

Stroke

American Stroke
AssociationSM

JOURNAL OF THE AMERICAN HEART ASSOCIATION

A Division of American
Heart Association



Multivariate Analysis of Predictors of Hematoma Enlargement in Spontaneous Intracerebral Hemorrhage

Yukihiko Fujii, Shigekazu Takeuchi, Osamu Sasaki, Takashi Minakawa and Ryuichi Tanaka

Stroke 1998;29:1160-1166

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75214
Copyright © 1998 American Heart Association. All rights reserved. Print ISSN: 0039-2499. Online
ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://stroke.ahajournals.org/cgi/content/full/29/6/1160>

Subscriptions: Information about subscribing to Stroke is online at
<http://stroke.ahajournals.org/subscriptions/>

Permissions: Permissions & Rights Desk, Lippincott Williams & Wilkins, a division of Wolters Kluwer Health, 351 West Camden Street, Baltimore, MD 21202-2436. Phone: 410-528-4050. Fax: 410-528-8550. E-mail:
journalpermissions@lww.com

Reprints: Information about reprints can be found online at
<http://www.lww.com/reprints>

Multivariate Analysis of Predictors of Hematoma Enlargement in Spontaneous Intracerebral Hemorrhage

Yukihiko Fujii, MD, PhD; Shigekazu Takeuchi, MD, PhD; Osamu Sasaki, MD, PhD;
Takashi Minakawa, MD, PhD; Ryuichi Tanaka, MD, PhD

Background and Purpose—We conducted this study to determine, through use of multivariate analyses, the independent predictors of hematoma enlargement occurring after hospital admission in patients with spontaneous intracerebral hemorrhage (ICH).

Methods—We reviewed 627 patients with ICH admitted within 24 hours of onset. The first CT was performed at admission and the second within 24 hours of admission, and a blood sample was taken for laboratory examinations. Univariate and multivariate analyses were performed to assess the relationships between hematoma enlargement and time from onset, consciousness level, CT findings, amount of alcohol consumption, systolic blood pressure at and after admission, clinical outcome, and hematologic parameters.

Results—Eighty-eight patients (14.0%) showed enlarged hematomas after admission. Multivariate analyses revealed that the following five factors were independently associated with hematoma enlargement: the time from onset (odds ratio [OR], 0.26 for a 1-SD change; 4.9 hours; $P<0.001$); the amount of alcohol consumption (OR, 1.50 for 1 SD; 46.3 g/d; $P=0.002$); the shape of hematoma (OR, 1.40 for 1 SD; 0.45 round; $P=0.006$); the presence of consciousness disturbance (OR, 1.38 for 1 SD; 0.50 coma; $P=0.026$); and the level of fibrinogen (OR, 0.74 for 1 SD; 87.1 mg/dL; $P=0.042$). Hematoma enlargement was an independent factor increasing the mortality rate in the ICH patients (OR, 1.57; $P<0.001$).

Conclusions—A particularly high likelihood of hematoma enlargement was observed in patients who (in order of importance) were admitted shortly after onset, who were heavy drinkers; who had an irregularly shaped hematoma, whose consciousness was disturbed, and who had a low level of fibrinogen. (*Stroke*. 1998;29:1160-1166.)

Key Words: alcohol drinking ■ blood coagulation disorders ■ tomography, x-ray computed
■ intracerebral hemorrhage ■ risk factors

An enlargement of a hematoma (hematoma growth) occurs not uncommonly in patients with spontaneous intracerebral hemorrhage (ICH) after their hospitalization¹⁻¹³ and worsens their clinical outcome.¹¹⁻¹³ In our previous review¹² of 419 patients with ICH, we estimated the incidence of hematoma growth (14.3%) and noted the presence of predictors of hematoma growth (viz, a short time interval between admission and onset, an irregularly shaped and large hematoma revealed by an initial CT scan, and liver dysfunction associated with chronic alcohol consumption). However, in that report we did not examine the interrelationships among those predictors. To the best of our knowledge, no attempts have been made to date to assess independent predictors of hematoma growth with use of multivariate analysis. We had the opportunity to review another series of over 200 ICH patients, and we assessed the following 4 additional variables as predictors of hematoma growth: alcohol consumption; severity of consciousness disturbance on admission; systolic blood pressure after admission; and pres-

ence of intraventricular hematoma at initial CT scan. These circumstances prompted us to conduct the present study.

