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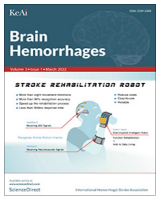

Research Article

Initial results of clazosentan with multiple-drug management for the prevention of cerebral vasospasm after aneurysmal subarachnoid hemorrhage

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ABSTRACT

Objective: Cerebral vasospasm is an unelucidated complication of subarachnoid hemorrhage. Various treatments exist against cerebral vasospasms however, consensus on the optimal treatment is lacking. We use clazosentan, which is used to prevent cerebral vasospasm, with multidrug combinations. In this study, we aimed to clarify the initial results of using clazosentan in multidrug combinations in the real world.

Methods: We retrospectively investigated 54 patients who were treated for subarachnoid hemorrhage and received clazosentan. We compared the results of these patients on the basis of two groups: those with good outcomes (modified Rankin scale score: 0–3) and poor outcomes (4–6) at discharge.

Results: Among the patients, poor outcome was observed in 19 patients (35.2 %). Angiographic vasospasms occurred in 10 patients (good outcome [n = 6] vs. poor outcome [n = 4]; p = 0.73), and symptomatic vasospasms occurred in 4 patients (n = 2 vs. n = 2, p = 0.61). The incidence of pleural effusion (28.6 % vs. 73.7 %, p < 0.01) and the mean daily fluid balance (303.5 mL/day vs. 785.4 mL/day, p < 0.01) were higher in the poor outcome group.

Conclusion: Pleural effusion and high positive balance may be associated with poor outcome. However, the number of cases examined was small; therefore, further large-scale studies with a bigger sample size are needed.

1. Introduction

Cerebral vasospasm is an unelucidated complication of subarachnoid hemorrhage (SAH) and a major cause of serious disability and death. However, the exact mechanism of this complication is unclear. Previous studies have reported a cerebral vasospasm incidence of more than 49 % in people who experienced SAH.[1] In addition, the incidence of angiographic vasospasm (AV) is reported to be 53 %, and symptomatic vasospasm (SV) is 16–28 %.[2,3] Although there is no consensus on the best existing prophylactic methods, a recent Japanese multicenter study demonstrated the efficacy of clazosentan. In this study, clazosentan, an endothelin A receptor antagonist, was found to significantly reduce morbidity and all-cause mortality associated with cerebral vasospasm.[4] On the basis of this result, clazosentan was approved in Japan in January 2022 and has been used at our institution as an addition to the existing multidrug treatment. This study was conducted to evaluate the initial results of adding clazosentan to this therapeutic regimen in patients with aneurysmal SAH.

2. Methods

2.1. Patient selection

We retrospectively reviewed the medical records of 63 patients who underwent surgical treatment for aneurysmal SAH at our institution between May 2022 and April 2023. A total of 54 patients (excluding 9 of 63 patients) for whom clazosentan was used to prevent postoperative cerebral vasospasm were included in the study. Patients treated after day 14 (n = 3), those who died before day 4 from SAH onset (n = 3), and those with causes other than de novo cerebral aneurysms (n = 2) were excluded. One

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patient who did not receive clazosentan was also excluded from the study. The exclusion criteria are shown in Fig. 1. This study was approved by the Institutional Review Board of Saitama Medical University International Medical Center. (institutional review board: 2023–116). Informed consent was waived because of the retrospective design of the study.

2.2. Data extraction

The following patient characteristics were analyzed: age, sex, Fisher group, World Federation of Neurosurgical Societies (WFNS) grade, intracranial aneurysmal size (maximum diameter), aneurysm location, creatinine level at admission, and comorbidities documented before surgery. Hypertension was defined as a history of systolic blood pressure $\geq$ 140 mm Hg or previous use of antihypertensive medication. Dyslipidemia was defined as a serum low-density lipoprotein cholesterol $\geq$ 140 mg/dL on admission or previous use of antihyperlipidemia medication. Diabetes mellitus was defined as hemoglobin A1c level $\geq$ 6.5 % on admission or previous use of medications for diabetes mellitus. Blood sample data, including minimum albumin, maximum sodium, and minimum hematocrit, were also evaluated for association with poor outcomes on the basis of previous studies showing such an association.[5,6,7] Average daily fluid balance, treatments administered for cerebral vasospasm, and modified Rankin Scale (mRS) scores at discharge were also determined. The mRS score was classified into two categories: 0–3 as a good outcome and 4–6 as a poor outcome.

