days of ICH onset between April 2004 and June 2011. Patients were classed as HD or non-HD, and clinical characteristics were compared between the two groups. ICH volume was measured on admission CT and follow-up CT scan (<24 h after admission). Hematoma enlargement was defined as a hematoma that increased by more than 33% of its initial volume. Early death was defined as all-cause death within 14 days of ICH onset. The factors associated with early death were determined using multivariate logistic regression analysis. ***Results:*** Five hundred and seven patients (320 males; 69.0 years old, interquartile range 59.0–79.0) were enrolled in the study. Thirty-six (7.2%) were receiving maintenance HD at the time of ICH and formed the HD group, and the remaining 471 patients formed the non-HD group. Use of antithrombotic agents prior to ICH was more common in the HD group than in the non-HD group (41.7 vs. 21.9%; p = 0.012). Brainstem (30.6 vs. 11.3%; p = 0.003) and lobar (19.4 vs. 6.6%; p = 0.013) hematoma locations were more common in the HD group than in the non-HD group. Enlargement of ICH volume was more common in the HD group than in the non-HD group (25.8 vs. 10.2%; p = 0.015). Early death was more common in the HD group than in the non-HD group (33.3 vs. 9.3%; p < 0.001). On the multivariate logistic regression analysis adjusted for age, sex and renal dysfunction, National Institutes of Health Stroke Scale score >20 [odds ratio (OR) 27.40, 95% confidence interval (CI) 9.69–77.44; p < 0.001], ICH volume >30 ml (OR 9.53, 95% CI 3.82–23.77; p < 0.001), HD (OR 6.42, 95% CI 1.39–29.76; p = 0.017), the use of antithrombotic agents (OR 3.04, 95% CI 1.22–7.56; p = 0.017) and glucose >150 mg/dl (OR 2.51, 95% CI 1.01–6.26; p = 0.047) were independent factors associated with early death. ***Conclusion:*** Maintenance HD is independently associated with early death in ICH patients.

Introduction

Intracerebral hemorrhage (ICH) accounts for 10–15% of all stroke; the mortality rate is high and it is associated with poor functional outcome [1]. Moreover, there are

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Takashi Shimoyama, MD
Department of Stroke Medicine, Kawasaki Medical School
557 Matsushima
Kurashiki City 701-0192 (Japan)
E-Mail t.shimo0702@gmail.com

few effective medical treatments for ICH [2]. The prognostic factors found to be associated with early mortality in previous reports were National Institutes of Health Stroke Scale (NIHSS) score >20 [3], ICH volume >30 ml [4], serum glucose >150 mg/dl [5], use of antithrombotic agents [6, 7] and serum D-dimer level >1.9 μg/dl [8].

Patients with end-stage renal disease have markedly advanced vascular disease when compared to the general population [9]. In particular, patients receiving maintenance hemodialysis (HD) are one of the highest-risk populations for bleeding [10]. Maintenance HD patients have a 3–10 times higher risk of ICH and worse prognosis than the general population [11–13]. Although ICH incidence and long-term outcomes in maintenance HD patients have been well described, there have been few reports on the detailed clinical features of maintenance HD patients who experience ICH. Although previous studies show that the mortality rate in HD patients with acute ICH is high [14–16], no evidence has yet indicated that HD is an independent factor associated with early death on multivariate analysis. Moreover, some results of studies varied widely. For example, Onoyama et al. [14] reported that lobar hemorrhages were more common in HD patients, whereas in another study [15], no significant differences were found with regard to the location of the hematoma. Therefore, we have hypothesized that in the setting of ICH, HD is associated with poor outcome and radiological findings in HD patients are different from those in non-HD patients. The aim of this study was to compare the neurological severity, ICH volume and hematoma location of ICH patients who were undergoing maintenance HD to those of ICH patients with no history of maintenance HD and to determine whether maintenance HD is independently associated with early death after ICH on multivariate logistic regression analysis.