The purposes of this study were to assess independent predictors, possibly applicable to ICH patients, of hematoma growth occurring after hospital admission and to determine which was the strongest predictor of hematoma growth. For these purposes, we reviewed the records of 627 patients admitted within 24 hours of the onset of ICH and examined with univariate and multivariate analyses the relationships between hematoma growth and time from onset, consciousness level, CT findings, amount of alcohol consumption, systolic blood pressure at and after admission, clinical outcome, and hematologic parameters. We thereby explored the possibility of preventing hematoma growth occurring after admission.

Subjects and Methods

Patient Population

This study was performed according to the human research guidelines of the Internal Review Board of Niigata University. Between

Received January 26, 1998; final revision received March 9, 1998; accepted March 9, 1998.

From the Department of Neurosurgery, Brain Research Institute, Niigata University, Niigata, Japan.

Correspondence to Yukihiko Fujii, MD, PhD, Department of Neurosurgery, Brain Research Institute, Niigata University, Asahimachi 1, Niigata 951, Japan. E-mail yfujii@bri.niigata-u.ac.jp

© 1998 American Heart Association, Inc.

January 1987 and December 1995, ICH was diagnosed in 835 patients at our hospital. Of these 835 patients, 157 who were admitted after 24 hours of onset were excluded. Thus, 678 patients were admitted to our hospital within 24 hours after onset of ICH. In addition to plain CT, all patients underwent contrast medium-enhanced CT, MR imaging/angiography, and/or cerebral angiography to exclude hemorrhage due to definite intracranial disease, such as a cerebral aneurysm. This series of patients did not include those receiving anticoagulation or antiplatelet therapy or those with hemorrhage due to intracranial aneurysm, arteriovenous malformation, moyamoya disease, cavernous hemangioma, or infectious endocarditis.

All patients admitted to our neurosurgical unit routinely undergo their first CT within 30 minutes of arrival and a second CT within 24 hours of admission. Of the 678 patients, 51 failed to undergo the second CT because of emergency surgery or death. Thus, 627 patients (median age, 62 years), all of whom underwent the first CT within 24 hours of onset and the second CT within 24 hours of admission, were reviewed in this retrospective study.

The sites of hematomas were the putamen in 259 patients (including 37 with large hematomas involving the thalamus), thalamus in 181, cerebellum in 65, subcortex in 60, brain stem in 55, and caudate head in 11.

CT Findings

CT scans were performed with 5-mm-thick slices in all patients, and the hematoma volume (in cubic centimeters) was determined with an area calculation program built into the CT scanner. To assess predictors of definite enlargement of hematoma likely to result in neurological deterioration, we determined the following criteria of hematoma growth after examining a number of cases. ICHs that met the following conditions were defined as exhibiting hematoma growth: (1) hematoma volume increased by >50% of the initial volume (1.5 times) and >2 cm³ between the first and second CT scans or (2) the volume increased by >20 cm³ between the first and second CT scans. In this study, we measured the volumes of intraparenchymatous hematomas excluding hematomas in the ventricles and did not regard an increase in the volume of intraventricular hematomas as hematoma growth because of the difficulties in distinguishing between growth and diffusion of a hematoma and also in measuring real hematoma volumes in cerebrospinal fluid. Hematomas were also classified by shape into the following 2 mutually exclusive types: (1) round, with round and smooth margins, and (2) irregular, with irregular, multinodular margins. The readers of the first CT scans were blinded to the results of the following scans and the clinical findings.

Data Collection

Immediately after admission, the patient's neurological findings were assessed, and systemic blood pressure was measured. Efforts were made to keep the systolic blood pressure below 150 mm Hg by giving calcium channel blockers. The amount of daily alcohol consumption was calculated with the following formula: the volume (cm³) of drink multiplied by the alcohol concentration (g/cm³) of the drink. The time of onset and the patient's medical history, including alcohol intake, were ascertained by interviewing the patient or the patient's family. We reviewed several measurements of systolic blood pressure approximately 1 hour after admission in all patients and used the mean of those values as the systolic blood pressure after admission. Within 1 hour of admission, 20 mL of blood was taken for laboratory studies. To evaluate hemostatic functions, the following parameters were assessed: platelet count; prothrombin time; activated partial thromboplastin time; fibrinogen level; and anti-thrombin III, plasminogen, and α_2 -antiplasmin activity. In addition, we evaluated the enhancement of platelet sensitivity with a modification of the method reported by Fishman et al.¹⁴ Enhancement of platelet sensitivity is defined as the lowest concentration of adenosine diphosphate that produces complete second-wave aggregation. The following parameters were also measured: glutamic-oxaloacetic transaminase, glutamic-pyruvic transaminase, alkaline phosphatase,

γ -glutamyl transpeptidase, and white and red blood cell counts. All records of the 627 patients were complete, with no data missing.

