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Treatment of aneurysmal subarachnoid hemorrhage in subacute phase; retrospective comparison of treatment in sub- and hyper-acute phases

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ABSTRACT

Objective: As soon as possible treatment initiation for aneurysmal subarachnoid hemorrhage (aSAH) is recommended. However, some patients require treatment in "subacute" phase of aSAH, defined in this study as "more than one day after the onset". To establish an optimal treatment strategy for these patients, we retrospectively analyzed the clinical experience of treating ruptured aneurysm with either clipping or coiling in subacute phase.

Methods: Patients treated for aSAH between 2015 and 2021were analyzed. Patients were divided into the hyperacute phase (within 24 hours) and subacute phase (later than 24 hours) groups. The subacute group was analyzed to determine whether the selected procedure and its timing affected postoperative course and clinical outcomes. In addition, we conducted a multivariate logistic regression analysis to determine the independent factors that affect clinical outcomes.

Results: Of 215 patients, 31 were treated in the subacute phase. While cerebral vasospasm at initial imaging was more frequently observed in subacute group, there was no difference in incidence of postoperative vasospasms. Patients in subacute group seemed to have better clinical outcomes due to the milder severity at the time of treatment initiation. Risk of angiographic vasospasm seemed to be higher in patients treated with clipping than coiling, while no difference was seen in clinical outcomes. Multivariate logistic regression analysis showed that the timing and selected treatment did not significantly affect the clinical outcome or the occurrence of delayed vasospasm.

Conclusions: Treatment of aSAH in the subacute phase may also result in favorable clinical outcomes, similar to patients treated in the hyperacute phase with mild presentation. However, further investigations are required to establish the optimal treatment strategies for such patients.

1. Introduction

Subarachnoid hemorrhage (SAH) caused by ruptured intracerebral aneurysm remains devastating stroke subtype despite advances in medical technology . Previous clinical trials have identified pretreatment rebleeding and delayed cerebral vasospasm (delayed ischemic neurological deficit, DIND) as major preventable complications of aneurysmal SAH (aSAH), which can lead to severe neurological sequelae or death . Pretreatment rebleeding, which typically occurs in hyperacute phase from onset, is the most serious risk factor for aSAH [1, 2]. Studies have shown the highest incidence of rebleeding occurs within the first 24 hours after onset, at rates of 4.1-17.3%.[3] Thus, guidelines recommend as soon as possible treatment by either surgical clipping or endovascular coiling [4, 5]. At our hospital, we provide continuous coverage for the treatment of ruptured aneurysms 24 hours a day, 7 days a week, starting from the hyperacute phase of onset, not depending on the patients' condition.

In clinical practice, there are cases where treatment for aSAH cannot be initiated during the hyperacute phase due to various reasons. However, the clinical characteristics of aSAH treatment during the subacute phase, such as clinical manifestation, post-procedural course, complications, and outcomes, are not well understood compared to those treated in the hyperacute phase. To our knowledge, no study has focused on patients who require treatment in the subacute phase of aSAH, and no consensus exists for such cases even in this advanced era [6]. We conducted retrospective review of clinical experiences in treating patients with aSAH and compared patients treated in the subacute and hyperacute phases. We further examined the influence of selected treatment and its timing on patients' outcomes. Our findings can be helpful to establish optimal treatment strategy for patients who require treatment in the subacute phase of aSAH.

2. Materials and methods

2.1. Study design

We retrospectively analyzed data from a prospectively maintained database of patients who were treated for nontraumatic SAH due to ruptured intracerebral aneurysms at our hospital between 2015 and 2021. The study protocol was approved by the institutional review board (#2-01039-00), and patient consent was waived due to the retrospective nature of the study. Of the 215 patients included in the study, 71 (33.0%) were male and 144 (67.0%) were female, with a mean age of 64.5±15.0 years. This study was conducted following the STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) guideline to ensure accurate reporting of observational studies.

2.2. Treatment strategy

Immediate investigation of the cerebral aneurysm was performed using (DSA) or three-dimensional computed tomography angiography (3D-CTA). Urgent treatment was performed 24/7 to prevent pretreatment rebleeding. Regarding the selection of the procedure to repair aneurysms, Endovascular coiling was the primary option for aneurysm repair, but direct clipping surgery was preferred for aneurysms accompanied by massive intracerebral hemorrhage (ICH) or subdural hematoma (SDH). Anatomically suitable aneurysms were treated with endovascular coiling. For patients in the vasospastic period (4-14 days from onset), endovascular coiling was the predominant strategy.