Material and Methods

Patients

We retrospectively examined the medical records of all ICH patients admitted to the department of stroke medicine of Kawasaki Medical School Hospital within 7 days of ICH onset between April 2004 and June 2011.

Inclusion criteria included radiologically documented ICH on admission and clinical data available (detailed below). We also included patients under warfarin with a prothrombin time international normalized ratio (PT-INR) of 1.5 or greater at diagnosis of ICH. Patients with traumatic ICH, vascular malformation, tumor, moyamoya disease, patients who were pregnant, pediatric patients or patients with hematologic disease such as idiopathic thrombocytopenic purpura, aplastic anemia, myelodysplastic syndromes and hemophilia were excluded.

We recorded the following clinical data for all patients: (1) age; (2) gender; (3) arterial blood pressure on admission; (4) presence or absence of vascular risk factors (detailed below); (5) presence or absence of atrial fibrillation; (6) maintenance HD; (7) previous stroke; (8) current smoking status; (9) history of alcohol consumption during the 3 months preceding admission; (10) preadmission use of antithrombotic agents such as antiplatelet agents and warfarin; (11) laboratory parameters on admission, namely white blood cell (WBC) count, red blood cell (RBC) count, platelet count, blood urea nitrogen (BUN), creatinine, estimated glomerular filtration rate (eGFR), glucose level, glycated hemoglobin (HbA1c) level, PT-INR and D-dimer level; (12) NIHSS score on admission, and (13) the presence or absence of early death.

Vascular risk factors included hypertension (a history of using antihypertensive agents, systolic blood pressure ≥140 mm Hg or diastolic blood pressure >90 mm Hg before ICH onset or 14 days after ICH), diabetes mellitus (the use of oral hypoglycemic agents or insulin, fasting blood glucose ≥126 mg/dl or HbA1c ≥6.4%), hyperlipidemia (the use of antihyperlipidemic agents or serum total cholesterol level ≥220 mg/dl), atrial fibrillation (detected by electrocardiogram in the emergency room or documented formerly), maintenance HD (dialysed 3 times a week for longer than 1 month before ICH onset) [14, 15] and previous stroke (cerebral infarction or ICH). We defined early death as all-cause death within 14 days of ICH onset and evaluated the cause of death from the medical chart and based on the results of autopsy when performed.

Neuroimaging

We recorded the following data from plain computed tomography (CT) scans alone performed on admission (baseline) and again within 24 h of admission (follow-up): (1) the location of hematoma; (2) baseline ICH volume, and (3) presence or absence of ICH expansion from baseline to follow-up. All CT scans were performed according to the protocol, with an image matrix of 340 × 340 and a slice width of 8–10 mm. Investigators who read the CT scans were blinded to the clinical information. The location of the ICH was classified as being in the basal ganglia, lobar, brainstem, cerebellum or elsewhere. The ICH volume was measured on baseline and follow-up CT scans according to the formula $A \times B \times C \times 0.5$ [17], where A and B represent the largest perpendicular diameters through the hyperdense area on the CT scan and C represents the thickness of the ICH (the number of 8- to 10-mm slices with hemorrhage). Hematoma enlargement was defined as a hematoma that grew by more than 33% of its initial volume from baseline to follow-up [18].

Analysis

To compare the clinical characteristics of ICH patients who were undergoing maintenance HD prior to ICH to those of ICH patients with no history of maintenance HD, we divided patients into an HD group and non-HD group. Clinical and neuroimaging characteristics were compared between the two groups (HD and non-HD) using a χ^2 test for categorical variables and a Mann-Whitney U test for continuous variables. Because the number of HD patients was small and the continuous variables were not normally distributed in the two groups, we performed nonparametric methods for continuous variables. Values of $p < 0.05$ were consid-

ered to indicate statistically significant differences between groups. We constructed separate Kaplan-Meier survival curves for the HD group and the non-HD group and used the log-rank test to determine the significance of survival characteristics between the two groups.

