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Marked Reduction of Cerebral Vasospasm with Intrathecal Urokinase Infusion Therapy after Endovascular Coil Embolization of the Aneurysmal Subarachnoid Hemorrhage: A Case Series

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Abstract

Delayed cerebral vasospasms after subarachnoid hemorrhage (SAH) are a risk factor for poor prognosis after successful treatment of ruptured intracranial aneurysms. Different strategies to remove clots from the subarachnoid space and prevent vasospasms have different outcomes. Intrathecal urokinase infusion therapy combined with endovascular treatment (EVT) can reduce the incidence of symptomatic vasospasms. To analyze the relationship between symptomatic vasospasms and residual SAHs after urokinase infusion therapy, we retrospectively reviewed the records of 348 consecutive patients managed with EVT and intrathecal urokinase infusion therapy for aneurysmal SAH at our institution between 2010 and 2021. Among them, 163 patients met the study criteria and were classified into two groups according to the presence of residual SAH in the cisterns, Sylvian fissures, and frontal interhemispheric fissure. The incidence of symptomatic vasospasms and the clinical outcomes were assessed. In total, eight (5.0%) patients developed symptomatic vasospasms. Patients with symptomatic vasospasms had a significantly higher incidence of residual SAH in the Sylvian or frontal interhemispheric fissures than those without (P <.0001). No patient with SAHs resolved by urokinase infusion therapy developed symptomatic vasospasms. However, the two groups did not differ significantly in terms of modified Rankin scale scores at discharge. Treatment with intrathecal urokinase infusion after EVT for aneurysmal SAH can substantially reduce the risk of clinically evident vasospasms.

Keywords: aneurysm, coil embolization, subarachnoid hemorrhage, urokinase, vasospasm

Introduction

Delayed cerebral vasospasm is a risk factor for poor prognosis after successful treatment of ruptured intracranial aneurysms. The incidence of angiographic vasospasm is 70%, and approximately 17%-40% of affected individuals develop neurologic symptoms.[1] Breakdown products of clots in the subarachnoid space play a considerable role.[2-4] Reilly et al. reported that vasospasms are best predicted using the initial subarachnoid clot volume and its clearance rate.[5] Therefore, previous studies attempted to increase the clot clearance rate to prevent vasospasms.[5-7] Although extensive removal of subarachnoid clots during surgery is believed to be effective in preventing vasospasms, it is sometimes difficult and may even be hazardous.[8] Among suggested alternatives, urokinase (UK) has been used to dissolve residual clots.[9,10]

Treatment for ruptured aneurysms has substantially changed with the development of endovascular therapy (EVT).[11] The current study aimed to assess the relationship between symptomatic vasospasms and residual SAH after EVT with intrathecal UK therapy although subarachnoid clots cannot be removed by EVT alone, which is correlated with higher risk of cerebral vasospasms (approximately

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30%).[12,13] Thus, EVT was used with intrathecal UK infusion, which, although it was off-label use, considerably reduced the incidence of symptomatic vasospasms.[13,14]

Materials and Methods

Patient population

This case series included 348 consecutive patients with saccular aneurysmal subarachnoid hemorrhage (SAH) who were admitted to our institution and received EVT between January 2010 and May 2021. Clinical and radiological data were retrospectively assessed. We excluded 185 patients: 114 with neurological deficits after EVT (as such conditions could obscure the clinical signs and symptoms of cerebral vasospasms), 49 without intrathecal UK therapy due to incomplete embolization or intraoperative perforation of the aneurysms, 20 who received treatment for 4 days or more after their index hemorrhage, and two who received UK infusions via Ommaya reservoirs. Finally, 163 patients with satisfactory neurological conditions before vasospasm onset were enrolled. Since it was a retrospective study, informed consent was not obtained. All procedures in this study were approved by the Institutional Review Board.