Fasudil hydrochloride [7] and cilostazol [8] were routinely administered postoperatively to prevent delayed vasospasm and DIND. Instead of nimodipine, nicardipine was continuously and intravenously administered between days 3 and 14 postoperatively [9]. Repeat imaging and angiography were performed between 6-14 days after onset to assess delayed vasospasm and DIND. In the present study, delayed vasospasm was defined as local vasospasm visible on either CT angiography, MR angiography or digital subtraction angiography[10]. DIND was defined as severe delayed vasospasm accompanied by neurological worsening for at least 2 hours [11]. When neurological deficits due to severe vasospasm were observed, endovascular treatment

was performed to rescue severe vasospasm and DIND.

2.3. Data collection

Patients treated within 24 hours of onset were classified as hyperacute treatment group, while patients treated after 24 hours were classified as subacute treatment group. The reason why we set the cut-off time at 24 hours is based on our institutional protocol for the treatment of aSAH (#2-01039-00), which clearly indicates that treatment of the aneurysm should be performed within 24 hours from its rupture. This is based on the reports that indicate a high risk of fatal re-bleeding within 24 hours from the initial rupture [2, 6]. Differences in clinical characteristics and postoperative course were analyzed between the two groups.

In this study, good-grade SAH was defined as World Federation of Neurosurgical Societies (WFNS) grade 1-2 on admission. The presence and severity of vasospasm were assessed pre- and post-operatively by evaluating cerebral vascular narrowing [12]. Clinical outcomes were evaluated after 3 months using the modified Rankin Scale (mRS), where scores of 0-2 indicated good outcomes and scores of 4-6 indicated poor outcomes.

2.4. Statistics

All statistical analyses were performed using GraphPad Prism 8 (GraphPad, La Jolla, CA). The data are expressed as the mean ± standard deviation (SD) or median [interquartile range (IQR)] for continuous variables. For categorical variables, the numbers of patients and percentages are shown. Fisher's exact test or χ^2 test was used to compare categorical variables. Mann–Whitney U test and unpaired Student's t-testt were used to compare continuous variables. Statistical significance was set at $P < 0.05$.

3. Results

3.1. Demographics

Table 1 summarizes the characteristics of 215 patients with aSAH. Of 215 patients in this study, 71 (33.0%) were male and 144 (67.0%) were female, with a mean age of 64.5±15.0 years. Of total, 85.6% (184) were treated within 24 h of onset and assigned to the hyperacute treatment group, while 14.4% (31) were treated later than 24 h and assigned to the subacute treatment group. The reasons for delayed treatment were "delayed presentation," "transfer from another hospital," "SAH overlooked at another hospital," and "aneurysm not detected at the initial examination" for 23, 4, 2, and 2 patients, respectively. The severity of aSAH was better in the subacute treatment group than in the hyperacute treatment group (median WFNS grade; 2 (1–3.5) vs 4 (2–5)). The difference in the proportion of patients with lower WFNS grades may be due to the tendency of patients with milder symptoms to delay seeking medical attention. Figure 1A summarizes the clues to diagnosis for patients in the subacute treatment group. Figure 1B summarizes the durations from onset to diagnosis and selected treatment. The pre-vasospastic period was defined as the time before 3 days from onset, while the vasospastic period was defined as the period between 4–14 days from onset [13]. The reasons for delayed treatment are summarized in Figure 1C.

3.2. Clinical course of patients treated in the subacute phase

Table 2 summarizes the data of clinical course in both subacute and hyperacute treatment groups. Angiographic vasospasm at the time of initial imaging, which is depicted as cerebral vascular narrowing at the time of initial imaging [12], seemed to be more frequently observed in the subacute treatment group (38.7%) than in the hyperacute treatment group (21.7%). However, there was no difference in the incidence of delayed vasospasm during the postoperative clinical course. This finding might be indicating that angiographic vasospasm at the time of diagnosis does not affect the risk of delayed vasospasm and DIND postoperatively. The final clinical outcome was rather better in the subacute treatment group, which was attributed to the less severe SAH at the time of diagnosis.