2.3. Procedures and patient follow-up

During surgical clipping, we placed ventricular drainage to modify intracranial pressure and provide surgical space. Additionally, cisternal drainage was performed for postoperative continuous cisternal irrigation.[8] Only ventricular drainage was used for endovascular treatments. AV was defined as internal artery narrowing of 34 % or greater on the basis of digital subtraction angiography, 3D computed tomography angiography, or magnetic resonance angiography images as previously described.[4] We investigated fluid balance, urine volume, and blood values during clazosentan dosing. Fluid balance was observed every 8 h. When the fluid balance was greater than 500 mL/8h, 20 mg of furosemide was administrated intravenously. When the fluid balance was minus 500 mL/8h, an additional 500 mL of saline was administered. In addition, 240 mL of red blood cell product was administered when blood data showed that the Hb level was less than 10, and albumin products were administered when blood tests showed albumin less than 3.0 g/dL. Pleural effusion and edema were diagnosed based on chest radiography or computed tomography images. Pulmonary edema was defined as the presence of bilateral butterfly shadows on chest radiography. According to the available evidence, our strategy to prevent cerebral vasospasm included a comprehensive treatment with multiple proven drugs and procedures comprising 1) fasudil, [9,10] which is a Rho-kinase inhibitor; two antiplatelet agents, namely, the thromboxane synthase inhibitor ozagrel sodium[11] and cilostazol,[12] which is a selective phosphodiesterase 3 inhibitor; atorvastatin[13]; cerebral cisternal irrigation with magnesium-containing artificial cerebrospinal fluid; and intraoperative local application of papaverine on the artery near the ruptured aneurysm.[8,14] Ozagrel sodium was not used in the endovascular treatment. The protocol for treating cerebral vasospasms at our institution is shown in Fig. 2. Treatments were discontinued at the discretion of the physicians in case of adverse events. In the case of hemorrhagic complications, we simultaneously discontinued clazosentan, fasudil hydrochloride hydrate, ozagrel sodium, cilostazol, and statin, which may contribute to bleeding. Clazosentan was also discontinued in cases of progressive fluid retention, as in pulmonary edema.

2.4. Statistical analyses

Demographic and clinical characteristics were compared between the groups via univariate analysis by using Chi-squared tests, Fisher's exact test, Student's *t*-test, and the Mann–Whitney *U* test. $P < 0.05$ was considered statistically significant. All statistical analyses were performed using EZR version 1.55 (Saitama Medical Center, Jichi Medical University, Saitama, Japan).

3. Results

During the study period, 54 patients underwent clazosentan treatment for cerebral vasospasm. Patient characteristics are