Clinical Outcome

Outcome was assessed by clinical follow-up for at least 3 months. All patients were classified into 1 of 5 mutually exclusive categories according to the Glasgow Outcome Scale¹⁵: good recovery, moderate disability, severe disability, vegetative state, and death.

Statistical Analysis

This is an exploratory analysis to assess the independent predictors of hematoma enlargement of ICH. First, we performed univariate analyses to detect the factors having a significant relationship with hematoma growth, ie, the predictors of hematoma growth. Then, with respect to these factors, we determined which variables were independently associated with hematoma growth and which were the strongest predictors of hematoma growth using multivariate analyses. The Cochran-Armitage method¹⁶ was used to assess the tendency for the incidence of hematoma growth to change in relation to consciousness level, amount of alcohol consumption, time after onset, systolic blood pressure, hematoma volume, and clinical outcome. The categories of systolic blood pressure and hematoma volume were chosen by data quartiles. The amount of daily alcohol consumption was classified into 3 categories because almost half of the patients in this study were nondrinkers. The time after onset was categorized according to that in our previous.¹² Ryan's method¹⁷ was used to assess differences in the incidence of hematoma growth among categories. A χ^2 analysis was used to test the association between hematoma growth and hematoma site, hematoma shape, and intraventricular hematoma. The Student and Welch *t* tests were used to assess the differences in age and hematologic parameters between the patient groups with and without hematoma growth. Values are expressed as mean \pm SEM. A multiple logistic regression analysis was used to identify factors independently associated with hematoma growth and mortality using dummy variables or the actual values of variables. Odds ratios in this study indicate those for 1-SD changes of explanatory variables. Analyses resulting in values of $P < 0.05$ were considered significant. To assess relationships between alcohol consumption and hematologic parameters, a multiple regression analysis was performed.

Results

Incidence of Hematoma Growth

Eighty-eight of the 627 patients (14.0%) demonstrated enlargement of their hematoma after the first CT scan. The mean ages of the patients with and without hematoma growth were 60.9 ± 1.3 and 62.9 ± 0.5 years, respectively. There was no significant difference in the mean age between the 2 patient groups. Of the 627 patients, 392 were male and 235 female. Their mean ages were 60.1 ± 0.6 and 66.8 ± 0.8 years, respectively. The incidence of hematoma growth in male patients (17.3%) was significantly higher than that in female patients (8.5%).

Univariate Analysis of Predictors of Hematoma Growth

Alcohol Consumption

The incidence of hematoma growth in the patients with no habit of alcohol consumption and those with mild (1 to 50 g/d) and heavy (>50 g/d) alcohol consumption was 8.6%, 15.3%, and 25.0%, respectively. The incidence of hematoma growth significantly increased as the amount of alcohol consumption increased. There was also a significant difference in the incidence of hematoma growth between the

TABLE 1. Differences in Hematologic Parameters Between Patients With and Without Hematoma Growth

Parameter	Normal Range	Hematoma	
		Yes (n=88)	No (n=539)
Blood coagulation system			
Prothrombin time, sec	10.6–13.9	11.9±0.1	11.7±0.03
Activated partial thromboplastin time, sec	25.4–34.4	27.1±0.4	26.6±0.1
Fibrinogen, mg/dL	150–380	241±8	286±4*
Antithrombin III, %	87–380	98±6	104±1*
Fibrinolytic system			
plasminogen, %	80–109	97±2	98±1
α ₂ -antiplasmin, %	85–120	87±2	94±1*
Platelet system			
platelet (×10 ⁴ /mm ³)	15.0–36.0	22.2±0.9	24.2±0.4*
Enhancement of platelet sensitivity, μmol	1.0–4.0	4.4±0.3	3.7±0.1*
Others			
White blood cell (×10 ⁴ /mm ³)	4.5–7.3	9.3±0.4	9.8±0.2
Hemoglobin, g/dL	11.6–16.3	13.6±0.2	13.8±0.1
glutamic-oxaloacetic transaminase, IU/L	<37	48±5	34±2*
Glutamic-pyruvic transaminase, IU/L	<40	33±3	28±1
γ-Glutamyl transpeptidase, IU/L	<60	160±26	86±6*

n indicates number of cases.

*There was a significant ($P<0.05$) difference between patients with and those without hematoma growth (by unpaired Student or Welch t test).

patients with mild and those with heavy alcohol consumption (Ryan's method).

Time Interval Between Onset and Admission

The time interval between onset and admission means the time interval between the appearance of neurological symptoms and completion of the first CT scan. The incidence of hematoma growth in patients admitted 0 to 1, >1 to 2, >2 to 4, >4 to 6, and >6 hours after onset was 21.4%, 16.9%, 14.0%, 6.8%, and 1.9%, respectively. The incidence of hematoma growth significantly decreased as the time after onset to admission increased.

