A proposed definition of symptomatic vasospasm based on treatment of cerebral vasospasm after subarachnoid hemorrhage in Japan: Consensus 2009, a project of the 25th Spasm Symposium

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Abstract

Background: There is a lack of unified information on diagnosis and treatment of cerebral vasospasm (CV) after subarachnoid hemorrhage (SAH) among the hospitals in Japan. Thus, the aim of the study was to define the current practice in this area based on a survey by Japanese neurosurgeons.

Methods: A survey on diagnosis and treatment of CV was sent to 414 hospitals each of which performs >100 neurosurgeries annually.

Results: Responses were received from 240 hospitals (58.0%). Because accurate criteria for diagnosis of symptomatic vasospasm (SVS) were used in only 33.8% of the hospitals, we proposed a clinical definition of SVS that was approved at the 25th Spasm Symposium (Consensus 2009). This definition is simplified as follows: (1) the presence of neurological worsening; (2) no other identifiable cause of neurological worsening; and (3) confirmation of vasospasm by medical examinations. The results also showed that the Fisher CT scale is used differently for patients with ICH or IVH, with 41.3% of cases with ICH/IVH based on SAH that met Fisher criteria classified into Fisher group 1, 2 or 3, and 46.3% classified into Fisher group 4. There were no major differences in prophylactic therapies of CV and therapy for cerebral ischemia among the hospitals. Endovascular treatment for vasospasm was performed in most hospitals (78.7%); however, the criteria differed among the hospitals: (1) angiographic vasospasm and SVS appeared (37.9%), (2) only when aggressive therapy was ineffective (41.4%).

Conclusion: We established a clinical definition of SVS based on the results of this survey (Consensus 2009).

Key Words: Cerebral vasospasm, definition, diagnosis, subarachnoid hemorrhage, survey
INTRODUCTION

The impact of cerebral vasospasm (CV) on the outcome of subarachnoid hemorrhage (SAH) has steadily declined because of medical and surgical advances, but it is still a major cause of morbidity and mortality.\textsuperscript{[3,14]} Cerebral angiography and computed tomography (CT), magnetic resonance imaging (MRI), transcranial Doppler (TCD), and single-photon emission CT (SPECT) are now used for the diagnosis of CV in almost all hospitals designated as emergency centers in Japan. Common recognition criteria for the pathological condition of CV are established, but there is a lack of shared information on the diagnosis and treatment of CV after SAH in Japan. To address this problem, a survey of Japanese neurosurgeons was done in 2008 as a project of the 25th Spasm Symposium to define the current practices associated with CV.

MATERIALS AND METHODS

A survey was sent to 414 hospitals with a neurosurgical department in Japan, at which more than 100 neurosurgeries are performed annually, to evaluate the approach to diagnosis and treatment of CV and to establish the definition of symptomatic vasospasm (SVS) used by most Japanese neurosurgeons. Most patients with SAH in Japan are immediately referred to one of these hospitals since they are designated as emergency centers. The survey included questions on (1) symptoms of SVS, (2) period from development of CV to diagnosis, (3) medical examinations for diagnosis of SVS, (4) diagnostic criteria for SVS, (5) classification of SAH on a CT scan (especially assignment to Fisher group), (6) type of cerebrospinal fluid (CSF) drain used during the vasospasm period, (7) prophylactic therapies for CV, (8) therapies for cerebral ischemia caused by CV, (9) type of endovascular treatment for CV, and (10) criteria for an indication of endovascular treatment for CV. Respondents chose from a list of possible symptoms, treatments, and medical examinations, or could give their own choice. For some questions, respondents could make multiple selections from a list of options. Respondents were also given a space for open comments. Responses were collected by the director of each hospital and tabulated by the faculty of the Department of Neurosurgery and Clinical Neuroscience, Yamaguchi University School of Medicine. Responses left blank and cryptic comments were excluded from analysis.

RESULTS

Symptoms of symptomatic vasospasm

A total of 240 hospitals (58.0%) responded to the survey. Symptoms that led to diagnosis of SVS after SAH were (1) focal deficit (97.1%), (2) motor paresis (95%), (3) decline in level of consciousness (94.6%), (4) no other identifiable cause of neurological worsening except CV (80.0%), (5) worsening headache (26.7%), (6) low-grade fever (12.5%), and (7) elevation of blood pressure (12.1%) [Figure 1]. Focal deficit and motor paresis were included as separate items, since cerebral ischemia in the area of penetrating branches of the middle cerebral artery (MCA) presents with motor paresis. The neurological deficit (focal deficit, motor paresis, and decline in consciousness) was diagnosed based on the Japan Coma Scale (JCS), Glasgow Coma Scale (GCS), and National Institute of Health Stroke Scale (NIHSS). Cerebral ischemia was defined as a decrease of at least 1 point on the GCS or an increase of at least 1 point on the JCS or NIHSS.\textsuperscript{[10]} The mean duration of symptoms due to vasospasm ranged from 4 to 17 days after SAH. In 81 hospitals (33.8%), diagnostic criteria for SVS were based on criteria defined by each hospital, with confirmation of vasospasm by medical examination required in 60 hospitals (74.0%).