3.3. Effect of treatment selection and its timing

Further data analysis was conducted (Table 3) to investigate whether the selected treatment (clipping surgery vs. endovascular coiling) and timing of treatment (pre-vasospastic vs. vasospastic period) had an impact on postoperative course and clinical outcomes for the subacute treatment group (n=31). Comparing patients who underwent clipping surgery to those who had endovascular coiling, the incidence of intracranial hemorrhage (ICH or SDH) was significantly higher in the former group (35.3% vs. 0.0%, p=0.013), which is consistent with the treatment selection protocol described in the Methods section. The incidence of delayed vasospasm was also significantly higher in patients treated with clipping than in those treated with coiling (76.5% vs. 21.4%, p=0.002), although there were no significant differences in the occurrence of DIND or severe vasospasm. The clinical outcome was not significantly different between the clipping group [3M mRS, 2 (0–3)] and coiling group [3M mRS, 0 (0–1.5)].

Comparing outcomes based on the timing of treatment, no significant differences were observed in the postoperative course and clinical outcomes between patients treated in the pre-vasospastic and vasospastic periods; there were no differences in the incidences of delayed vasospasm, DIND, or clinical outcome [median mRS at 3 months: 0 (0–2) vs. 2 (0–3)]. These results suggest that good clinical outcomes can be achieved even when treating aSAH in the vasospastic period if optimal treatment selection and postoperative management strategies are used to prevent delayed vasospasm. The detailed clinical data of each patient enrolled in the 'subacute' treatment group are presented in the supplementary tables.

3.4. Analysis of Factors Affecting Clinical Outcome and Delayed Vasospasm

We conducted univariate regression analysis to identify the risk factors for poor clinical outcome (mRS 4-6) and occurrence of delayed cerebral vasospasm. The results are presented in Table 4. Age, severity of SAH (WFNS grade), complicated ICH or ASH, selected treatment,

delayed vasospasm, and hydrocephalus were found to be significant risk factors for poor clinical outcome. However, treatment timing, hyperacute versus subacute, did not affect the clinical outcome. For the occurrence of delayed vasospasm, gender, severity of SAH (WFNS grade), complicated ICH or ASH, selected treatment, and hydrocephalus were significant risk factors. Again, treatment timing did not affect the occurrence of delayed cerebral vasospasm.

Further multivariate regression analysis (Table 5) revealed that age and severity of SAH, and gender and hydrocephalus were the independent risk factors for poor clinical outcome and the occurrence of delayed cerebral vasospasm, respectively. However, the timing of treatment and selected treatment (clipping or coiling) were not independent risk factors for either study endpoint.

4. Discussion

Immediate treatment with clipping or coiling to repair the ruptured aneurysm is recommended for aSAH patients and is usually performed within the hyperacute phase, defined as 24 hours from SAH onset. Previous studies [1, 2, 6] have shown the importance of urgent treatment in preventing pretreatment rebleeding and achieving better clinical outcomes. Van Donkelaar et al. [1] had demonstrated that there were 23 cases (1.1%) of pretreatment death due to rebleeding, with a median interval of 2 days (IQR, 1–4) from presentation. Authors had argued the importance of urgent treatment in patients with aSAH [1]. Another study group performed prospective clinical trial to determine the optimal treatment timing for aSAH [6]. Authors had found significantly better clinical outcomes in patients treated in hyperacute phase (mRS of 0–2, 90%; rebleeding, 0%) than in those treated in subacute phase (mRS of 0–2, 45%; rebleeding, 40%) [6]. The authors also concluded that immediate treatment for aSAH within the hyperacute phase should be the standard treatment strategy. Another very interesting paper [14] published recently has revealed a higher incidence of pretreatment rebleeding in very small aneurysms located in the anterior communicating artery, emphasizing the significance to

prevent rebleeding. On the other hand, recent publication [15] that employed propensity score matching comparison for their clinical data reported that ultra early treatment (within 24 hours) for aSAH was not associated with improved neurological outcomes. The optimal timing of treatment for aSAH remains a subject of debate. In actual clinical settings, there are cases where treatment intervention is unavoidably delayed due to various reasons. Here-in, we retrospectively analyzed our clinical data focusing on the treatment of aSAH in sub-acute phase, to elucidate the clinical characteristics of these patients.

