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Original Article

Serum Sodium Levels to Predict Endovascular Treatment-Needed Vasospasm Following Low-Grade Aneurysmal Subarachnoid Hemorrhage: A Retrospective Multicenter Study

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Objective: Symptomatic vasospasm (SVS) affects the outcomes of patients with subarachnoid hemorrhage (SAH) and often requires endovascular treatment. Hyponatremia is a predictor of SVS; however, no guidelines have recommended an absolute serum sodium value for SVS prevention. This study aimed to identify factors that influence SVS in patients with low-grade SAH and determine a specific threshold of serum sodium level that predicts SVS.

Methods: We conducted a multicenter, retrospective study of 216 patients with aneurysmal SAH grades I–III (World Federation of Neurological Societies scale). Patients were divided into the endovascular treatment-needed vasospasm (etVS) group (n = 29) and non-etVS group (n = 187). The minimum serum sodium level (minNa) was determined in the initial 2 weeks after SAH onset.

Results: The minNa of the etVS group (median 132 mmol/L) was significantly lower compared to that of the non-etVS group (median 136 mmol/L) (p <0.001). The receiver operating characteristic curve revealed that a threshold minNa of 133 mmol/L predicted the development of etVS (sensitivity 0.797 and specificity 0.552), and the area under the curve was 0.703 (95% confidence interval [CI]: 0.591–0.815). The odds ratios for etVS in patients with a minNa ≤128 mmol/L and 129–132 mmol/L were 6.79 (95% CI: 2.24–20.51) and 2.96 (95% CI: 0.90–9.73), respectively, when compared to those with a minNa 133–136 mmol/L.

Conclusion: Serum sodium levels were a predictor of etVS in patients with low-grade SAH. This is the first study to identify a threshold of serum sodium level for predicting etVS, aiding clinicians in setting a management goal for SVS prevention.

Keywords endovascular treatment-needed vasospasm, hyponatremia, serum sodium level, subarachnoid hemorrhage, symptomatic vasospasm

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Introduction

Symptomatic vasospasm (SVS) is an important factor affecting the outcome of aneurysmal subarachnoid hemorrhage (SAH), affecting 15%–37% of patients.[1–3] The prevention and prediction of SVS is crucial, as it also often requires endovascular treatment.[4–6] Previous studies have found several predictors of SVS, including hyponatremia,[2,7,8] SAH thickness,[9,10] and cerebrospinal drainage.[11–13] Hyponatremia has been reported in 25%–39% of patients with SAH.[1,7,14–16] Despite this incidence rate, no recommendation regarding the absolute serum sodium level to prevent SVS is outlined in the American Heart Association/American Stroke Association or the

European Stroke Organization guidelines. Therefore, we believe that defining a threshold of the serum sodium level would help predict SVS in patients with SAH.

This multicenter retrospective study aimed to clarify the relationship between hyponatremia and SVS in patients with SAH. Additionally, we aimed to define the ideal serum sodium level required for SVS prevention. This study included patients with low-grade SAH since the symptoms of vasospasm (VS) are difficult to recognize in the presence of disturbed consciousness or neurological deficits.

Materials and Methods

Study design and patient selection

We conducted a multicenter, retrospective study of 216 patients with aneurysmal low-grade SAH, which was defined as grades I–III according to the World Federation of Neurological Societies (WFNS) scale, who were admitted to X1 Hospital, X2 Hospital, and X3 Hospital between January 2011 and December 2020. We excluded high-grade SAH patients because symptoms may not be fully detectable. A total of 224 records were analyzed, and patients with an SAH caused by a ruptured saccular aneurysm confirmed with 3-dimensional computed tomography angiography (3D-CTA) or digital subtraction angiography (DSA) were included in the study. We excluded patients under 20 years of age, those who died from causes other than VS, or those who were discharged in less than 2 weeks after SAH onset. The ethics institutional review board of Osaka University approved the study (approval number 19486); furthermore, the requirement for informed consent was waived due to the retrospective nature of the study.