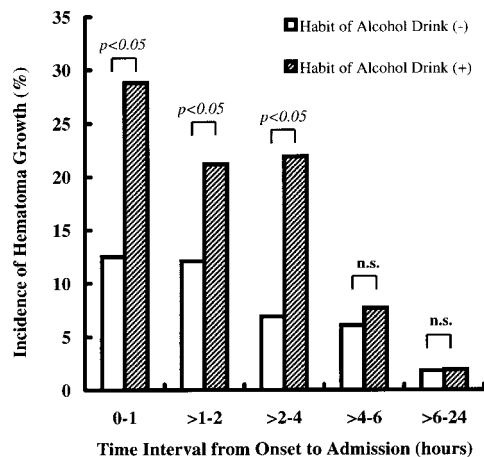
Consciousness at Admission

The incidence of hematoma growth (20.0%) in 315 patients with consciousness disturbance was significantly higher than that (8.0%) in 312 patients with no consciousness disturbance.

Systolic Blood Pressure

On admission, the incidence of hematoma growth in patients with normal systolic blood pressure (<150 mm Hg), those with mildly increased blood pressure (150 to 175 mm Hg), those with high systolic blood pressure (>175 to 200 mm Hg), and those with extremely high systolic blood pressure (>200 mm Hg) was 8.4%, 13.6%, 14.3%, and 21.5%, respectively. There was a significant increase in the incidence of hematoma growth with higher values of systolic blood pressure at admission. After admission, the incidence of hematoma growth in patients with normal systolic blood pressure (<145 mm Hg), those with relatively high blood

pressure (145 to 160 mm Hg), those with high blood pressure (>160 to 175 mm Hg), and those with extremely high systolic blood pressure (>175 mm Hg) was 6.5%, 13.0%, 14.1%, and 21.7%, respectively. The incidence of hematoma growth also significantly increased with higher values of systolic blood pressure after admission.



Bar graph showing the incidence of hematoma growth in 5 groups classified by time of hospital admission after onset. Significant ($P<0.05$) differences were found in the incidence between patients with and without a habit of daily alcohol consumption who underwent the first CT scan 0 to 1 hours, >1 to 2 hours, and >2 to 4 hours after onset (χ^2 analysis). n.s. indicates not significant.

TABLE 2. Evaluation of Independent Predictors of Hematoma Growth by Multiple Logistic Regression Analysis in 627 Patients With Spontaneous Intracerebral Hemorrhage

Variable	1 SD	Odds Ratio*	95% Confidence Interval	P
Gender (female/male)	0.48	1.039	0.755–1.430	0.813
Alcohol consumption, g/d†	46.3	1.497	1.155–1.942	0.002
Interval to admission, h†	4.92	0.255	0.128–0.511	<0.001
Consciousness level (no/yes)†	0.50	1.377	1.037–1.829	0.028
Systolic blood pressure at admission, mg Hg	31.9	1.050	0.822–1.341	0.695
Shape of hematoma (round/irregular)†	0.45	1.402	1.105–1.779	0.006
Intraventricular hematoma (no/yes)	0.50	1.263	0.963–1.657	0.091
γ -Glutamyl transpeptidase, IU/L	167	1.179	0.952–1.460	0.132
fibrinogen, mg/dL†	87.1	0.737	0.549–0.989	0.042
Enhancement of platelet sensitivity, μ mol	2.55	1.220	0.950–1.567	0.119

*Odds ratios indicate changes (ratio) in the probability of hematoma growth occurring after admission when explanatory variables increase by 1 SD.

†These variables are significantly ($P<0.05$) and independently associated with hematoma growth (by multiple logistic regression analysis).

Sites of Hematoma

Although there was a significant and overall difference in the incidence of hematoma growth among the patient groups classified by site of hematoma (χ^2 analysis), no significant difference in the incidence of hematoma growth was found between any 2 patient groups classified by site except the 2 groups with putaminal and thalamic hemorrhage (Ryan's test).

CT Findings

The incidence of hematoma growth in the irregularly shaped hematomas (23.0%) was significantly higher than in those of the round type (10.4%). The incidence of hematoma growth in the patients with an intraventricular hematoma (17.6%) was also significantly higher than in those without (10.4%).