Clinical course

After SAH diagnosis, patients initially maintain a systolic blood pressure below 140 mmHg. An external ventricular drain (EVD) was placed immediately if neuroimaging or clinical features indicated elevated intracranial pressure or symptomatic acute hydrocephalus. Simple or balloon-assisted coil embolization was performed under general anesthesia within 72 h of onset. A lumbar drain was inserted after EVT in patients without EVD. UK (60,000 IU in 10 mL normal saline) was administered once a day via the lumbar drain or EVD after removing a similar amount of cerebrospinal fluid (CSF). Due to discomfort, patients were sedated during UK administration via the lumbar drain. Typically, drains were closed unless there were signs of acute hydrocephalus, including a decreased level of consciousness. Computed tomography (CT) was performed daily during UK infusion to evaluate the clot volume. SAH resolution was defined as the day on which there was no residual SAH in all cisterns, bilateral Sylvian fissures, and the proximal portion of the frontal interhemispheric fissure (Fig. 1). SAHs in convexities were ignored because they are irrelevant for vasospasm development.[5] UK infusion was initiated 1 day after EVT, and treatment was continued until either the SAH volume stopped changing, rendering further UK infusions ineffective, or the SAH had disappeared.

Fasudil was administered intravenously to prevent cerebral vasospasms within 14 days of onset. Patients judged to be at high risk of thrombotic complications after coil embolization were given aspirin or clopidogrel. No other preventive treatment was administered unless symptomatic vasospasms occurred.

To radiologically assess the presence of vasospasms, patients underwent routine surveillance magnetic resonance (MR) imaging at approximately 7 and 14 days after ictus, even in the absence of symptomatic vasospasms. Patients with symptomatic vasospasms received intrathecal nicardipine as salvage therapy.

Definition of vasospasms

An independent neurosurgeon radiologically determined the presence of vasospasms using MR angiography. Symptomatic vasospasm was defined using the following clinical and radiological criteria: onset of new neurological deficits such as confusion, disorientation, or decreased level of consciousness with or without focal deficit during posthemorrhagic days 4-14; no other causes of neurological deterioration, including intracranial hemorrhage, cerebral infarction, hydrocephalus, and cerebral edema based on head CT scan results; lack of other identifiable causes of neurological deterioration, such as electrolyte disturbance, hypoxia, drug toxicity, infection, and seizure; and concurrent radiologic vasospasm in the affected vascular territory. Cerebral infarction caused by vasospasm was diagnosed if a delayed ischemic deficit sustained beyond the risk period of cerebral vasospasms and the diffusion-weighted MR imaging revealed a region of cerebral infarction in a vascular distribution consistent with the patient's vasospasm. Patients with embolic infarctions caused by EVT were excluded. The senior authors reviewed the clinical course and radiological data of patients to determine whether vasospasms had occurred.

Clinical variables

All medical records and neuroimages were reviewed, and data on factors correlated with symptomatic vasospasms were collected. We obtained data including age, sex, history of hypertension and diabetes mellitus, alcohol and smoking status, WFNS grade[15] and Hunt and Kosnik grade[16] upon admission, Fisher scale[17] on admission CT scan, and aneurysm location. The primary outcome measures were clinically evident vasospasm, radiologic vasospasm, residual SAH after UK infusion, and modified Rankin scale (mRS) score at discharge and 1-3-month follow-up. The secondary outcomes included the incidence of complications attributed to UK therapy, length of acute hospital stay, and duration of drain use.

Statistical analysis

Statistical analysis was performed using JMP Pro 16 software (SAS Institute, Japan). Fisher's exact test was used to compare categorical variables between two groups, and the chi-square test of independence was used to analyze contingency data in three groups or more. To ensure accuracy, two groups were combined into a single group if certain