In the present study, angiographical vasospasm at the time of initial imaging was more frequently observed in subacute treatment group (38.7%) than in hyperacute treatment group (21.7%). However, there were no differences in incidences of delayed symptomatic vasospasm and DIND between the hyperacute (7.4 %) and subacute (9.7 %) treatment groups. Previous studies [12, 16] reported that ultra-early angiographic vasospasm, defined as cerebral arterial narrowing within 48 h from onset, was a significant risk factor for the occurrence of delayed symptomatic vasospasm and poor clinical outcomes, which is in contrast to our findings. This discrepancy may be explained by the treatment selection bias and current advances in endovascular techniques. Some retrospective studies [17] have shown that endovascular treatment is more effective in preventing vasospasm due to its less invasiveness to cerebral vessels. Although it is still controversial, this was the main reason why we predominantly selected endovascular treatment for patients with ultra-early angiographic vasospasm, even if only mild vascular narrowing was observed. Furthermore, sophisticated endovascular techniques and improved postoperative management strategies to prevent vasospasm may have contributed to our findings. Supporting our speculation, incidence rate of delayed vasospasm (7.7%) in our study was even lower than that reported in recent report that investigated factors related to delayed vasospasm (14.5%) [17].

In our further assessment of patients treated in the subacute phase of aSAH, we did not detect significant differences in clinical outcomes according to treatment method (clipping vs. coiling)

or treatment timing (pre-vasospastic vs. vasospastic period). We did find, however, that incidence of postoperative "angiographical" vasospasm was significantly higher in patients treated with clipping surgery than in those treated with endovascular coiling, which is consistent with previous reports [17]. However, this increased incidence of “angiographical” vasospasm was not directly linked to the differences in clinical outcomes. This positive finding may be indicating that our treatment selection protocol is reasonable and allows us to achieve good clinical outcomes and implies that our postoperative management is effective in preventing aggravation of delayed vasospasm. Moreover, as per a recent interesting publication [18], early permanent CSF diversion surgery during the vasospastic period has been found to be effective in preventing the incidence of meningitis without increasing the risk of cerebral vasospasm. This early surgical intervention may also effective to provide beneficial in achieving favorable clinical outcomes in patients at a high risk of delayed vasospasm. Detailed investigation of our past clinical experience revealed that eight patients required direct clipping surgery in vasospastic period. For such patients at high risk of delayed vasospasm and DIND, a novel medical approach may be effective. Clazosentan, antagonist of endotheline-1 receptor, appears to be a good candidate [19]. A recently published large randomized clinical trial [20] showed that inhibition of endotheline-1 by administration of clazosentan strongly reduced the incidence and aggregation rates of postoperative vasospasm with few adverse effects. This novel and promising treatment would be helpful to improve clinical outcomes in such challenging cases.

Our study had limitations, including its retrospective nature, variable baseline characteristics, and small sample size. Treatment selection was based on physician decisions, which may have influenced our analysis. Further larger, controlled cohort studies are needed to determine optimal management strategies for aSAH in the subacute phase. Given these limitations, we were unable to adjust or control the data when comparing the clinical outcomes between the subacute and hyperacute treatment groups. To definitively verify our hypothesis, future studies with higher statistical power are needed.

5. Conclusion

The present study reveals that good clinical outcomes can be expected in patients with aSAH who are treated in the subacute phase, as seen in those treated in the hyperacute phase with less severity. Although clipping surgery seems to have a high risk of delayed vasospasm, surgical timing and selected treatment did not affect clinical outcome or occurrence of delayed vasospasm. Further investigation is warranted to elucidate an optimal treatment strategy for subacute treatment of aSAH.

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CRediT AUTHORSHIP CONTRIBUTION STATEMENT

Kota Kurisu: Conceptualization, Data curation and analysis, Writing - original draft. Masaaki Hokari: Conceptualization, Data curation. Kazuki Uchida, Katsuyuki Asaoka, Minoru Ajiki, Tatsuro Takada, Koji Itamoto: Data curation. Miki Fujimura: Supervision.

Declaration of Competing Interest

None

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Figure legends

Figure 1. Clinical characteristics of patients treated in the subacute phase of aneurysmal SAH (A) Clues to diagnosis. (B) Duration from onset to diagnosis. (C) The reason for delayed treatment.