Hematoma Volume

The relationship between hematoma growth and hematoma volume was examined in 259 patients with a putaminal hemorrhage. The incidence of hematoma growth was 6.5% in patients with a small (<10 cm³) putaminal hematoma, 16.7% in those with a medium-sized hematoma (>10 to 20 cm³), 21.4% in those with a large hematoma (>20 to 40 cm³), and 29.1% in those with a huge hematoma (>40 cm³). The incidence of hematoma growth significantly increased with an increase in volumes of putaminal hematoma (the Cochran-Armitage method).

Laboratory Parameters

Fibrinogen levels, antithrombin III and α_2 -antiplasmin activity, and platelet counts were significantly lower in the patients

TABLE 3. Evaluation of Independent Predictors of Hematoma Growth by Multiple Logistic Regression Analysis in 259 Patients With Putaminal Hemorrhage

Variable	1 SD	Odds Ratio	95% Confidence Interval	P
Gender (female/male)	0.48	1.286	0.804–2.058	0.296
Alcohol consumption, g/d†	51.6	1.530	1.023–2.290	0.040
Interval to admission, h†	4.27	0.326	0.143–0.756	0.009
Consciousness level (no/yes)	0.50	1.333	0.848–2.096	0.214
Systolic blood pressure at admission, mm Hg	32.8	1.051	0.725–1.524	0.793
Shape of hematoma (round/irregular)†	0.49	1.527	1.008–2.314	0.047
Intraventricular hematoma (no/yes)†	0.48	1.778	1.153–2.741	0.010
γ -Glutamyl transpeptidase, IU/Liter	191	1.390	0.974–1.983	0.071
Fibrinogen, mg/dL	84.9	0.859	0.578–1.277	0.453
Enhancement of platelet sensitivity, μ mol	2.72	1.263	0.867–1.840	0.225
Hematoma volume, cm ³	31.4	0.733	0.466–1.154	0.181

†These variables are significantly ($P<0.05$) and independently associated with hematoma growth (by multiple logistic regression analysis).

TABLE 4. Evaluation of Independent Factors Associated With Mortality in 627 Patients With Spontaneous Intracerebral Hemorrhage by Multiple Logistic Regression Analysis

Variable	1 SD	Odds Ratio	95% Confidence Interval	P
Age, y	11.9	1.980	1.421–2.760	<0.001
Gender (female/male)†	0.48	1.462	1.054–2.030	0.023
Alcohol consumption, g/d	46.3	1.070	0.774–1.479	0.683
Consciousness level (no/yes)†	0.50	3.818	2.830–5.149	<0.001
Systolic blood pressure at admission, mm Hg	31.9	1.095	0.839–1.430	0.502
Intraventricular hematoma (no/yes)	0.50	1.295	0.952–1.761	0.100
Shape of hematoma (round/irregular)†	0.45	1.519	1.180–1.956	0.001
Hematoma growth (no/yes)†	0.35	1.566	1.124–1.968	<0.001

†These variables are significantly ($P<0.05$) and independently associated with mortality (by multiple logistic regression analysis).

with hematoma growth than those with no growth (Table 1). The levels of enhancement of platelet sensitivity were significantly higher (ie, platelet aggregability was lower) in the patients with hematoma growth than in those with no growth. The levels of glutamic-oxaloacetic transaminase and γ -glutamyl transpeptidase in the patients with hematoma growth were significantly higher than in those with no growth.

Multivariate Analysis of Predictors of Hematoma Growth

In view of the presence of interrelationships among predictors of variables associated with hematoma growth (Figure), we used a multiple logistic regression analysis to determine the independent predictors of hematoma growth (Table 2). Systolic blood pressure after admission was not included in the multivariate analyses because the relationship between elevated systolic blood pressure after admission and hematoma growth is more likely caused by the increased intracranial pressure. The multivariate analysis revealed the presence of 5 independent predictors of hematoma growth: the amount of alcohol regularly consumed (OR, 1.50; $P=0.002$), the time interval between onset and admission (OR, 0.26; $P<0.001$), the presence of consciousness disturbance (OR, 1.38; $P<0.001$), the shape of the hematoma (OR, 1.40; $P<0.001$), and the level of fibrinogen (OR, 0.74; $P=0.037$).

To ascertain whether the volume of hematoma was an independent predictor of hematoma growth, we also performed a multivariate analysis of 11 variables, including hematoma volume, in the 259 putaminal hemorrhage patients (Table 3). This analysis revealed that the volume of hematoma was not independently associated with hematoma growth (OR, 0.73; $P=0.18$) among the 11 factors assessed.

The other variables in this multivariate analysis (namely, gender, systolic blood pressure at admission and after admission, levels of γ -glutamyl transpeptidase, and enhancement of platelet sensitivity) were not independent predictors of hematoma growth because of their interrelationships. Although the presence of intraventricular hematoma was an independent predictor of hematoma growth in the patients with putaminal hemorrhage, it was not one in the entire patient population with ICH.