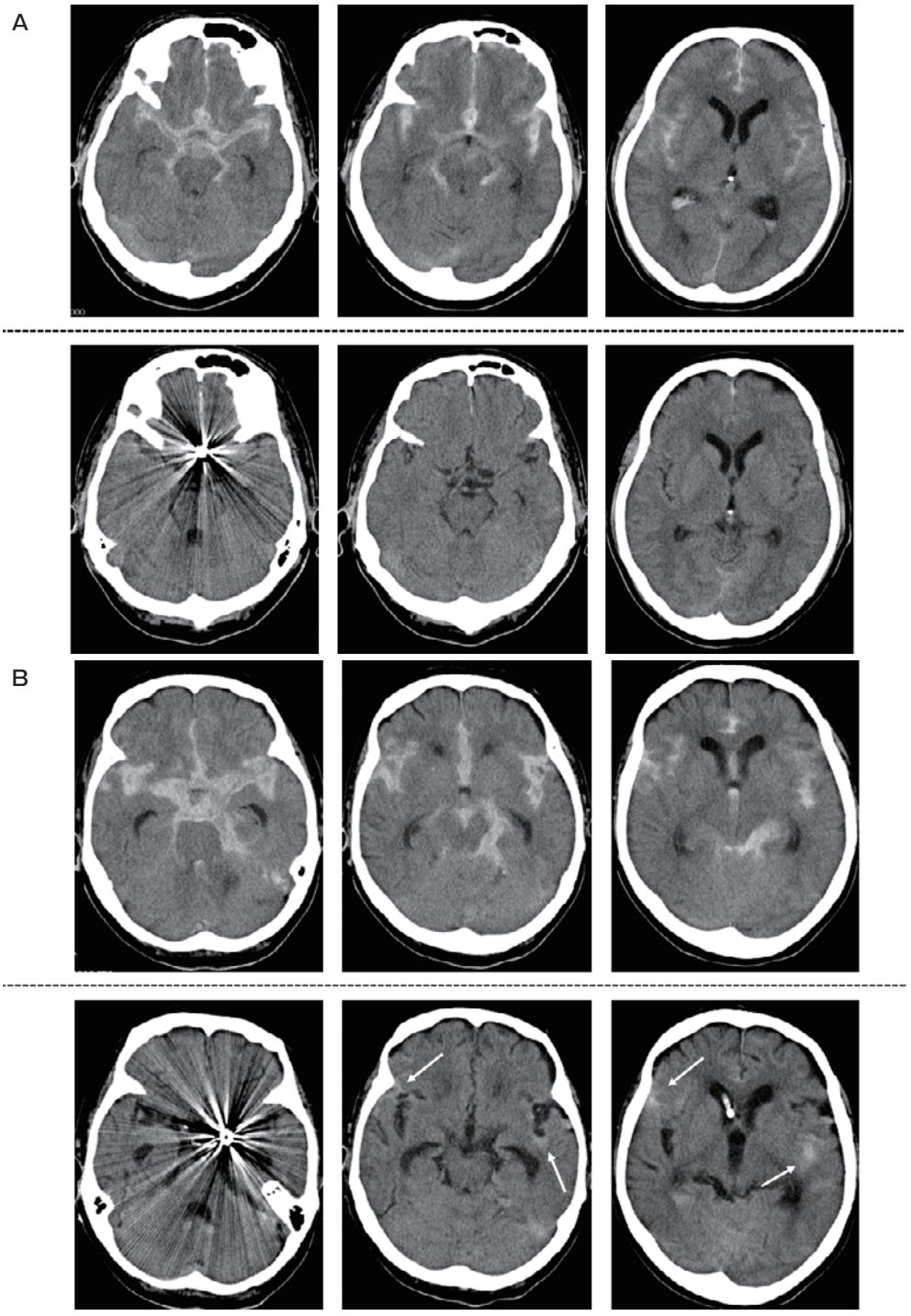

Fig. 1 **A *Upper panel*: Non-contrast-enhanced axial computed tomography (CT) image of a 59-year-old male patient with a ruptured anterior communicating artery aneurysm indicating grade 3 subarachnoid hemorrhage based on the Fisher scale. There was a dense clot within the basal cisterns and Sylvian fissures. The patient received endovascular and urokinase (UK) infusion therapy via a lumbar drain. *Lower panel*: CT scan performed after the third UK infusion showing almost complete lysis of the subarachnoid clots in the basal cistern, Sylvian fissure, and interhemispheric fissure. The patient was classified into Group A. B *Upper panel*: CT image of a 73-year-old female patient with ruptured left internal carotid artery aneurysm revealing diffuse thick and dense subarachnoid hemorrhage surrounding the brain stem and the Sylvian fissures. She received endovascular therapy and UK infusion via the external ventricular drain. *Lower panel*: CT scan performed after the fourth UK infusion showing complete lysis of the subarachnoid clots in the basal cistern. However, subarachnoid clots in the Sylvian fissure (arrow) remained. This patient was classified into Group B.**

contingency groups had small sample sizes. For continuous variables, the Mann-Whitney *U*-test was used to compare two groups with continuous data. Statistical significance was set at $P < .05$. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Results

Demographic characteristics

This study included 163 patients (54 men, 109 women; mean age 58.9 ± 13.0 years). Table 1 shows the baseline characteristics of the participants. After intrathecal UK infusion, 51 (31%) patients had residual SAH.