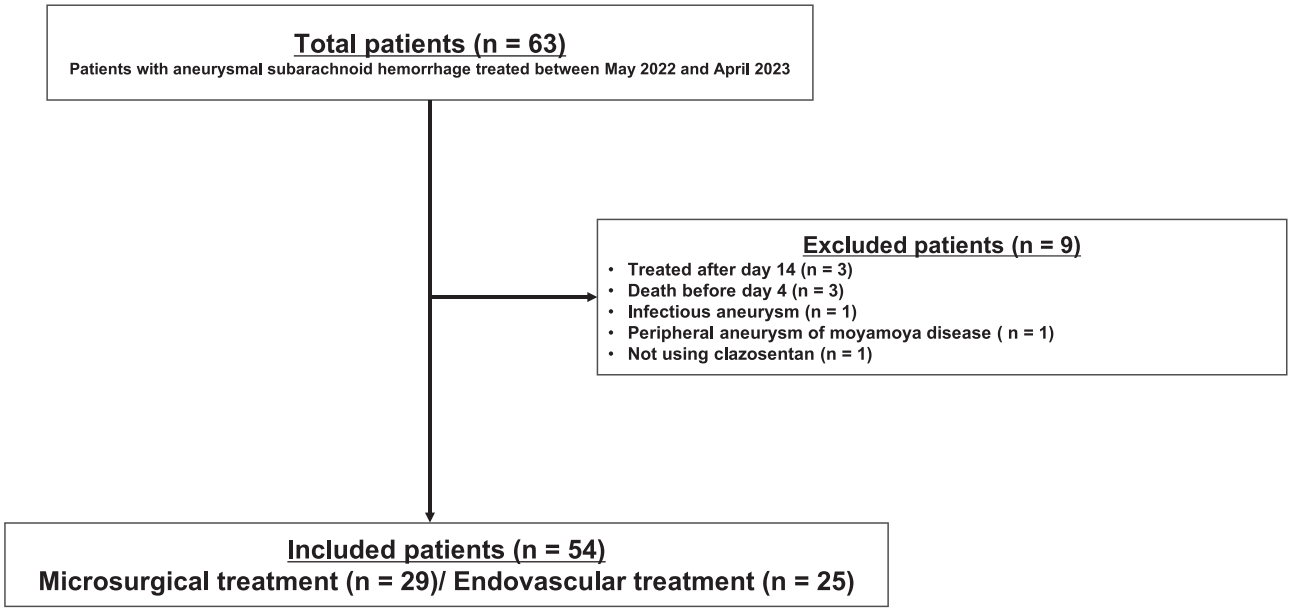

Fig. 1. Flow diagram summarizing cases included in the study.