Relationship of Hematoma Growth and Clinical Outcome

In the 627 patients, the outcome at 3 months after onset was a good recovery in 134 (21.4%), moderate disability in 132 (21.1%), severe disability in 214 (34.1%), vegetative state in 40 (5.9%), and death in 107 (17.1%). The incidence of hematoma growth according to outcome was good recovery, 1.5%; moderate disability, 6.1%; severe disability, 15.4%; vegetative state, 20.0%; and death, 34.6%. There was a significant association between hematoma growth and poor clinical outcome. In addition, 37 of the 88 patients with hematoma growth died. The mortality rate for the patients with hematoma growth (42.1%), as a matter of course, was quite significantly higher than for those with no growth (13.0%). Multiple logistic regression analysis revealed that hematoma growth was an independent, though the third strongest, factor associated with an increase in the mortality rate in ICH patients (Table 4).

Discussion

Mortality in patients with hematoma growth was extremely high. Although their mortality rate was 42.1%, the actual mortality rate appeared to be $>50\%$, because all 51 patients excluded from this study for missing the second CT progressively deteriorated and died; although it was unverified, they appeared to have had hematoma growth. If hematoma growth could be prevented, the overall clinical outcome for ICH patients would be dramatically improved. This study addressed independent predictors of hematoma growth applicable to ICH patients on admission.

Definition of Hematoma Growth

To assess risk factors for definite enlargement of hematoma likely to result in neurological deterioration, we defined hematoma growth as the increase of its volume by 1.5 times and 2 cm³ or by 20 cm³. Kazui et al¹⁸ proposed a cutoff value for the diagnosis of increased hematoma size on CT, ie, the increase of its volume by 1.4 times or 12.5 cm³, based on a receiver operating characteristic curve analysis. Their report seems to support the validity of our definition of hematoma growth. The frequency of hematoma growth they reported

(20.1%) was different from that in the present study (14.0%), a difference which appears to be attributable mainly to the difference in the cutoff value in defining hematoma growth.

Hematoma Growth and Hemostatic Systems

Both univariate and multivariate analyses revealed close relationships between hematoma growth and impairment of the blood coagulation system and platelet systems. Influence of intracerebral hemorrhage itself (ie, intraparenchymal hematoma without intraventricular hematoma) on the hemostatic system is so subtle that it is hardly detectable, even with use of sensitive markers for hemostatic activation, such as the thrombin-antithrombin complex.¹⁹ Thus, the abnormalities noted in the coagulation and platelet studies seem to be risk factors for hematoma growth and not a reflection that bleeding is continuing.

Predictors of Hematoma Growth

Our present study revealed that the following 5 factors were independently associated with the hematoma growth after admission.

Chronic Alcohol Consumption

Study results indicated that the amount of daily alcohol consumption was the second strongest predictor of hematoma growth after admission. The incidence of hematoma growth in the patients who had no habit of alcoholic consumption was extremely low, and it increased with the increasing level of alcohol intake. The amount of alcohol consumption was independently associated with hematoma growth. Although a number of investigators reported that heavy alcohol intake was a risk factor for the occurrence of ICH,^{20–25} there was no report statistically confirming habitual alcohol consumption as an independent risk factor for hematoma growth. We previously reported²⁶ that liver dysfunction with chronic alcohol consumption was associated with impairment of the hemostatic system, such as hypocoagulability and platelet hypoaggregability. Thus, the fact that heavy alcohol consumption is an independent predictor of hematoma growth may be attributable to the hemostatic impairment. Hence, heavy alcohol intake can be considered a risk factor for as well as a predictor of hematoma growth, because it is a habit that patients acquired before the onset of ICH.

Short Interval From Onset

This study confirmed that the interval from onset to admission was the strongest predictor of hematoma growth. As previously reported, the incidence of hematoma growth decreases as the time interval from onset increases, and hematoma growth rarely occurs in patients admitted more than 6 hours after onset.^{11–13,18} From the standpoint of hematoma formation, active bleeding seems to be mostly stabilized within 6 hours of onset. Thus, patients admitted early after onset have a high likelihood of undergoing a CT scan before the stabilization of hematoma formation. Hence, a short time interval between onset and admission does not seem to be a risk factor for hematoma growth after admission, although it is an important and independent predictor of hematoma growth.