Figure 1 illustrates the flow of patient selection. During the study period, 224 patients with low-grade aneurysmal SAH were admitted to the 3 hospitals. Among them, 8 patients were excluded; 2 were <20 years of age, 2 were discharged before sufficient follow-up during the VS period, and 4 died from causes other than VS within 2 weeks after SAH onset. Therefore, 216 patients were included in the final analysis comprising 71 men, and 145 women. The median age at onset was 63 years (mean, 62 years; range, 25–93 years).

Outcomes

The primary outcome was defined as the endovascular treatment-needed vasospasm (etVS). At all institutions, endovascular treatment was performed in case of stenosis with symptoms, severe stenosis >67%,[17] or flow stagnation associated with the stenosis. The methods of endovascular treatment for SVS included intra-arterial fasudil hydrochloride injection and percutaneous transluminal angioplasty (PTA). Moreover, the secondary outcomes included the duration of hospital stay and the modified Rankin Scale (mRS) score at the time of discharge.

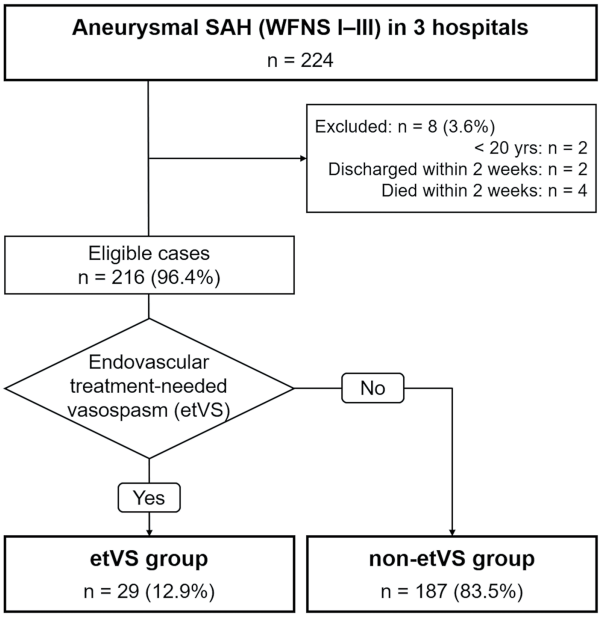

Fig. 1 A flowchart of patient selection and classification. SAH, subarachnoid hemorrhage; WFNS, World Federation of Neurological Societies

Measurement and management of serum sodium levels

The serum sodium levels of all patients were examined on admission (adNa) and were monitored frequently throughout their hospitalization. We set a goal of managing serum sodium levels within the normal range by oral or intravenous sodium chloride supplementation and, in some patients, oral administration of fludrocortisone acetate. We reviewed and determined the minimum serum sodium level (minNa) of each patient during the initial 2 weeks after the onset of SAH.

Management protocol

All patients with SAH were managed in the intensive care unit or stroke care unit for at least 2 weeks after the onset of SAH. All ruptured aneurysms were treated with endovascular interventions or craniotomy surgery based on an interdisciplinary consensus. Large-sized SAH necessitated cerebrospinal fluid drainage and one or multiple external ventricular, cisternal, or lumbar drainage. All patients

remained normovolemic and normotensive. Nimodipine is not available in Japan; therefore, intravenous fasudil hydrochloride was administered prophylactically, which is recommended in the Japanese Guidelines for the Management of Stroke. Oral antiplatelet drugs, such as cilostazol, were administered in patients who underwent endovascular treatment for ruptured aneurysms. Transcranial Doppler ultrasonography was used to monitor VS; on the contrary, DSA, 3D-CTA, or magnetic resonance angiography were used to evaluate angiographic VS approximately 7 days after the onset of SAH in all patients.

Statistical analysis

All statistical analyses were performed using R 3.6.3 for Windows (www.R-project.org; R Foundation for Statistical Computing, Vienna, Austria). Categorical variables were examined using Fisher's exact test and presented as the frequency (percentages). Continuous variables were assessed using the Mann–Whitney U test and presented as the median and range. The thresholds were calculated by receiver operating characteristic (ROC) analysis using the Youden index. Odds ratios (ORs) were calculated using a simple logistic regression analysis. Statistical significance was set at $p < 0.05$.