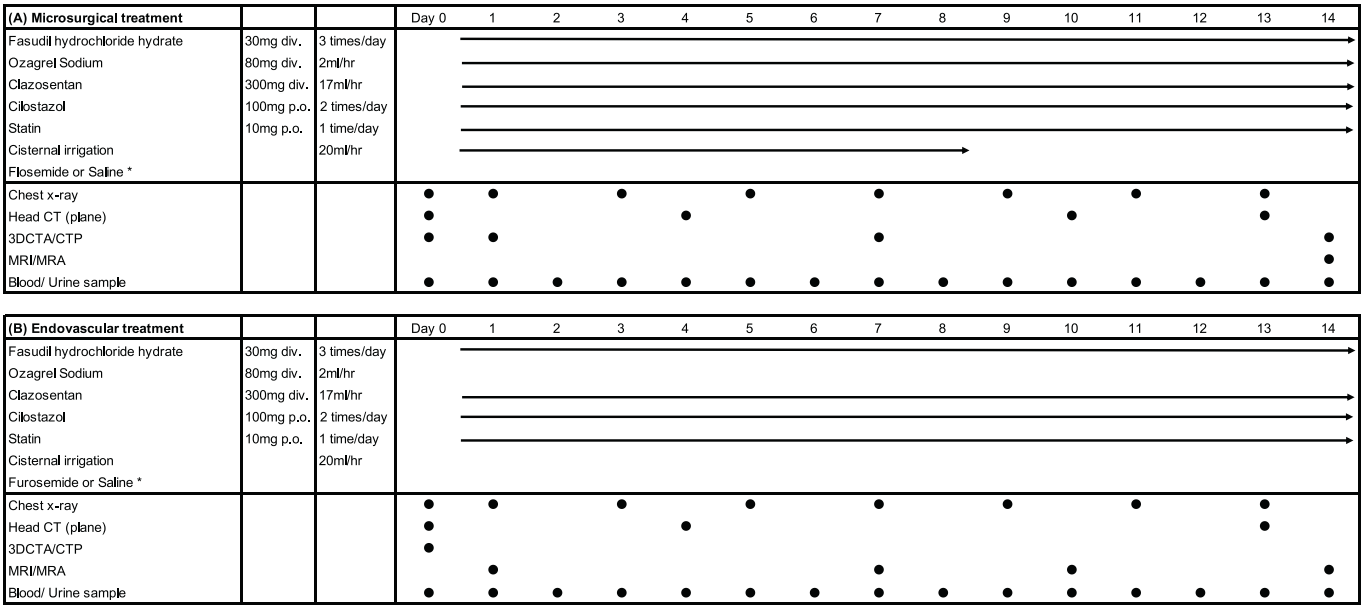

Fig. 2. Treatment protocols for vasospasm in our institution (A) Microsurgical treatment, (B). Endovascular treatment.

shown in Table 1. The mean age of patients was 62.4 years, and 35 (64.8 %) were female. A medical history of hypertension was present in 25 patients (46.3 %), diabetes in 4 patients (7.4 %), and hyperlipidemia in 12 patients (22.2 %). WFNS grades on admission were severe (grades 4–5) in 20 patients (37.0 %), and Fisher group 3 was identified in 41 patients (75.9 %). The anterior communicating artery was the most common aneurysm site, accounting for 18 cases (33.3 %), followed by the middle cerebral artery in 14 cases (25.9 %). A total of 29 patients (53.7 %) received microsurgical treatment, and 25 (46.3 %) received endovascular treatment. Poor outcome at discharge was observed in 19 patients (35.2 %).

In the group with poor outcomes, the mean age was significantly higher (good outcome: 57.8 years vs. poor outcome: 71.0 years, $p < 0.01$) and the WFNS grade was more severe on admission ($p < 0.01$). There were no significant differences in sex (60.0 % vs. 73.7 %, $p = 0.38$) or presence of hypertension (37.1 % vs. 63.2 %, $p = 0.09$), diabetes mellitus (5.7 % vs. 10.5 %, $p = 0.61$), or hyperlipidemia (22.2 % vs. 21.9 %, $p = 0.73$). The imaging findings

Table 1
Baseline characteristics of patients with aneurysmal subarachnoid hemorrhage at admission.

	Total n = 54	Good outcome n = 35	Poor outcome n = 19	P value
Age, y, mean (SD)	62.4 (±15.1)	57.8 (±12.7)	71.0 (±15.7)	< 0.01
Female sex, n (%)	35 (64.8 %)	21 (60.0 %)	14 (73.7 %)	0.38
Comorbidities, n (%)				
Hypertension	25 (46.3 %)	13 (37.1 %)	12 (63.2 %)	0.09
Diabetes mellitus	4 (7.4 %)	2 (5.7 %)	2 (10.5 %)	0.61
Hyperlipidemia	12 (22.2 %)	7 (20.0 %)	5 (26.3 %)	0.73
WFNS grade, n (%)				< 0.01
I	22 (40.7 %)	21 (60.0 %)	1 (5.3 %)	
II	12 (22.2 %)	8 (22.9 %)	4 (21.1 %)	
III	0 (0 %)	0 (0 %)	0 (0 %)	
IV	10 (18.5 %)	5 (14.3 %)	5 (26.3 %)	
V	10 (18.5 %)	1 (2.9 %)	9 (47.4 %)	
Fisher group, n (%)				0.84
1	3 (5.6 %)	2 (5.7 %)	1 (5.3 %)	
2	9 (16.7 %)	7 (20.0 %)	2 (10.5 %)	
3	41 (75.9 %)	25 (71.4 %)	16 (84.2 %)	
4	1 (1.9 %)	1 (2.9 %)	0 (0 %)	
Size of aneurysms, mm, mean (SD)	5.8 (±3.1)	5.79 (±3.1)	5.88 (±3.27)	0.92
Location of the aneurysms, n (%)				0.21
ACA	3 (5.6 %)	2 (5.7 %)	1 (5.3 %)	
Acom	18 (33.3 %)	11 (31.4 %)	7 (36.8 %)	
ICA	10 (18.5 %)	4 (11.4 %)	6 (31.6 %)	
MCA	14 (25.9 %)	12 (34.3 %)	2 (10.5 %)	
Posterior circulation	9 (16.7 %)	6 (17.1 %)	3 (15.8 %)	
Microsurgical treatment	29 (53.7 %)	17 (48.6 %)	12 (63.2 %)	0.40

SD: standard deviation, WFNS: World Federation of Neurosurgical Societies, ACA: anterior cerebral artery, Acom: anterior communicating artery, ICA: internal carotid artery, MCA: middle cerebral artery.