Consciousness Disturbance

This study also revealed that the presence of consciousness disturbance was an independent predictor of hematoma growth; that is to say, the patients with disturbed consciousness had a likelihood of having hematoma growth after admission. No prior study has found an association between hematoma growth and consciousness level. Although the reason for the high incidence of hematoma growth inpatients with consciousness disturbance is unclear, consciousness disturbance seems to represent a number of factors, including hematoma size. Consciousness disturbance, though an independent predictor of hematoma growth, cannot be regarded as a risk factor for hematoma growth because it appears as a matter of course after onset of ICH and worsens with hematoma growth.

Irregularly Shaped Hematomas

The present study corroborated our previous report that the incidence of hematoma growth in patients with an irregularly shaped hematoma noted on initial CT was higher than in those with a round hematoma, and it also revealed that the shape of the hematoma was independently associated with hematoma growth. As mentioned in our previous study,¹² irregularly shaped hematomas seem to indicate active bleeding from multiple arterioles. Hence, although an irregularly shaped hematoma on initial CT is an independent predictor of hematoma growth, it does not seem to be a risk factor for hematoma growth.

Low Levels of Fibrinogen

A low level of fibrinogen was also an independent predictor of hematoma growth. It is well known that fibrinogen is converted to fibrin by thrombin. Fibrins are cross-linked to each other in the presence of factor XIII to become fibrin polymers, which are the final products of the coagulation cascade (the secondary hemostasis). Fibrinogen also plays an important role in primary hemostasis, ie, platelet aggregation. Glycoprotein IIa/IIIb on the surface of platelets requires fibrinogen for aggregation. Thus, decreased levels of fibrinogen may be associated with an impairment of both primary and secondary hemostasis. In the multivariate analysis, fibrinogen levels may represent the function of both blood coagulation and platelet aggregation. Hence, the low level of fibrinogen seems to be a risk factor as well as a predictor of hematoma growth.

Prevention of Hematoma Growth

In the present study, we found 5 independent predictors of hematoma growth, including 2 risk factors for hematoma growth. The 3 factors—ie, a short time interval from onset, the presence of consciousness disturbance, and an irregularly shaped hematoma—seem to relate to the natural time course of hematoma growth. Unfortunately, we are unable to identify any method to completely prevent hematoma growth after hospital admission. However, careful observation of the following patients is advisable because of the high likelihood of hematoma growth: patients who are heavy drinkers, who are admitted shortly after onset, who have an irregularly shaped hematoma on the initial CT, and whose fibrinogen level is low. Administration of agents to improve their

impaired hemostasis, if possible, may reduce the incidence of hematoma growth. Systolic blood pressure after admission, we believe, should be kept low so as not to accelerate hematoma growth, although systolic blood pressures at and after admission were not a independent factor associated with hematoma growth. As prophylaxis against hematoma growth, the amount of daily alcohol intake should be reduced.

Study Limitations

It should be kept in mind that our results are likely to have been biased by a number of factors. For example, our exclusion of the patients who missed the second CT scan might have biased the results. There may also be possible bias because of referral patterns and prehospital deaths, measurement error of CT volumes, and other variables. Our results may also be confounded by variables not represented in the multivariate analysis (eg, age, race, comorbidity, and recent alcohol consumption) and multicollinearity. There are also limits in generalizing our results to other patient populations.

Conclusion

Our study results indicate that there are 5 independent predictors of hematoma growth possibly applicable to ICH patients on hospital admission. These independent predictors, listed in order of importance, are (1) a short time interval between onset and admission, (2) habitual alcohol consumption, (3) consciousness disturbance, (4) an irregularly shaped hematoma shown on initial CT scan, and (5) low levels of fibrinogen.

Acknowledgments

We express our sincere gratitude to Dr Kazuo Endo, Department of Hygiene, and Dr Naohito Tanabe, Department of Public Health, Niigata University, for their assistance in statistical analysis. We also thank Noriko Sakai for her laboratory assistance and Chikako Shiino for her help in retrieving patient records.