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Table1. Demographics of patients both treated in hyper-acute and sub-acute phase of subarachnoid hemorrhage

	Over all	Hyperacute treatment	Subacute treatment
Patients	215	184	31
Age (y.o)	64.5±15.0	64.5±15.1	63.8±14.5
Gender, Male (%)	71 (33.0%)	63 (34.2%)	8 (25.8%)
WFNS Grade	4 [2-5]	4 [2-5]	2 [1-3.5]
Grade1-2(%)	97 (45.1%)	76 (41.3%)	21 (67.7%)
Grade3-5(%)	118 (54.9%)	108 (58.7%)	10 (32.3%)
Aneurysm Size(mm)	5.9±3.1	5.9±3.2	6.2±2.8
ICH or SDH (%)	67 (31.2%)	60 (32.6%)	7 (22.6%)
Location (%)			
ACA	69 (32.1%)	60 (32.6%)	9 (29.0%)
MCA	59 (27.4%)	51 (27.7%)	8 (25.8%)
ICA	60 (27.9%)	51 (27.7%)	9 (29.0%)
VA-BA	27 (12.6%)	22 (12.0%)	5 (16.1%)

Table 2. Clinical features (pre-operative findings and post-operative course) of patients treated in subacute phase

	Over all	Hyperacute treatment	Subacute treatment
Patients	215	184	31
Pre-operative findings			
Angiographical vasospasm	52 (24.2%)	40 (21.7%)	12 (38.7%)
mild vasospasm	50 (23.3%)	40 (21.7%)	10 (32.3%)
severe vasospasm	2 (0.9%)	0 (0.0%)	2 (6.5%)
Hydrocephalus	95 (44.2%)	83 (45.1%)	12 (38.7%)
Selected treatment			
Clipping	133 (61.9%)	116 (63.0%)	17 (54.8%)
Coiling	84 (38.1%)	68 (37.0%)	14 (45.2%)
Post-operative course†			
Angiographical vasospasm	112 (57.1%)	96 (58.9%)	16 (51.6%)
DIND, Symptomatic vasospasm	15 (7.7%)	12 (7.4%)	3 (9.7%)
Delayed hydrocephalus	69 (35.2%)	56 (34.4%)	13 (41.9%)
Clinical Outcome			
3months mRS	2 [0-4]	2 [1-5]	0 [0-2.5]
mRS 0-2	128 (59.5%)	105 (57.1%)	23 (74.2%)
mRS 4-6	66 (30.7%)	62 (33.7%)	4 (12.9%)

† Twenty-one patients who died early in post-operative course was excleded.