Table 2
Treatments and outcomes of patients with aneurysmal subarachnoid hemorrhage.

	Total n = 54	Good outcome n = 35	Poor outcome n = 19	P value
Dosing period, days, mean (SD)				
Fasudil hydrochloride hydrate 90 mg/day	11.6 (±6.9)	11.6 (±7.8)	10.0 (±9.20)	0.41
Ozagrel sodium 80 mg/day	6.1 (±6.0)	5.6 (±6.0)	7.1 (±6.1)	0.38
Cilostazol 200 mg/day	11.1 (±4.5)	11.9 (±3.6)	9.6 (±5.5)	0.07
Atorvastatin calcium hydrate 10 mg/day	10.7 (±5.5)	10.8 (±5.5)	10.6 (±5.8)	0.93
Clazosentan sodium 300 mg/day	10.3 (±3.7)	11.0 (±3.1)	9.0 (±4.3)	0.05
Continuous cisternal irrigation, n (%)	20 (37.0 %)	10 (58.8 %)	10 (83.3 %)	0.23
Cerebral vasospasm, n (%)				
Symptomatic	4 (7.4 %)	2 (5.7 %)	2 (10.5 %)	0.61
Angiographic	10 (18.5 %)	6 (17.1 %)	4 (21.1 %)	0.73
Pulmonary edema, n (%)	11 (20.4 %)	5 (14.3 %)	6 (31.6 %)	0.17
Pleural effusion, n (%)	24 (44.4 %)	10 (28.6 %)	14 (73.7 %)	< 0.01
Blood exam during dosing clazosentan, mean (SD)				
Minimum Alb, g/dL	2.7 (±0.3)	2.8 (±0.3)	2.6 (±0.3)	< 0.01
Maximum Na, mEq/L	145.9 (±5.6)	144.7 (±4.3)	148.1 (±6.9)	0.03
Minimum HCT, %	27.8 (±3.3)	28.4 (±3.4)	26.6 (±2.8)	0.04
Average daily fluid balance, mL/day, mean (SD)	473.1 (±516.7)	303.5 (±425.1)	785.4 (±534.5)	< 0.01
Urine volume, mL/day, mean (SD)	2,622.1 (±906.9)	2,874.5 (±940.8)	2,157.1 (±630.6)	< 0.01
Red blood cell transfusion volume, mL, mean (SD)	293.4 (±416.5)	252.0 (±447.6)	369.6 (±350.6)	0.33
Albumin transfusion volume, mL, mean (SD)	283.1 (±295.5)	228.3 (±447.6)	383.9 (±315.4)	0.06

SD: standard deviation, mRS: modified Rankin Scale, Alb: albumin, max: maximum, min: minimum, HCT: hematocrit.

showed that there were no significant differences in the Fisher group (p = 0.84), aneurysm size (5.8 mm vs. 5.9 mm, p = 0.92), or aneurysm location (p = 0.21) between the two groups.