References

- Huckman MS, Weinberg PE, Kim KS, Davis DO. Angiographic and clinico-pathologic correlates in basal ganglionic hemorrhage. *Radiology*. 1970;95:79–92.
- Kowada M, Yamaguchi K, Matsuoka S, Ito Z. Extravasation of angiographic contrast material in hypertensive intracerebral hemorrhage. *J Neurosurg*. 1972;36:471–473.
- Mizukami M, Araki G, Mihara H, Tomita T, Fujinaga R. Arteriographically visualized extravasation in hypertensive intracerebral hemorrhage: report of seven cases. *Stroke*. 1972;3:527–537.
- Herbstein DJ, Schaumburg HH. Hypertensive intracerebral hematoma: an investigation of the initial hemorrhage and rebleeding using chromium Cr 51-labeled erythrocytes. *Arch Neurol*. 1977;30:412–414.
- Kelly RE, Berger JR, Scheinberg P, Stokes N. Active bleeding in hypertensive intracerebral hemorrhage: computed tomography. *Neurology*. 1982;32:852–856.
- Hornel TL, Selhorst JB, Kishore PR. Active bleeding in hypertensive intracranial hemorrhage. *Neurology*. 1983;33:1393–1394.
- Kase CS, Mohr JP. General features of intracerebral hemorrhage. In: Barnett HJM, Mohr JP, Stein BM, Yatsu FM, eds. *Stroke: Pathophysiology, Diagnosis, and Management*. New York, NY: Churchill Livingstone; 1986:497–523.
- Chen ST, Chen SD, Hsu CY, Hogan EL. Progression of hypertensive intracerebral hemorrhage. *Neurology*. 1989;39:1514–1518.
- Broderick JP, Brott TG, Tomsick T, Barsan W, Spilker J. Ultra-early evaluation of intracerebral hemorrhage. *J Neurosurg*. 1990;72:195–199.
- Fujitsu K, Muramoto M, Ikeda Y, Inada Y, Kim I, Kuwabara T. Indication for surgical treatment of putaminal hemorrhage. *J Neurosurg*. 1990;73:518–525.
- Mayer SA, Acco RL, Shi T, Mohr JP. Neurologic deterioration in non-comatose patients with supratentorial intracerebral hemorrhage. *Neurology*. 1994;44:1379–1384.
- Fujii Y, Tanaka R, Takeuchi S, Koike T, Minakawa T, Sasaki O. Hematoma enlargement in spontaneous intracerebral hemorrhage. *J Neurosurg*. 1994;80:51–57.
- Brott T, Broderick J, Kothri R, Barsan W, Tomsick T, Sauerbeck L, Spilker J, Duldner J, Khoury J. Early hemorrhage growth in patients with intracerebral hemorrhage. *Stroke*. 1997;28:1–5.
- Fishman SJ, Wylonis LJ, Glickman JD, Cook JJ, Warsaw DS, Fisher CA, Jorkasky DJ, Niewiarowski S, Addonizio VP. Cyclosporin A augments human platelet sensitivity to aggregating agents by increasing fibrinogen receptor availability. *J Surg Res*. 1991;51:93–98.
- Jennet B, Bond M. Assessment of outcome after severe brain damage: a practical scale. *Lancet*. 1975;1:480–484.
- Armitage P. Test for linear trends in proportions and frequencies. *Biometrics*. 1955;11:375–386.
- Ryan LM. Efficiency of aged-adjusted test in animal carcinogenicity experiments. *Biometrics*. 1985;41:524–531.
- Kazui S, Naritomi H, Yamamoto H, Sawada T, Yamaguchi T. Enlargement of spontaneous intracerebral hemorrhage. *Stroke*. 1996;27:1783–1787.
- Fujii Y, Takeuchi S, Tanaka R, Sasaki O, Koike T. Hemostasis in spontaneous subarachnoid hemorrhage. *Neurosurgery*. 1995;37:226–234.
- Beghi E, Boglium G, Cosso P, Fiorelli G, Lorini C, Mandelli M, Bellini A. Stroke and alcohol intake in a hospital population: a case-control study. *Stroke*. 1995;26:1691–1696.
- Donahue RP, Abbott RD, Reed DM, Yano K. Alcohol and hemorrhagic stroke: the Honolulu Heart Program. *JAMA*. 1986;255:2311–2314.
- Gill JS, Shipley MJ, Tsementzis SA, Hornby RS, Gill SK, Hitchcock ER, Beevers DG. Alcohol consumption: a risk factor for hemorrhagic and non-hemorrhagic stroke. *Am J Med*. 1991;90:489–497.
- Hansagi H. Alcohol consumption and stroke mortality: 20-year follow-up of 15,077 men and women. *Stroke*. 1995;26:1768–73.
- Kiyohara Y, Kato Y, Iwamoto H, Nakayama K, Fujishima M. The impact of alcohol and hypertension on incidence in a general Japanese population: the Hisayama Study. *Stroke*. 1995;26:368–372.
- Monforte R, Estruch R, Graus F, Nicolas JM, Urbano-Marquez A. High ethanol consumption as risk factor for intracerebral hemorrhage in young and middle-aged people. *Stroke*. 1990;21:1529–1532.
- Fujii Y, Takeuchi S, Tanaka R, Koike T, Sasaki O, Minakawa T. Liver dysfunction in spontaneous intracerebral hemorrhage. *Neurosurgery*. 1994;35:592–596.