Results

Overall patient cohort

The median time from SAH onset to admission was 0 days (mean, 1 day; range, 0–10 days). One patient developed SAH while hospitalized for another disease, which was considered 0 days. The median interval to check serum sodium levels was 1.5 days (mean, 1.6 days; range, 1.0–5.0 days), that is, almost daily in many cases. We divided the patients into 2 groups: the etVS (29 patients) and non-etVS group (187 patients). All etVS patients underwent intra-arterial fasudil hydrochloride administration; additionally, 4 patients underwent PTA. Of the etVS group, 23 (79%) were symptomatic.

Comparison of the etVS and non-etVS groups

Table 1 summarizes the characteristics of each group. A significant difference was observed regarding the minNa between the etVS (median, 132 mmol/L) and the non-etVS (median, 136 mmol/L) groups ($p < 0.001$, **Fig. 2A**). There was no significant difference between the 2 groups in terms of the adNa, gap between adNa and minNa, or interval to check serum sodium levels.

Threshold for predicting etVS and the association between etVS and minNa

The ROC curve revealed that a threshold of 133 mmol/L for minNa predicted the development of etVS with a sensitivity and specificity of 0.797 and 0.552, respectively. The positive and negative predictive values were 0.920 and 0.296, respectively. Additionally, the area under the curve was 0.703 (95% confidence interval [CI]: 0.591–0.815, **Fig. 2B**). The incidence of etVS increased drastically when the minNa was <133 mmol/L. The incidence of etVS in patients with a minNa ≤128 mmol/L, 129–132 mmol/L, 133–136 mmol/L, and ≥137 mmol/L were 38%, 21%, 8%, and 8%, respectively; and the ORs for etVS were 6.79 (95% CI: 2.24–20.51), 2.96 (95% CI: 0.90–9.73), 1 (reference), and 0.89 (95% CI: 0.29–2.78), respectively (**Fig. 2C**).

Comparison of two groups based on the minNa

Table 2 illustrates the differences between the groups with a minNa <133 mmol/L and minNa ≥133 mmol/L. The group with a minNa <133 mmol/L had a significantly longer hospital stay ($p = 0.004$) and worse mRS score at discharge ($p = 0.019$) than the group with minNa ≥133 mmol/L; however, no significant difference was observed in factors such as age or WFNS grade, which potentially affected the duration of hospitalization or mRS scores at discharge.

Day of development of the minNa and etVS

The median day for developing the minNa was 8 days (mean, 7.3 days; range, 0–14 days) after SAH onset with no difference between the etVS and non-etVS groups (**Table 1**). In the 29 patients with etVS, etVS occurred at 8 days (median) (mean, 8.4 days; range, 1–15 days) after the onset of SAH. A gap was observed between the days of developing the minNa and etVS onset; particularly, the minNa was developed earlier by a median of 1 day compared to the onset of etVS (mean, 0.7 days) (**Fig. 2D**). Moreover, among 16 patients with a minNa <133 mmol/L, the day when the serum sodium level first fell below 133 mmol/L (<133Na) preceded the day of etVS onset by a median of 1 day (mean, 1.6 days).

Serum sodium level on admission and etVS

In 7 patients, adNa levels were <133 mmol/L. Among them, 4 were admitted on the day of onset; the others were admitted 2, 7, and 10 days after onset, respectively. Among these 7 patients, 3 who were (43%) admitted at 0, 7, and