Postoperative course and management are shown in Table 2. Patients with a poor prognosis tended to be treated with clazosentan (11.0 days vs. 9.0 days, p = 0.05). There was no significant difference in the duration of treatment with fasudil (11.6 days vs. 10.0 days, p = 0.41), ozagrel (5.6 days vs. 7.1 days, p = 0.38), cilostazol (11.9 days vs. 9.6 days, p = 0.07), or atorvastatin (10.8 days vs. 10.6 days, p = 0.93) between the two groups. There was no significant difference in the patients who received continuous cisternal irrigation between the two groups (58.8 % vs. 83.3 %, p = 0.23). AV and SV occurred in 18.5 % and 7.4 % of patients, respectively, with no significant difference in either condition between the two groups (AV: 17.1 % vs. 21.1 %, p = 0.73; SV: 5.7 % vs. 10.5 %, p = 0.61). Pleural effusion was significantly more common in patients with poor outcomes (28.6 % vs. 73.7 %, p < 0.01), but there was no significant difference in pulmonary edema between the two outcome groups (14.3 % vs. 31.6 %, p = 0.17). In the postoperative blood sample data, the levels of minimum albumin (2.8 g/dL vs. 2.6 g/dL, p < 0.01) and minimum hematocrit were significantly lower in the poor outcome group. By contrast, the maximum sodium level was significantly higher in the poor outcome group (144.7 mEq/L vs. 148.1 mEq/L, p = 0.03). Finally, mean daily fluid balance was significantly higher in the poor outcome group (303.5 mL/day vs. 785.4 mL/day, p < 0.01), whereas urine volume was significantly lower in the poor outcome group (2,874.5 mL/day vs. 2,157.1 mL/day, p < 0.01). The mean red blood cell transfusion volume (252.0 vs. 369.6 mL, p = 0.33) and mean intravenous albumin volume (228.3 vs. 383.9 mL, p = 0.06) were not significantly different between the two groups.

4. Discussion

This study examined the real-world outcomes of adding clazosentan to a combination of multiple drugs to prevent cerebral vasospasms. AV and SV were present in 18.5 % and 7.4 % of the 54 patients examined, respectively. All patients with SV were in the endovascular treatment group. The study found that patients who were older and had more severe grades had poor outcomes. Postoperatively, poor outcomes were associated with pleural effusion, lower minimal albumin and hematocrit levels, and higher maximal sodium levels. Furthermore, a higher daily fluid balance was found to be associated with poor outcomes.

Cerebral vasospasm, which is a possible complication after SAH, can cause cerebral infarction. Several studies have been conducted to identify methods to prevent this complication and assess the effectiveness of the management approach and the drugs used. Previous studies have reported the effectiveness of ozagrel sodium, fasudil hydrochloride, continuous cisternal irrigation, cilostazol, and statins in preventing cerebral vasospasms.[9,11,12,14,15] However, management methods differ across facilities. When these drugs were used, the incidence rates of cerebral vasospasm, AV, and SV were 49.2 %,[1] 53.1 %, and 16.0 %–28.9 %, respectively.[2,3] A recent study showed that the incidence of cerebral vasospasm with single-agent clazosentan was 16.1 %.[4] In the current study, the incidence of SV was 7.4 % with the use of clazosentan in combination with multiple drugs, which is lower than that shown in existing reports.

As shown in the previous Phase III trial,[4] approximately 11 % of the patients have difficulty continuing clazosentan due to adverse events, such as pleural effusion or pulmonary edema. In our study, there were also cases of early discontinuation due to adverse events and because physicians aimed for early termination of intravenous infusion in elderly patients with low WFNS grades. In addition, the longer duration of treatment with clazosentan tended to be associated with good outcomes. Therefore, the early discontinuation of clazosentan might worsen these outcomes. However, this trend could be attributed to the small number of cases.

Previous reports have suggested that the use of clazosentan is associated with fluid retention complications.[4,16,17] In a phase III study, 16.5 % of patients reported pleural effusion, and 11.9 % reported pulmonary edema.[4] In this study, the incidence of pleural effusion and pulmonary edema was higher than previously reported, with rates of 44.4 % and 20.4 %, respectively. A study suggested that clazosentan can alleviate cerebral vasospasm, but it does not appear to have any effect on prognosis.[18] The other study showed that pleural effusion and pulmonary edema are significantly associated with poor prognosis.[17] In the current study, on the basis of recommendations from the phase III trial, the daily fluid balance was managed with a goal of less than 500 mL/day.[4] The actual average daily fluid balance was 473.1 mL/day. The poor outcome group showed a mean daily fluid balance of 785.4 mL/day. In addition, the poor outcome group had a significantly lower daily