Incidence of symptomatic vasospasms

In total, eight (5.0%) of the 163 patients developed symptomatic vasospasms causing mild hemiparesis, aphasia, and decreased levels of consciousness. All patients underwent reinsertion of the lumbar drain if it had been removed and received intrathecal nicardipine. Two patients (1.2%) presented with vasospasm-induced cerebral infarction. One patient each developed hemiparesis and mild aphasia. They were transferred to a rehabilitation facility approximately 1 month after EVT.

Patients with and without vasospasms differed significantly in terms of residual SAH after UK infusion therapy ($P < .0001$). Eight patients with symptomatic vasospasms had residual SAH, even after UK infusion therapy. The relationship between residual SAH after UK infusion and clinical course was examined. Patients were divided into two subgroups according to the presence of residual SAH (Table 2). Group A included patients with SAHs in the cisterns, bilateral Sylvian fissures, or proximal portion of the frontal interhemispheric fissure that resolved after UK infusion therapy. In contrast, Group B comprised patients with residual SAH after UK infusion. This group had a higher percentage of patients with a history of SAH or diabetes mellitus. However, the severity of SAH upon admission, Fisher scale, duration from onset to treatment, and drain type did not differ significantly.

Table 3 shows the relationship between residual SAH after UK infusion therapy and clinical outcomes. In total, eight (16%) of 51 patients in Group B and none in Group A developed symptomatic vasospasms ($P < .0001$). Furthermore, 40 (80%) patients in Group B and 35 (31%) in Group A developed radiologic vasospasms ($P < .0001$). The mean lengths of hospitalization were 25 and 21 days in Groups B and A, respectively ($P = .003$). Moreover, the mean number of UK infusions (Group A: 2.3 times, Group B: 2.8 times) and mean duration of drain use (Group A: 4.5 days, Group B: 5.4 days) significantly differed between the two groups.

Outcomes

Outcomes were dichotomized into good (mRS scores 0-2) and poor (mRS scores 3-6) outcomes at discharge. In total, 110 (98%) of 112 patients in Group A and 41 (90%) of 51 patients in Group B had good outcomes. However, the results did not differ significantly ($P = .07$).

Shunt-dependent hydrocephalus

Chronic hydrocephalus that required a CSF diversion procedure occurred in eight patients (4.9%). Ventriculoperitoneal shunt placement was necessary in two patients in Group A (1.8%) and six patients in Group B (12%). The difference was statistically significant ($P = .01$).

Incidence of complications

There were no cases of aneurysm re-rupture after UK administration. Two patients had complications during intrathecal UK therapy. One (0.6%) had intracerebral hemorrhage and the other (0.6%) had bacterial meningitis. These complications were not associated with morbidity or mortality.

Discussion

We analyzed the data of 163 patients with aneurysmal SAH who received EVT and intrathecal UK infusion therapy during the acute phase. Only patients who were able to follow instructions promptly and respond verbally with good orientation after EVT and who were without initial focal neurological deficits, were enrolled. The inclusion criteria were strict for the following reasons: first, even minimal symptoms caused by vasospasms should be evaluated; second, patients with postoperative neurological deficits frequently received prophylactic treatment, such as continuous CSF drainage and intrathecal nicardipine administration during the vasospasm risk period, at the discretion of the attending physicians. Thus, it was challenging to comprehensively evaluate the UK effects. This study evaluated the relationship between residual SAHs after EVT with intrathecal UK infusion and symptomatic vasospasms in detail.

The proportion of patients with symptomatic vasospasms was considerably lower in this study (5.0%) than in previous reports (16%-32%).[18-21] Patients with SAH tolerated the UK infusion therapy after EVT well. We administered fasudil intravenously to prevent cerebral vasospasms. Zhao et al. reported an incidence of symptomatic vasospasms of 15.2% in the fasudil group.[22] Considering the fasudil effects, UK infusion therapy was effective in preventing symptomatic cerebral vasospasms.