Assessment of symptomatic vasospasm

In the 60 hospitals in which diagnostic criteria for SVS and confirmation by medical examination were used, a diagnosis of SVS required (1) information on the diameter of the artery (91.7%), (2) new low density area (LDA) on CT scans associated with CV (53.3%), (3) measurement of cerebral blood flow (CBF; 26.7%), and (4) TCD (16.7%) [Figure 2a]. In all 240 hospitals, the methods of choice for examination of the diameter of the cerebrovascular spasm were cerebral angiography (70.7%), three-dimensional CT angiography (3D-CTA; 29.4%), and MR angiography (MRA; 26.7%) [Figure 2b]. The degree of luminal narrowing was categorized as mild (0–33% arterial narrowing), moderate (34–66% narrowing), or severe (67–100% arterial narrowing).\textsuperscript{[10]} TCD vasospasm was defined as mean flow velocities >120 cm/sec (81.3%) in the MCA and >90 cm/sec (85.2%) in the anterior cerebral artery (ACA). Assessment of cerebrovascular spasm was made (1) at the time of development of a new symptom or symptomatic worsening (72.8%), (2) in regular screening (39.7%), and (3) at another time (7.3%).
Fisher CT scale
The classification on the Fisher CT scale\(^{(6)}\) for patients with SAH and intracerebral hemorrhage (ICH) or intraventricular hemorrhage (IVH) at each hospital is shown in Figure 3. It is clear from the results that the Fisher CT scale, the most common method for assessing SAH on CT scans and for predicting SVS after SAH, is used differently among hospitals for patients with significant ICH or IVH in Japan. SAH patients with ICH or IVH were classified as: (1) Fisher group 4 for all patients (46.3%), (2) Fisher group 1, 2, or 3 with ICH/IVH based on SAH that met the Fisher criteria for patients with subarachnoid clot (41.3%), (3) Fisher group 4 for patients without subarachnoid clot (16.3%), and (4) another classification (10.0%).

Surgical treatment modality and drainage system
The first choice methods for obliteration of the aneurysm were (1) neck clipping (42.5%), (2) coil embolization (8.3%), and (3) neck clipping or coil embolization based on aneurysm features and progression of neurological and medical conditions (49.2%). In most hospitals, the CSF drain was placed during the vasospasm period after neck clipping (89.5%) and coil embolization (83.3%). The CSF drains placed after neck clipping were (1) a cisternal drain (86.8%), (2) a lumbar drain (34.2%), and (3) an external ventricular drain (31.6%). The CSF drains placed after coil embolization were (1) a lumbar drain (94.8%), (2) an external ventricular drain (7.9%), and (3) a cisternal drain (1.8%). Cisternal irrigation therapy was performed in 23.1% of hospitals after neck clipping and in 11.2% after coil embolization.

Prophylactic therapies for cerebral vasospasm
The prophylactic therapies for CV in most hospitals were (1) volume control (99.6%), (2) treatment for cerebral salt wasting syndrome (CSWS; 96.3%),\(^{(8,12)}\) (3) blood pressure control (95.8%), and (4) intravenous administration of fasudil hydrochloride, a protein kinase inhibitor (92.5%) \[Figure 4a\].\(^{(26,27)}\) The use of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) for prevention of CV was performed in 43 hospitals (18.0%). Volume control was categorized into hypervolemic therapy (43.2%) and normovolemic therapy (56.8%) \[Figure 5b\].\(^{(16)}\) Similarly, blood pressure control was categorized into hypertensive therapy (40.8%) and normotensive therapy (59.2%) \[Figure 4b\].\(^{(24)}\)

Therapies for cerebral ischemia
The main therapies for cerebral ischemia caused by CV were (1) intravenous administration of edaravone, a free radical scavenger (60.0%),\(^{(19)}\) (2) intravenous administration of fasudil hydrochloride (51.3%), (3) intravenous administration of sodium ozagrel, a thromboxane A2 (TXA2) synthetase inhibitor (34.6%),\(^{(29)}\) and (4) triple-H (hypervolemia, hemodilution, and hypertension) therapy (27.1%) \[Figure 5a\].\(^{(22,25)}\) The criteria used to indicate treatment for cerebral ischemia caused by CV were (1) angiographic vasospasm in large extraparenchymal arteries with or without SVS (26.1%), (2) appearance of SVS (60.2%), and (3) new LDA on CT scans associated with CV (7.1%), and other criteria (6.6%) \[Figure 5b\].