Table 1 Patient characteristics based on etVS

Variable n (%)/median (range)*	etVS n = 29 (13.4%)	Non-etVS n = 187 (86.6%)	*p* Value
Baseline characteristics			
Age (y)	60 (36–84)*	64 (25–93)*	0.915
Sex (male)	9 (31.0)	62 (33.2)	1
Onset to admission (day)	0 (0–10)*	0 (0–9)*	0.238
Aneurysm location (anterior circulation)	28 (96.6)	175 (93.6)	1
WFNS grade			1
I	15 (51.7)	99 (52.9)	
II	11 (37.9)	69 (36.9)	
III	3 (10.3)	19 (10.2)	
Hunt and Kosnik grade			0.867
I	14 (48.3)	80 (42.8)	
II	10 (34.5)	74 (39.6)	
III	5 (17.2)	33 (17.6)	
Fisher group			0.318
1	2 (6.9)	3 (1.6)	
2	4 (13.8)	31 (16.6)	
3	23 (79.3)	148 (79.1)	
4	0 (0)	5 (2.7)	
Patient history			
Hypertension	12 (41.4)	81 (43.3)	1
Diabetes mellitus	1 (3.4)	13 (7.0)	0.699
Dyslipidemia	2 (6.9)	25 (13.4)	0.545
Past subarachnoid hemorrhage	2 (6.9)	8 (4.3)	0.627
Smoking	2 (6.9)	19 (10.2)	0.747
Family history			
Subarachnoid hemorrhage	0 (0)	5 (2.7)	1
Treatment			
Aneurysm treatment modality			0.548
Endovascular	18 (62.1)	102 (54.5)	
Craniotomy	11 (37.9)	85 (45.5)	
Cerebrospinal fluid drainage	22 (75.9)	128 (68.4)	0.519
Intravenous fasudil hydrochloride	27 (93.1)	174 (93.0)	1
Intravenous ozagrel sodium	12 (50.0)[1]	64 (39.5)[2]	0.377
Oral antiplatelet drug	23 (79.3)	151 (80.7)	0.805
Statin	11 (37.9)	78 (41.7)	0.840
Serum sodium level			
adNa (mmol/L)	139 (127–149)*	140 (127–147)*	0.138
minNa (mmol/L)	132 (119–139)*	136 (115–145)*	<0.001
Onset to minNa (day)	9 (0–14)*	8 (0–14)*	0.496
Gap between adNa and minNa (mmol/L)	5 (0–21)*	4 (0–22)*	0.092
Interval to check serum sodium level (day)	1.4 (1.0–2.5)*	1.5 (1.0–5.0)*	0.175

[1]Five missing values
[2]Twenty-five missing values
adNa, serum sodium level on admission; etVS, endovascular treatment-needed vasospasm; minNa, minimum serum sodium level in the initial 2 weeks from the onset of subarachnoid hemorrhage; WFNS, World Federation of Neurosurgical Societies

10 days developed etVS. By contrast, among 208 patients with an adNa ≥133 mmol/L, 26 developed etVS. The incidence of etVS was higher in patients with an adNa <133 mmol/L compared to those with an adNa ≥133 mmol/L ($p = 0.053$).

Discussion

This study identified factors related to etVS in patients with low-grade SAH; additionally, we determined the threshold of serum sodium levels to predict etVS. This