Qian et al. reported a meta-analysis of the effect of continuous CSF drainage on clinical outcomes in patients with aneurysmal SAH. They found that CSF drainage reduced the occurrence of symptomatic vasospasm compared to no CSF drainage (18.8% vs. 41.4%).[18] In the present study, drains were typically kept closed until removal so as to validate the effect of UK therapy alone. Although

Table 1 Characteristics of 163 patients included in the analysis

Variable	Overall	Group		P value
		No vasospasm	Vasospasm	
Number of patients	163	155	8	
Mean age ± SD (y)	58.9 ± 13.0	58.5 ± 12.7	66.9 ± 17.8	.08
Female (%)	109 (69)	102 (66)	7 (88)	.27
Medical history				
Prior SAH (%)	4 (2)	4 (3)	0 (0)	.81
Hypertension (%)	77 (47)	72 (46)	5 (63)	.47
Dyslipidemia (%)	21 (13)	20 (13)	1 (13)	.99
Diabetes mellitus (%)	15 (9)	13 (8)	2 (25)	.16
Preference				
Smoking (%)	52 (32)	49 (32)	3 (38)	.71
Alcohol (%)	71 (44)	70 (45)	1 (13)	.14
Hydrocephalus prior to EVT	31 (19)	30 (19)	1 (13)	.52
WFNS grade				
I	76 (47)	73 (47)	3 (38)	
II	69 (42)	65 (42)	4 (50)	
III	2 (1)	2 (1)	0 (0)	
IV-	16 (10)	15 (10)	1 (13)	.91
Hunt & Kosnic grade				
I	7 (4)	7 (5)	0 (0)	
II	120 (74)	113 (73)	7 (88)	
III	28 (17)	27 (17)	1 (13)	
IV-	8 (5)	8 (5)	0 (0)	.6
Fisher scale				
1	1 (1)	1 (1)	0 (0)	
2	21 (14)	21 (14)	0 (0)	
3	138 (84)	132 (85)	6 (75)	
4	3 (2)	1 (1)	2 (25)	.35
Aneurysm location				
ICA	69 (42)	67 (43)	2 (25)	
Acom	50 (31)	48 (31)	2 (25)	
MCA	27 (17)	24 (15)	2 (25)	
ACA	14 (9)	12 (8)	2 (25)	
Posterior circulation	4 (2)	4 (3)	0 (0)	.41
Coil day				
0	57 (35)	55 (35)	2 (25)	
1	88 (54)	85 (55)	3 (38)	
2	11 (7)	9 (6)	2 (25)	
3	7 (4)	6 (4)	1 (13)	.1
Drainage route				
EVD	33 (20)	31 (20)	2 (25)	
Lumbar drain	130 (80)	124 (80)	6 (75)	.66
Residual SAH post-UK ※	51 (31)	43 (28)	8 (100)	< .0001*

SAH, subarachnoid hemorrhage; ICA, internal carotid artery; Acom, anterior communication artery; MCA, middle cerebral artery; ACA, anterior cerebral artery; EVD, extra ventricular drainage; UK, urokinase
※Remaining SAH in the sylvian fissures or proximal portion of the frontal interhemispheric fissure after intrathecal UK infusion therapy.
*Asterisk indicates statistically significant difference.

Table 2 Baseline characteristics for patients focused on residual subarachnoid hemorrhage after urokinase
Group A: No remaining SAH in either sylvian fissures or frontal interhemispheric fissure after intrathecal UK infusion
Group B: Remaining SAH in the sylvian fissures or frontal interhemispheric fissure after intrathecal UK infusion