Endovascular treatment for vasospasm
Endovascular treatment for vasospasm was performed in most hospitals (78.7%). Treatment modalities or vasodilatory agents included (1) intra-arterial injection of fasudil hydrochloride (84.1%),\(^{(21,28)}\) (2) balloon angioplasty (55.4%),\(^{(21)}\) (3) intra-arterial injection of papaverine...
hydrochloride (38.6%),[18,21] and (4) intra-arterial injection of calcium channel blockers (7.4%) [Figure 6a].[1,21] The criteria used to indicate endovascular treatment for vasospasm were (1) angiographic vasospasm in large extraparenchymal arteries with or without SVS (19.5%), (2) angiographic vasospasm in large extraparenchymal arteries with SVS (37.9%), and (3) aggressive therapy for angiographic and SVS was ineffective (41.4%), and (4) other criteria (1.1%) [Figure 6b].

**Discussion**

It is clear from the results of this survey that there is no consensus among Japanese hospitals on the criteria for diagnosis of SVS. Since standardized care for CV requires accurate diagnostic criteria for SVS, we proposed a clinical definition of SVS based on the results of this survey at the 25th Spasm Symposium (Stroke 2009) in Japan. This definition (Consensus 2009) was approved and is as follows: (1) the presence of neurological worsening including focal deficit, decline in level of consciousness, and motor paresis; (2) no other identifiable cause (intracranial disorder and systemic complication) of neurological worsening; and (3) confirmation of vasospasm by medical examinations including evidence of vasospasm on cerebral angiography, 3D-CTA, and MRA; new LDA on CT scans associated with CV; reduced CBF; and elevation of mean blood flow velocity in the cerebral arteries using TCD ultrasonography. Symptoms of worsening headache, low-grade fever, and elevation of blood pressure are included as reference information since these are not necessarily ischemic symptoms. For patients in whom subtle changes are difficult to detect in a neurological examination, we recommend using a medical examination (with diffusion- and perfusion-weighted MRI, if possible) to identify patients with an ischemic condition. In addition, we are planning to perform a further prospective study of the incidence of SVS in SAH patients in Japan based on the Consensus 2009 criteria.

The results of this survey indicated no major differences in prophylactic treatment of CV among the hospitals. Treatment including volume control, blood pressure control, treatment of CSWS, and intravenous administration of fasudil hydrochloride were common. In a placebo-controlled, double-blind trial,[20,26,27] fasudil hydrochloride, a Rho-kinase inhibitor, significantly reduced the incidences of angiographically demonstrated CV after SAH by 38% (from 61% in the placebo group to 38% in the fasudil hydrochloride group), LDA on CT by 58% (from 38 to 16%), and SVS by 30% (from 50 to
than hypertensive therapy. These results indicate that control is achieved with normotensive therapy, rather than hypervolemic therapy, and blood pressure predominantly achieved using normovolemic therapy, CV in Japan. Currently, volume control in Japan is case that statins have added to standard therapy for CV. From the results of this survey, it is not necessarily the whether the use of these agents are effective for CV. pleiotropic effects of statins in acute SAH have not been vasodilation by upregulating eNOS.

Recently, there has been increasing interest in the use of this drug is commonly used for suppression of CV. treatment of CV are covered by health insurance, and hydrochloride (dose of 60 mg per day) for prophylactic administration of fasudil, a free radical scavenger, and sodium ozagrel, a TXA2 synthetase inhibitor; Edaravone (3-methyl-1-phenyl-2-pyrazolin-5-one) is a potent free radical scavenger that is widely used in Japan to improve functional outcomes in patients with acute ischemic stroke. Oxyhemoglobin released from a subarachnoid clot may be a key substance that evokes free radical reactions such as peroxide production. Thus, scavenging of free radicals in the subarachnoid space may ameliorate CV, and intravenous edaravone is widely used for treatment of cerebral ischemia caused by CV in Japan. In a randomized study, edaravone reduced the incidence of cerebral ischemia by 50% (from 21% in the control group to 10% in the edaravone group). The results of this survey indicate that treatment for cerebral ischemia was given mainly in cases with appearance of SVS, and that prophylactic treatment of CV was continued in cases with angiographic vasospasm in large extraparenchymal arteries without symptoms.

Cisternal drainage has been used in Japan to eliminate residual clot after surgical removal since the late 1980s. The results of this survey show that a CSF drain was placed during the vasospasm period after neck clipping or coil embolization in most hospitals. A cisternal drain was mainly used after neck clipping, and a lumbar drain was used after coil embolization. CSF drainage from the lateral ventricles is more likely to contribute to stasis of hemorrhage within the subarachnoid spaces, compared to drainage from a cisternal or lumbar drain. Therefore, in Japan, an external ventricular drain is mainly used in patients with clinical features of elevated intracranial pressure (ICP) to allow control of ICP.