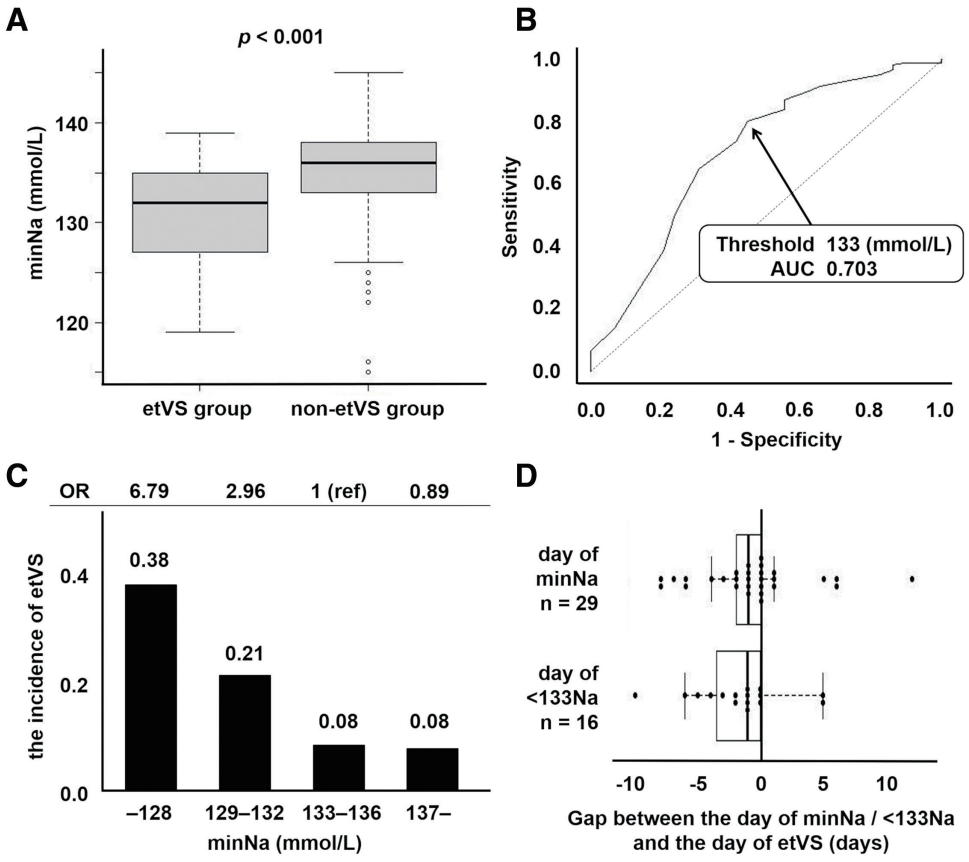

Fig. 2 Comparison of the etVS and non-etVS groups. (**A**) Box-and-whisker plots representing the minNa of the etVS group and non-etVS group during the initial 2 weeks after the onset of subarachnoid hemorrhage. The median minNa of the etVS and non-etVS groups was 132 mmol/L and 136 mmol/L, respectively. *p*-Value for the Mann–Whitney U test: <0.001. (**B**) The ROC curve for detecting patients with etVS based on the minNa. Threshold for minNa: 133 mmol/L. Sensitivity: 0.797. Specificity: 0.552. Area under the curve: 0.703 (95% CI: 0.591–0.815). (**C**) The incidence of etVS and ORs based on the minNa. The incidence of etVS increased drastically when the minNa was <133 mmol/L. (**D**) Box-and-whisker plots representing a gap between the day of developing the minNa or the day when the serum sodium level first fell below 133 mmol/L (<133Na) and the day of etVS onset. The minNa was demonstrated earlier by a median of 1 day compared to etVS (mean, 0.7 days); additionally, the day when the serum sodium level first fell below 133 mmol/L (<133Na) preceded the day of etVS onset by a median of 1 day (mean, 1.6 days). CI, confidence interval; etVS, endovascular treatment-needed vasospasm; minNA, minimum serum sodium level; ORs, odds ratios; ROC, receiver operating characteristic

may allow clinicians to manage the serum sodium levels of patients with SAH after the initial 2 weeks of onset for SVS prevention.

Hyponatremia secondary to SAH is a complex condition involving multiple pathologies, including the syndrome of inappropriate antidiuretic hormone secretion and cerebral salt wasting syndrome.[18] Some studies have shown that hyponatremia is induced by elevated levels of serum atrial natriuretic peptide,[16] serum brain natriuretic peptide,[19] or both.[20] However, the mechanism of hyponatremia remains unelucidated.

Hyponatremia can decrease plasma osmolarity,[21,22] leading to decreased extracellular fluid volume, which results in the worsening of VS.[23,24] Intravascular hypovolemia may occur in patients with SAH despite normal hemodynamic indices, such as heart rate and blood pressure.[25] Therefore, treatment of hyponatremia and appropriate fluid management are necessary to maintain intravascular fluid volume. This study found a correlation between etVS and hyponatremia (**Table 1**); additionally, we found an inverse relationship between the minNa and etVS risk (**Fig. 2C**). Furthermore, we confirmed that hyponatremia preceded SVS (**Fig. 2D**), similar to the findings of a previous study.[2] Therefore, appropriate hyponatremia management may be significant for SVS prevention.