Variable	Group		P value
	Group A	Group B	
Number of patients (%)	112	51	
Mean age ± SD (y)	57.9 ± 13.1	61.0 ± 12.6	.16
Female (%)	72 (64)	37 (73)	.37
Medical history (%)			
SAH	0 (0)	4 (8)	.0088*
Hypertension	54 (48)	23 (45)	.73
Dyslipidemia	17 (15)	4 (8)	.22
Diabetes mellitus	6 (5)	9 (18)	.018*
Preference (%)			
Smoking	41 (37)	11 (22)	.07
Alcohol	54 (48)	16 (31)	.09
Hydrocephalus prior to EVT (%)	24 (21)	7 (14)	.29
WFNS grade (%)			
I	57 (51)	19 (37)	
II	45 (40)	24 (47)	
III	2 (2)	0 (0)	
IV-	8 (7)	8 (16)	.16
Hunt & Kosnic grade (%)			
I	6 (5)	1 (2)	
II	86 (77)	34 (67)	
III	16 (14)	12 (24)	
IV-	4 (4)	4 (8)	.77
Fisher scale (%)			
1	1 (1)	0 (0)	
2	20 (18)	2 (4)	
3	90 (80)	47 (92)	
4	1 (1)	2 (4)	.068
Aneurysm location (%)			
ICA	53 (47)	16 (31)	
Acom	34 (30)	16 (31)	
MCA	12 (11)	14 (27)	
ACA	10 (9)	4 (8)	
Posterior circulation	3 (3)	1 (2)	.09
Coil day (%)			
0	33 (29)	24 (47)	
1	66 (59)	22 (43)	
2	7 (6)	4 (8)	
3	6 (5)	1 (2)	.12
Drainage route (%)			
EVD	25 (22)	9 (18)	
Lumbar drain	87 (78)	42 (82)	.77

SAH, subarachnoid hemorrhage; UK, urokinase; EVT, endovascular treatment; ICA, internal carotid artery; Acom, anterior communication artery; MCA, middle cerebral artery; ACA, anterior cerebral artery; EVD, extra ventricular drainage
*Asterisk indicates statistically significant difference.

Table 3 Outcomes for patients focused on residual subarachnoid hemorrhage after urokinase

Outcomes	Group A	Group B	P value
	n = 112	n = 51	
Mean number of doses of UK ± SD (times)	2.3 ± 0.86	2.8 ± 0.87	.0004*
Mean duration of drain insertion ± SD (days)	4.5 ± 2.2	5.4 ± 3.0	.045*
Symptomatic vasospasm (%)	0 (0)	8 (16)	< .0001*
Radiologic vasospasm (%)	35 (31)	41 (80)	< .0001*
Mean length of hospitalization ± SD (days)	21.3 ± 7.2	25.3 ± 9.1	.0031*
Shunt-depended hydrocephalus (%)	2 (2)	6 (12)	.01*
Discharge mRS (%)			
0	26 (23)	6 (12)	
1	55 (49)	23 (45)	
2	29 (26)	17 (33)	
3	2 (2)	4 (8)	
4-6	0 (0)	1 (2)	.07
3-month mRS (%)			
0	49 (44)	15 (29)	
1	50 (45)	19 (37)	
2	13 (12)	14 (27)	
3	0 (0)	1 (2)	
4-6	0 (0)	0 (0)	
Lost follow-up	0 (0)	2 (4)	.17

UK, urokinase; mRS, modified Rankin scale
*Asterisk indicates statistically significant difference.

the results cannot be simply compared due to different patient backgrounds, we believe that intrathecal UK therapy was more effective than continuous CSF drainage for preventing symptomatic vasospasm.

There was no significant difference in terms of age, aneurysm location, and Fisher scale, which are risk factors for symptomatic vasospasm, between the groups with and without symptomatic vasospasms.[4,23] In this study, the absolute number of patients with symptomatic vasospasms was small, and the analysis focused on patients who did not have neurological deficits. Thus, the results did not differ significantly. In contrast, patients with residual SAH, even after UK infusion therapy, likely experienced progression to symptomatic vasospasms. The presence of residual SAH significantly differed in the univariate analysis (Table 2).

Next, we focused on residual SAH after UK infusion therapy (Table 3). In patients with residual SAH, the incidence of symptomatic vasospasms was 16.0%, which is similar to that of previous studies. Notably, symptomatic vasospasms were not observed in Group A, in which SAH was not detectable in the cisterns, bilateral Sylvian fissures, and proximal portion of the frontal interhemispheric fissure after intrathecal UK infusion. By inducing the breakdown of clots in the subarachnoid space early after EVT, we may have suppressed the production of spasmogens that can trigger vasospasms.[24] Furthermore, with early drain removal maybe being an important factor, patients without residual SAH had a significantly shorter average length of hospital stay, and rehabilitation went well. In contrast, in a phenomenon that is attributed to the small number of patients presenting with permanent neurological deficits in both groups, the outcomes, evaluated using the mRS scores at discharge and after 3 months, did not significantly differ between the two groups.