To compare the clinical characteristics of patients who experienced early death after ICH and those who did not, we divided patients into an early death group and a survivor group according to their early death status. Clinical and neuroimaging characteristics were compared between the two groups (early death and survivors) using a χ^2 test for categorical variables and a Mann-Whitney U test for continuous variables. Because the number of early deaths was small and the continuous variables were not normally distributed in the two groups, we performed nonparametric methods for continuous variables. Values of $p < 0.05$ were considered to indicate statistically significant differences between groups.

Multivariate logistic regression analysis was performed to identify variables that were independently associated with early death. Logistic models included HD and other potentially predictive variables according to previous reports (baseline NIHSS score >20 [3], baseline ICH volume >30 ml [4], glucose >150 mg/dl [5], use of antithrombotic agents [6, 7] and D-dimer >1.9 μg/dl [8]). Areas under the curves of the continuous variables (NIHSS score, ICH volume, glucose and D-dimer) were calculated to differentiate the early death group from the survivor group. These factors were included in the multivariate logistic analysis adjusted for age, sex and renal dysfunction (eGFR <60 ml/min/1.73 m^2) [19].

All statistical analyses were performed using Statistical Package for the Social Sciences software for Windows (SPSS version 17.0, Chicago, Ill., USA). Continuous variables are expressed as medians and interquartile range. The medical ethics committee of Kawasaki Medical University approved the study.

Results

Between April 2004 and July 2011, a total of 525 ICH patients were admitted to the department of stroke medicine of Kawasaki Medical School Hospital within 7 days of ICH onset. Of these, 18 patients were excluded because blood samples were not measured completely. As a result, 507 patients (320 males; 69.0 years old, 59.0–79.0) were enrolled in the present study.

Clinical Characteristics of HD and Non-HD ICH Patients

Thirty-six patients (7.2%) were receiving maintenance HD at the time of ICH and formed the HD group. The baseline characteristics and laboratory data of the HD and non-HD groups are shown in table 1. Of the vascular risk factors, diabetes mellitus ($p < 0.001$) and previous stroke ($p < 0.001$) were more common in the HD group than in the non-HD group. With regard to the use of antithrombotic agents, taking warfarin prior to admission was more common in the HD group than in the non-HD group ($p < 0.001$). The median duration of receiving HD was 6.0 years (3.1–11.0). Diabetic nephropathy was the major cause of primary renal disease for HD (47.2%). Among the laboratory findings, RBC ($p < 0.001$) and HbA1c ($p < 0.001$) were lower, and BUN ($p < 0.001$), creatinine ($p < 0.001$), eGFR ($p < 0.001$) and D-dimer ($p = 0.036$) were higher in the HD group than in the non-HD group.

Table 2 shows the NIHSS score, ICH characteristics, treatments and clinical outcomes of the HD and non-HD groups. The NIHSS score and ICH volume on admission were similar in the HD group and the non-HD group. However, severe neurological deficits (NIHSS score >20) on admission were more frequent in the HD group than in the non-HD group ($p = 0.015$). Thirty-six patients did not have follow-up CT due to death within 24 h of admission or severe general status. Follow-up CT scans were obtained in the remaining 471 patients. Enlargement of ICH volume from baseline to follow-up was more common in the HD group than in the non-HD group ($p = 0.015$). Brainstem (30.6 vs. 11.3%; $p = 0.003$) and lobar (19.4 vs. 6.6%; $p = 0.013$) hematoma locations were more common in the HD group than in the non-HD group. With regard to treatment, there were no significant differences between the two groups in the use of surgical evacuation and tracheostomy. Early death was more common in the HD group than in the non-HD group (33.3 vs. 9.8%; $p < 0.001$). No significant differences in the causes of early death were observed between the two groups. The survival rate curve for the HD group was lower than that for the non-HD group ($p < 0.001$, log-rank test; fig. 1).