urine output. Therefore, pleural effusions due to increased fluid volume may have contributed to the poor outcome in this study. There are two possible reasons for the increased incidence of pleural effusions in this study. First, at our institution, chest radiographs were taken routinely at least once every two days, thus making it easier to recognize the occurrence of pulmonary complications. Second, the administration of multiple drugs with clazosentan inevitably increases infusion volume compared with single-agent administration. For good outcomes, pleural effusions should be controlled under strict infusion management, including the use of diuretic agents.

In this study, postoperative hypernatremia, hypoalbuminemia, and hemodilution were associated with poor outcomes. Several studies revealed that hypernatremia and low albumin levels after SAH have been associated with poor outcomes.[5,6] In a study on clazosentan, Eagles et al. reported that an increase in sodium concentration from baseline values at admission led to worse outcomes.[19] Furthermore, Muraoka et al. reported that decreased albumin levels due to clazosentan use was an independent risk factor for pulmonary edema.[20] They also mentioned that pulmonary edema occurs in patients with a positive fluid balance because of decreased serum albumin levels and increased intravascular volume. In this study, hematocrit was used as an indicator of hemodilution, and a lower minimum hematocrit was associated with poorer outcomes. Hemodilution was previously considered one of the triple H therapy for cerebral vasospasm; however, hemodilution with hypervolume is now not recommended because of increased complications.[21] A positive fluid balance can lead to hypervolemia. In the present study, decreased urine output and increased fluid balance led to a decrease in hematocrit. This may have caused hypervolemia, which in turn worsened patient outcomes. The use of sodium diuretics and simple water diuresis may be acceptable.

Several reports suggest that age and WFNS grade are related or influence the outcome of subarachnoid hemorrhages. Goldberg et al.[22] reported that the increasing age and poorer WFNS grade are associated with a higher hazard ratio of death. In addition, Ikawa et al.[23] revealed that increasing age and WFNS grade are important predictors of outcome. In this study, increasing age and WFNS grade may have affected the outcome in multidrug treatment with clazosentan and in previous treatments.

This study has several limitations. First, this was a single-center retrospective study, and the number of cases was too small to draw a definitive conclusion, such as adjusting for age and WFNS grade. However, treatment protocols for preventing cerebral vasospasms following SAH vary among institutions. Single-center studies, such as this study, minimize these variations. Although the use of multiple medications did not allow us to determine the effect of clazosentan alone, this study used real-world data based on multidrug treatment for the prevention of cerebral vasospasm. This study was based on the current treatment protocol, and we did not compare our results with those of other cases before the addition of clazosentan to the regimen. Further studies should be conducted to make this comparison.

5. Conclusions

We reported the initial results of a study on the real-world use of multiple-drug management with clazosentan to prevent cerebral vasospasm after SAH. Not only pleural effusion and high positive balance but also age, WFNS grade, hypernatremia, hypoalbuminemia, hemodilution, and low urine volume may be associated with poor outcomes. Considering the side effects of clazosentan, a more meticulous approach to fluid, electrolyte, and albumin management compared with previous practices may contribute to better outcomes.

CRediT authorship contribution statement

Tatsuki Kimura: Writing – original draft, Investigation, Formal analysis, Data curation, Conceptualization. **Kaima Suzuki:** Writing – review & editing, Project administration, Methodology. **Hiroki Sato:** . **Aoto Shibata:** . **Yushiro Take:** Investigation, Visualization. **Hidetoshi Ooigawa:** Writing – review & editing, Project administration. **Masataka Yoshimura:** Resources, Project administration. **Shinya Kohyama:** Resources, Supervision. **Hiroki Kurita:** Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Ethics Approval and Consent to Participate

This study was approved by the Institutional Review Board of Saitama Medical University International Medical Center (institutional review board: 2023–116). Informed consent was waived because of the retrospective design of the study.

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