Regarding patient background, the factors affecting SAH resolution were histories of SAH and diabetes mellitus (Table 2). Group B of patients with residual SAH had a higher proportion of patients with a past history of SAH than Group A. The resolution of a new hemorrhage might be delayed because remnants of previous SAH may obstruct CSF circulation. Our study also found a significant association between residual SAH and a history of diabetes mellitus. To the best of our knowledge, no prior research has shown such a relationship. Previous studies have shown that idiopathic normal-pressure hydrocephalus may be associated with diabetes mellitus among older individuals. Arteriosclerotic diseases such as diabetes mellitus and hypertension, which can cause vascular encephalopathy, may promote the development of idiopathic normal-pressure

hydrocephalus.[25,26] Thus, CSF absorption could be defective in these patients, resulting in delayed clot resolution in the subarachnoid space.

In connection with CSF flow dynamics, we investigated the incidence of hydrocephalus in the chronic phase. Chronic hydrocephalus that required CSF diversion procedures developed in 12.0% of patients in Group B, compared to 1.8% in Group A. It seems that clot resolution in the subarachnoid space may reduce the incidence of CSF malabsorption and chronic hydrocephalus. Additionally, as mentioned above, several patients in Group B with impaired CSF circulation developed chronic hydrocephalus due to poor resolution of the subarachnoid clot.

In cases of poor SAH resolution, the use of other intrathecal fibrinolytic therapies, including tissue-type plasminogen activator (tPA), which is effective for clot lysis, should have been considered. Usui et al demonstrated that postoperative administration of intrathecal tPA is effective for cleaning a clot and reducing the incidence of angiographic vasospasm and subsequent infarctions.[27] Intrathecal tPA therapy may be an alternative when UK is not readily available, although careful consideration is required in terms of safety.

One patient each developed hemorrhage and bacterial meningitis without affecting their outcomes, with regard to complications. With patients in the current study receiving multiple UK infusions at 60,000 IU per infusion, based on previous findings,[13,14] clinical trials used wide ranges of UK dosages (10,000-180,000 IU), administered via single boluses, multiple injections, and continuous infusions,[7,10,12-14,27-30] and the therapeutic outcomes were excellent with a low incidence of hemorrhagic complications. UK administration should be done with caution because of the risk of re-rupture, in case of incomplete coil embolization. Intrathecal UK infusion therapy was concluded to be safe and effective for preventing symptomatic vasospasms after aneurysmal SAH, as while an infection risk exists because this therapy requires repeated drug injections via EVD or lumbar drain, since the drains can be removed relatively early, the occurrence of bacterial meningitis can be limited.

Study limitations

This study assessed the presence of SAH in the Sylvian fissures and the proximal portion of the frontal interhemispheric fissure, not the total SAH volume which can include clots over the convexities. A previous study showed that proximal clot volumes are important for vasospasm prediction.[31]

We also defined the period from onset to the 14th day as the period of cerebral vasospasms but did not consider delayed cerebral vasospasms afterward. Some patients may have developed vasospasms after the 14th day.

Finally, in this study, the quantity and quality of information obtained from medical records were limited, where this was a retrospective analysis using prospectively collected data from one registry. Notably, some patients with neurological deficits were excluded from analyses. Therefore, this nonrandomized study was affected by selection bias to some degree. Few patients in this study developed permanent neurological deficits, which may be due to UK effects, as well as the strict selection of patients in good general conditions. The exclusion of patients with neurological deficits and the absence of a control group are major limitations of this study. Further prospective randomized controlled studies with a larger sample size should be conducted. Nevertheless, we believe that our findings support the development of further antivasospastic regimens after SAH.

Conclusion

Intermittent intrathecal UK infusion therapy can be safe and effective for preventing symptomatic vasospasms after EVT for aneurysmal SAH, as patients whose SAH disappeared with UK infusion did not develop symptomatic vasospasm.

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Conflicts of Interest Disclosure

All authors declare that they have no conflicts of interest concerning the materials or methods used in this study, or the findings presented in this manuscript. The content of this article has not been previously published or presented elsewhere.

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