Factors Associated with Early Death after ICH

In total, 58 patients died within 14 days of ICH onset and formed the early death group. The baseline characteristics and laboratory data of the early death and survivor groups are shown in table 3. Of the vascular risk factors, atrial fibrillation ($p < 0.001$), HD ($p < 0.001$) and previous stroke ($p < 0.001$) were more common in the early death group than in the survivor group. The use of antithrombotic agents prior to admission was more common in the early death group than in the survivor group ($p < 0.001$). Among the laboratory findings, white blood cell count ($p < 0.001$), BUN ($p = 0.004$), creatinine ($p = 0.001$), glucose ($p < 0.001$), PT-INR ($p = 0.003$) and D-dimer ($p < 0.001$) were higher in the early death group than in the survivor group. RBC ($p = 0.001$) and eGFR ($p < 0.001$) were lower in the early death group than in the

Table 1. Baseline characteristics and laboratory data of HD and non-HD ICH patients

	HD group (n = 36)	Non-HD group (n = 471)	p
Age, years	60.5 (54.8–69.8)	70.0 (60.0–79.0)	<0.001
Male, n	23 (63.9)	297 (63.1)	1.000
Systolic blood pressure, mm Hg	198.0 (160.0–225.3)	178.0 (156.0–198.0)	0.011
Diastolic blood pressure, mm Hg	102.0 (90.5–116.8)	100.0 (84.0–110.0)	0.102
Risk factors, n			
Hypertension	31 (86.1)	362 (76.9)	0.299
Diabetes mellitus	19 (52.8)	84 (17.8)	<0.001
Hyperlipidemia	4 (11.1)	89 (18.9)	0.370
Atrial fibrillation	2 (5.6)	28 (5.9)	1.000
Previous stroke	15 (41.7)	106 (22.5)	0.014
Smoking	15 (41.7)	213 (45.2)	0.731
Alcohol	8 (22.2)	213 (45.2)	0.008
Antithrombotic agents, n	15 (41.7)	103 (21.9)	0.012
Antiplatelets	11 (30.6)	87 (18.5)	0.083
Warfarin	10 (27.8)	23 (4.9)	<0.001
Duration of receiving HD, years	6.0 (3.1–11.0)	–	–
Primary renal disease for HD, n			
Diabetic nephropathy	17 (47.2)	–	–
Chronic glomerulonephritis	12 (33.3)	–	–
Hypertensive nephrosclerosis	2 (5.9)	–	–
Other or undetermined	5 (13.9)	–	–
Laboratory data			
WBC, /μl	6,700.0 (5,030.0–9,160.0)	7,400.0 (5,800.0–10,200.0)	0.068
RBC, ×10,000/μl	334.5 (305.8–390.0)	433.0 (390.0–469.0)	<0.001
Platelets, ×10,000/μl	18.6 (14.7–24.0)	20.1 (16.4–24.6)	0.109
BUN, mg/dl	45.0 (31.3–64.8)	15.0 (13.0–19.0)	<0.001
Creatinine, mg/dl	8.4 (6.6–10.9)	0.68 (0.53–0.85)	<0.001
eGFR, ml/min/1.73 m^2	5.0 (4.2–6.9)	81.1 (63.8–98.0)	<0.001
Glucose, mg/dl	147.0 (110.8–190.5)	135.0 (113.0–167.0)	0.462
HbA1c, %	4.8 (4.5–5.4)	5.4 (5.1–5.8)	<0.001
PT-INR	1.03 (0.96–1.28)	1.03 (0.97–1.12)	0.337
D-dimer, μg/dl	1.0 (0.6–2.1)	0.7 (0.5–1.7)	0.036

Figures in parentheses represent interquartile ranges or percentages, as appropriate.

survivor group. The NIHSS score ($p < 0.001$) and the ICH volume ($p < 0.001$) on admission were higher in the early death group than in the survivor group. Enlargement of ICH volume from baseline to follow-up was more common in the early death group than in the survival group ($p = 0.003$).