The Fisher CT scale is the most common method for assessment of SAH on CT scans and for predicting SVS after SAH. However, significant differences in Fisher group criteria for patients with ICH or IVH were found among hospitals. SAH patients with ICH or IVH were almost evenly classified into two groups: (1) Fisher group 4 for all SAH patients with ICH or IVH and (2) Fisher group 1, 2, or 3 with ICH/IVH based on SAH that met the Fisher criteria for patients with subarachnoid clot. The Fisher CT scale is incomplete in its description because it does not allow classification of patients with ICH or IVH based on Fisher group 3 SAH, which is commonly seen in clinical practice. The majority of current evidence seems to support the suggestion that the presence of significant IVH is also a risk factor for vasospasm, and other classification schemes based on CT scans, such as the modified Fisher scale, are required to stratify the risk of vasospasm more.

535%), and decreased the number of patients with a poor clinical outcome associated with vasospasm (moderate disability or worse on the Glasgow Outcome Scale at 1 month after SAH) by 54% (from 26 to 12%). In Japan, the medical costs of intravenous administration of fasudil hydrochloride (dose of 60 mg per day) for prophylactic treatment of CV are covered by health insurance, and this drug is commonly used for suppression of CV. Recently, there has been increasing interest in the use of statins for the prevention of CV. Statins improve endothelial function and blood flow by reducing vascular inflammation, inhibiting vascular smooth muscle cell proliferation and platelet aggregation, and promoting vasodilation by upregulating eNOS. Thus far, the pleiotropic effects of statins in acute SAH have not been evaluated clinically, and there is still controversy as to whether the use of these agents are effective for CV. From the results of this survey, it is not necessarily the case that statins have added to standard therapy for CV in Japan. Currently, volume control in Japan is predominately achieved using normovolemic therapy, rather than hypervolemic therapy, and blood pressure control is achieved with normotensive therapy, rather than hypertensive therapy. These results indicate that prophylactic treatment of CV with the so-called triple-H therapy has been modified in Japan.

The main therapies for cerebral ischemia caused by CV included intensive therapies such as intravenous administration of edaravone, a free radical scavenger, fasudil hydrochloride, and sodium ozagrel, a TXA2 synthetase inhibitor; Edaravone (3-methyl-1-phenyl-2-pyrazolin-5-one) is a potent free radical scavenger that is widely used in Japan to improve functional outcomes in patients with acute ischemic stroke. Oxyhemoglobin released from a subarachnoid clot may be a key substance that evokes free radical reactions such as peroxide production. Thus, scavenging of free radicals in the subarachnoid space may ameliorate CV, and intravenous edaravone is widely used for treatment of cerebral ischemia caused by CV in Japan. In a randomized study, edaravone reduced the incidence of cerebral ischemia by 50% (from 21% in the control group to 10% in the edaravone group). The results of this survey indicate that treatment for cerebral ischemia was given mainly in cases with appearance of SVS, and that prophylactic treatment of CV was continued in cases with angiographic vasospasm in large extraparenchymal arteries without symptoms.

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accurately. Then, we are planning further prospective study about the relation of SVS to the extent and location of subarachnoid blood visualized by CT scan.

Our survey indicates that endovascular treatment for vasospasm was performed safely and that intra-arterial injection of fasudil hydrochloride was the most common treatment modality and vasodilatory agent. Endovascular treatment is recommended in the Guidelines for the Management of CV (Class II b, Level of Evidence B), but the criteria used to indicate endovascular treatment for vasospasm are not well defined. Indeed, the results of this survey show that these criteria are not standardized in Japan, and further studies are required to establish the criteria for indication of endovascular treatment for vasospasm based on the clinical outcome.

CONCLUSIONS

In this study, we established a clinical definition of SVS, which we refer to as Consensus 2009. In Japan, most hospitals provide similar treatment for CV, but with significant differences in Fisher group criteria for patients with ICH or IVH, and in the criteria used to indicate endovascular treatment for vasospasm. This survey has several limitations. First, although the respondents were given space for open comments, they were mainly constrained by the questionnaire design (respondents chose from a list of possible choices). Second, although the response rate of 58.0% was acceptable compared to other studies, there may also have been a nonresponse bias since we do not have information from 42.0% of the targeted hospitals. We conclude that future studies should address establishment of criteria for diagnosis and treatment of SVS based on clinical outcome. A prospective study of the diagnosis, incidence, and treatment of SVS in SAH patients in Japan based on the Consensus 2009 criteria and the modified Fisher scale is now being conducted by our group.

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