In this study, we investigated the relationship between hyponatremia and etVS. We used etVS instead of SVS because patients with severe angiographic VS receive treatment despite being asymptomatic. Angiographic VS patients may be overtreated; however, the incidence of etVS was not higher compared to that observed in previous reports of SVS.[1–3]

Table 2 Patient characteristics and outcome based on minNa

Variable n (%)/median (range)*	minNa		*p* Value
	<133 mmol/L n = 54 (25.0%)	≥133 mmol/L n = 162 (75.0%)	
Baseline characteristics			
Age (y)	65 (36–93)*	62 (25–89)*	0.147
Sex (male)	22 (40.7)	49 (30.2)	0.181
Onset to admission (day)	0 (0–10)*	0 (0–9)*	0.557
Aneurysm location (anterior circulation)	51 (94.4)	151 (93.2)	0.525
WFNS grade			0.472
I	25 (46.3)	89 (54.9)	
II	23 (42.6)	57 (35.2)	
III	6 (11.1)	16 (9.9)	
Hunt and Kosnik grade			0.348
I	21 (38.9)	73 (45.1)	
II	20 (37.0)	64 (39.5)	
III	13 (24.1)	25 (15.4)	
Fisher group			0.655
1	2 (3.7)	3 (1.9)	
2	8 (14.8)	27 (16.7)	
3	42 (77.8)	129 (79.6)	
4	2 (3.7)	3 (1.9)	
Treatment			
Aneurysm treatment modality			0.874
Endovascular	31 (57.4)	89 (54.9)	
Craniotomy	23 (42.6)	73 (45.1)	
Endpoint			
etVS	16 (29.6)	13 (8.0)	<0.001
Duration of hospital stay (day)	36 (18–111)*	27 (14–197)*	0.004
Modified Rankin Scale at discharge			0.019
0–2	29 (53.7)	116 (71.6)	
3–6	25 (46.3)	46 (28.4)	

etVS, endovascular treatment-needed vasospasm; minNa, minimum serum sodium level in the initial 2 weeks from the onset of subarachnoid hemorrhage; WFNS, World Federation of Neurosurgical Societies

This study found that hyponatremia may affect hospitalization duration and poor prognosis at discharge (**Table 2**), which is similar to previous studies.[18,26,27] Furthermore, a previous study reported that the incidence of SVS was 6.1%, and 69.6% of patients had a good prognosis (mRS score: 0–2) at 1 month after the SAH onset by setting the target of serum sodium level >140 mmol/L.[28] Hence, a more aggressive and strict control of serum sodium levels may be more critical than most clinicians currently hypothesize. Therefore, further prospective studies are required.

In addition to hyponatremia, the incidence of SVS depends on the difference in treatment modalities and the presence of cerebrospinal fluid drainage.[9,11–13] However, no studies have clarified the mechanism for reducing SVS; additionally, some studies investigating low-grade SAH are controversial (WFNS grade I–III).[3,29] Therefore, further studies should focus on patients whose neurological symptoms can be easily assessed.

This study had several limitations. First, this was a multicenter retrospective study; additionally, no standardized treatment method for hyponatremia and indication criteria for endovascular treatment for SVS were strictly established. Second, the exact pathology of hyponatremia and the mechanisms of VS onset remain unknown. Therefore, hyponatremia may have been an incidental parameter of VS, and other factors potentially triggered it. Third, some patients were hospitalized a few days after the onset. These patients may develop the minNa early, and some may have hyponatremia even before the onset; however, we believe that the importance of management of serum sodium levels is unquestionable. Fourth, etVS was not strictly equal to SVS; therefore, some patients with severe angiographic VS on follow-up were treated, even if they

were asymptomatic. On the other hand, some patients may not have been given endovascular treatment for some reason. Finally, this study examined mRS at discharge, and the impact of hyponatremia on long-term prognosis, such as mRS at 90 days, may be altered.

Conclusion

Our study revealed a clear relationship between hyponatremia and etVS in patients with low-grade SAH; furthermore, the threshold of serum sodium level for predicting etVS was established. This study may provide clinicians with an ideal serum sodium level to prevent etVS in the initial 2 weeks while managing patients with aneurysmal SAH.

Data Availability

The anonymized data that support the findings of this study are available from the corresponding author upon reasonable request.

Disclosure Statement

The authors declare that they have no conflicts of interest.

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