Multivariate Logistic Regression Analysis for Factors Associated with Early Death

Table 4 shows the results of the multivariate logistic regression analysis for factors associated with early death adjusted for age, sex and renal dysfunction. Areas under the curves of the continuous variables calculated to differentiate the early death group from the survivor group were as follows: NIHSS score, 0.910; ICH volume, 0.886; glucose, 0.753, and D-dimer, 0.689. Multivariate logistic regression analysis demonstrated that NIHSS score >20 [odds ratio (OR) 27.40, 95% confidence interval (CI) 9.69–77.44; $p < 0.001$], ICH volume >30 ml (OR 9.53, 95% CI 3.82–23.77; $p < 0.001$), HD (OR 6.42, 95% CI 1.39–29.76; $p = 0.017$), the use of antithrombotic agents (OR 3.04, 95% CI 1.22–7.56; $p = 0.017$) and glucose >150 mg/dl (OR 2.51, 95% CI 1.01–6.26; $p = 0.047$) were independent factors associated with early death.

Table 2. Neurological severity, ICH characteristics, treatments and clinical outcomes of HD and non-HD ICH patients

	HD group (n = 36)	Non-HD group (n = 471)	p
NIHSS score on admission	15.5 (5.0–28.0)	12.0 (5.0–19.0)	0.144
NIHSS score >20, n	14 (38.9)	99 (21.0)	0.015
ICH volume on admission, ml	10.6 (4.0–47.8)	7.6 (3.4–17.7)	0.347
ICH volume enlargement, n	8/31 (25.8)	45/440 (10.2)	0.015
Location of hematoma, n			
Ganglionic-thalamus	17 (47.2)	349 (74.1)	0.002
Lobar	7 (19.4)	31 (6.6)	0.013
Brainstem	11 (30.6)	53 (11.3)	0.003
Cerebellum	1 (2.8)	34 (7.2)	0.499
Other	0 (0.0)	4 (0.8)	1.000
Treatments, n			
Surgical evacuation	1 (2.8)	13 (2.8)	1.000
Tracheostomy	3 (8.3)	18 (3.8)	0.181
Early death, n	12 (33.3)	46 (9.8)	<0.001
Cause of early death, n			
Brain herniation or hydrocephalus	11 (91.7)	43 (93.5)	
Pulmonary embolism	0 (0.0)	1 (2.2)	
Congestive heart failure	0 (0.0)	1 (2.2)	
Acute myocardial infarction	0 (0.0)	1 (2.2)	
Stopping hemodialysis	1 (8.3)	0 (0.0)	

Figures in parentheses represent interquartile ranges or percentages, as appropriate.

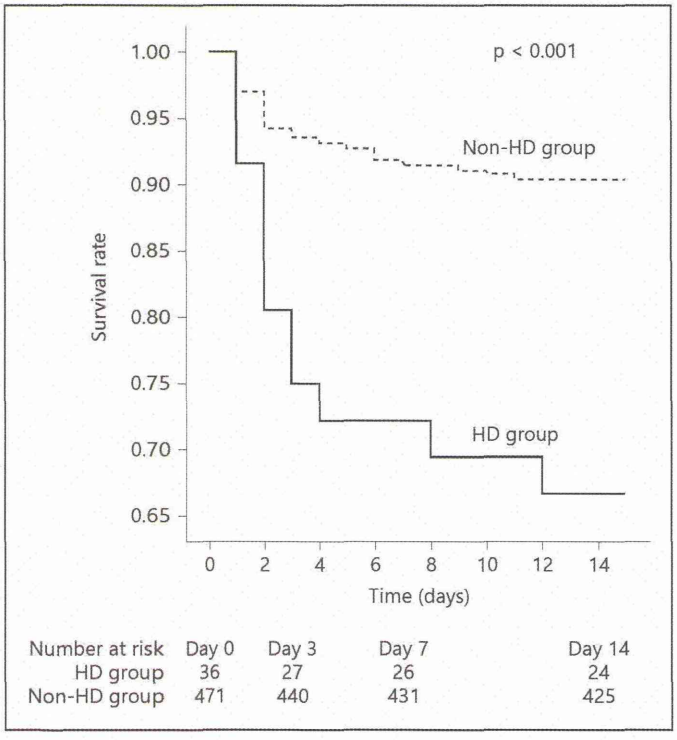

Fig. 1. Kaplan-Meier curves for ICH patients on maintenance HD (HD group) and not on maintenance HD (non-HD group). The p value was determined by the log-rank test.

Discussion

Of 507 patients with acute ICH, 7.2% were receiving maintenance HD prior to ICH onset. The 14-day mortality rate was 33.3% for HD ICH patients and 9.5% for non-HD ICH patients, and maintenance HD was identified as an independent factor associated with early death after ICH. This is the first report demonstrating an independent relationship between HD and early death in ICH patients. Brainstem and lobar hematoma were more frequently found in HD patients than in non-HD patients.

Previous cohort studies report that the incidence of ICH in HD patients is 3–10 times higher than that in the general population [11–13]. Although stroke incidence and subtype in HD patients have been well described, this is the first report of the prevalence in patients who were receiving maintenance HD at the time of ICH among a cohort of ICH patients. We found that HD was independently associated with early death in patients with acute ICH. The 14-day mortality rate was 3.5 times higher than that in non-HD ICH patients. Previous studies report that the mortality rate in HD patients with acute ICH is 41–67% [14–16]. The following factors have been identified as being factors associated with early death in ICH patients: severe neurological deficit on admission [3],

Table 3. Baseline characteristics and laboratory data of ICH patients who suffered early death and those who survived

	Early death (n = 58)	Survivors (n = 449)	p
Age, years	74.5 (63.0–82.0)	69.0 (59.0–78.0)	0.013
Male, n	35 (60.3)	285 (63.5)	0.666
Systolic blood pressure, mm Hg	189.0 (160.0–218.5)	178.0 (156.5–198.0)	0.062
Diastolic blood pressure, mm Hg	100.5 (86.0–114.5)	100.0 (84.0–110.0)	0.477
Risk factors, n			
Hypertension	48 (82.8)	345 (76.8)	0.403
Diabetes mellitus	15 (25.9)	88 (19.6)	0.297
Hyperlipidemia	5 (8.6)	88 (19.6)	0.047
Atrial fibrillation	11 (19.0)	19 (4.2)	<0.001
Hemodialysis	12 (20.7)	24 (5.3)	<0.001
Previous stroke	28 (48.3)	93 (20.7)	<0.001
Smoking	26 (44.8)	202 (45.0)	1.000
Alcohol	19 (32.8)	202 (45.0)	0.091
Antithrombotic agents, n	28 (48.3)	90 (20.0)	<0.001
Antiplatelets	21 (36.2)	77 (17.1)	0.001
Warfarin	12 (20.7)	21 (4.7)	<0.001
Laboratory data			
WBC, /μl	9,250 (6,900–11,925)	7,200 (5,615–9,615)	<0.001
RBC, ×10,000/μl	393.5 (349.8–433.3)	434.0 (389.0–469.5)	0.001
Platelets, ×10,000/μl	21.2 (15.4–25.1)	20.0 (16.4–24.5)	0.997
BUN, mg/dl	18.0 (14.0–29.0)	16.0 (13.0–20.0)	0.004
Creatinine, mg/dl	0.82 (0.66–1.45)	0.69 (0.53–0.88)	0.001
eGFR, ml/min/1.73 m^2	63.1 (33.9–82.8)	80.2 (62.7–97.6)	<0.001
Glucose, mg/dl	175.0 (149.5–220.3)	133.0 (111.0–162.0)	<0.001
HbA1c, %	5.3 (5.0–5.7)	5.4 (5.1–5.8)	0.136
PT-INR	1.08 (1.0–1.36)	1.03 (0.97–1.11)	<0.001
D-dimer, μg/dl	1.6 (0.6–4.2)	0.6 (0.5–1.4)	0.003
NIHSS score on admission	28.0 (25.8–30.0)	11.0 (5.0–17.0)	<0.001
ICH volume on admission, ml	54.4 (14.6–124.3)	6.9 (3.1–13.2)	<0.001
ICH volume enlargement, n	8/28 (28.6)	45/443 (10.2)	0.003

Figures in parentheses represent interquartile ranges or percentages, as appropriate.

Table 4. Multivariate logistic regression analysis for factors associated with early death after ICH adjusted for age, sex and renal dysfunction (eGFR <60 ml/min/1.73 m^2)

Variable	Early death		
	OR	95% CI	p
NIHSS score >20	27.40	9.69–77.44	<0.001
ICH volume >30 ml	9.53	3.82–23.77	<0.001
Hemodialysis	6.42	1.39–29.76	0.017
Antithrombotic agents	3.04	1.22–7.56	0.017
Glucose >150 mg/dl	2.51	1.01–6.26	0.048
D-dimer >1.9 μg/dl	1.89	0.71–5.04	0.205

large hematoma volume [4], hyperglycemia [5], use of antithrombotic agents [6, 7] and high D-dimer levels [8]. Chronic kidney disease is associated with an increased risk of ICH [19] and poor outcome after ICH [20]. However, to the best of our knowledge, this is the first report demonstrating an independent relationship between HD and early death in ICH patients, adjusted for renal dysfunction. Maintenance HD patients have increased inflammatory activation [21] and disturbances of the coagulation system [22]. Inflammation and blood coagulation abnormalities are known to play a key role in early hematoma expansion and perihematoma brain edema after ICH [23]. Therefore, it is possible that a systemic

reaction induced by maintenance HD may cause subsequent hematoma growth and result in the high mortality rate.

Brainstem hemorrhages were more common in HD patients than in non-HD patients. Toyoda et al. [15] described the clinical features of stroke in a maintenance HD population and reported that the hematoma sites were similar between HD patients and normal renal function patients with ICH. However, the number of HD patients with ICH was small. These authors also identified that vertebrobasilar territory infarct was more prevalent in HD patients [15]. We expected that vertebrobasilar territory stroke (both ischemic and hemorrhagic) would be more frequently observed in HD patients in the present study, because an arteriovenous shunt in the forearm for HD may alter the flow velocity of the posterior circulation and cause vulnerability in the vertebrobasilar artery [15].

Interestingly, lobar hemorrhages were also more common in HD patients. This supports a previous report of an association between lobar hemorrhage and HD at the time of ICH [14]. The most common causes of lobar hemorrhage are cerebral amyloid angiopathy [24], high blood pressure and the use of antithrombotic agents [6]. In the present study, 43% of HD patients were taking antithrombotic agents prior to ICH, compared to only 26% of non-HD patients. This high use of antithrombotic agents may have increased the incidence of lobar hemorrhage in the HD patients. Moreover, chronic systemic heparinization, which is inevitable in HD treatment, may play a role in increasing the incidence of lobar hemorrhage. The site of hematoma likely differs for HD patients and non-HD patients, and more patients are needed to confirm this hypothesis.

This study was retrospectively performed at a single center, and the number of HD patients was small. Furthermore, hematoma enlargement was not assessed in all patients. Finally, the frequency of brainstem hematoma was high in the HD patients, and we evaluated hematoma size and enlargement without discrimination between supratentorial and infratentorial location. Large collaborative studies are required to reach a more definitive conclusion.

In conclusion, we found that patients receiving maintenance HD at the time of ICH had a higher incidence of early death, and maintenance HD was independently associated with early death. In addition, brainstem and lobar hematomas were more frequently found in ICH patients receiving maintenance HD at the time of ICH.

Disclosure Statement

The authors declare no financial or other conflict of interests.

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