Table 3. Effect of selected procedure and its timing on post-operative course

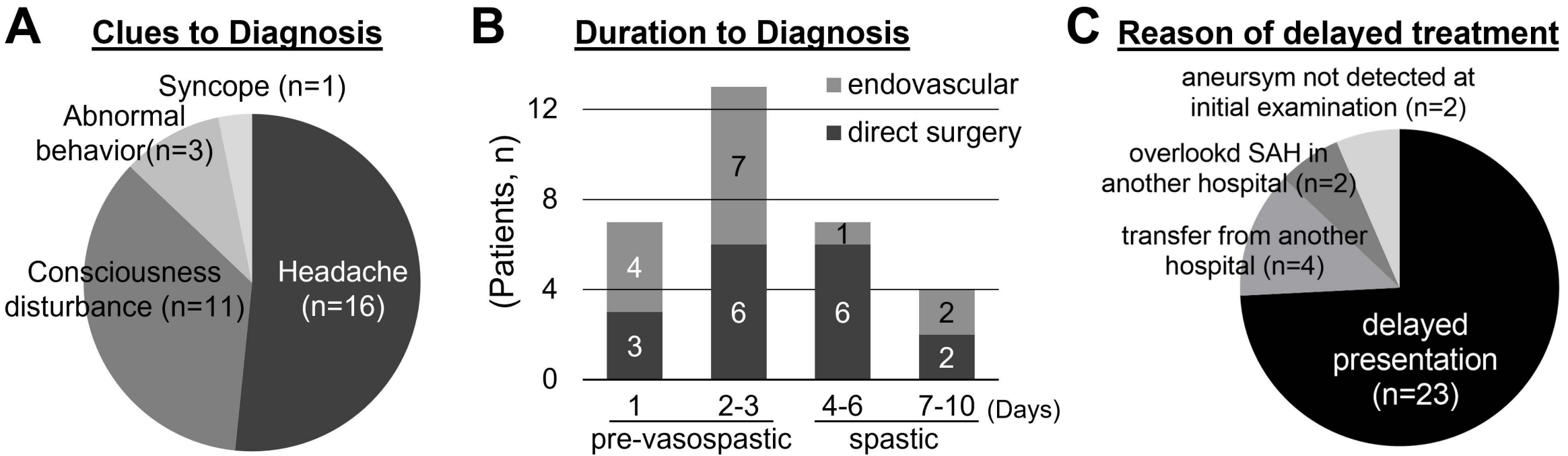
	Selected procedure			Timing of treatment			
	clipping n=17	coiling n=14	p value	day1-3 n=20	day4-10 n=10	day14 n=1	p value
WFNS Grade	2 [1-3]	2 [1.25-3.5]	0.836	2 [1-3.25]	2 [1-4]	1	0.390
Grade1-2(%)	11/17 (64.7%)	11/14 (78.6%)	0.397	15/20 (68.8%)	6/10 （60.0%）	1/1(100.0%)	0.398
preoperative vasospasm	7/17 (41.2%)	5/14 (45.5%)	0.756	6/20 (30.0%)	6/10 (60.0%)	0/1（0.0%）	0.114
preoperative hydrocephalus	5/17 (29.4%)	7/14 (50.0%)	0.242	9/20 (45.0%)	3/10 (30.0%)	0/1（0.1%）	0.429
ICH or SDH	6/17 (35.3%)	0/14 (0.0%)	0.013*	3/20 (15.0%)	3/10 (30.0%)	0/1（0.0%）	0.333
Post-operative Course							
angiographical vasospasm	13/17 (76.5%)	3/14 (21.4%)	0.002**	10/20 (50.0%)	6/10 (60.0%)	0/1（0.0%）	0.605
symptomatic vasospasm, DNDS	3/17 (17.6%)	0/14 (0.0%)	0.098	2/20 (10.0%)	1/10 (10.0%)	0/1（0.0%）	1.000
delayed hydrocephalus	7/17 (41.2%)	6/14 (42.9%)	0.925	9/20 (45.0%)	4/10 (40.0%)	0/1（0.0%）	0.795
Clinical Outcome							
3M mRS	2 [0-3]	0 [0-1.5]	0.117	0 [0-2]	2 [0-3]	0	0.220
3M mRS 0-2	12/17 (70.6%)	11/14(78.6%)	0.613	16/20 (80.0%)	6/10 (60.0%)	1/1(100.0%)	0.243
3M mRS 4-6	3/17 (17.6%)	1/14(7.1%)	0.385	2/20 (10.0%)	2/10 (20.0%)	0/1（0.0%）	0.448

Table 4. Univariate covariate logistic regression analysis in patients of aneurysmal subarachnoid hemorrhage

Univariate regression analysis	Univariate		
	Odds ratio	95% CI	p value
Poor clinical outcome (mRS 4-6)			
Age	0.946	0.919-0.971	<0.001*
Gender (Femal /Male)	0.720	0.333-1.481	0.3858
Timing (Hyperacute/ Subacute)	0.430	0.122-1.181	0.1355
less WFNS grade (0-2)	0.080	0.026-0.197	<0.001*
Aneurysm size	0.918	0.832-1.015	0.09
ICH or ASH	0.258	0.128-0.513	<0.001*
Anterior circulation	1.969	0.628-8.693	0.2955
Treatment (Clipping /Coiling)	2.495	1.188-5.655	0.020*
Delayed vasospasm	3.095	1.471-7.025	0.004*
DIND	0.797	0.257-2.997	0.7105
Hydrocephalus	0.319	0.158-0.633	<0.001*
Occurrence of delayed vasospasm			
Age	0.987	0.967-1.007	0.196
Gender (Femal /Male)	0.485	0.260-0.895	0.021*
Timing (Hyperacute/ Subacute)	0.733	0.338-1.597	0.430
less WFNS grade (0-2)	0.381	0.209-0.682	0.001*
Aneurysm size	0.989	0.898-1.084	0.807
ICH or ASH	0.323	0.158-0.631	0.001*
Anterior circulation	0.910	0.994-6.578	0.056
Treatment (Clipping /Coiling)	1.929	1.067-3.512	0.030*
Hydrocephalus	0.274	0.138-0.521	<0.001*
favorable clinical outcome (mRS0-2)	0.440	0.229-0.822	0.012*

Table 5. Multivariate regression analysis in patients of aneurysmal SAH

Multivariate regression analysis	Multi variate		
	Odds ratio	95% CI	p value
Poor clinical outcomes (mRS0-2)			
Age	0.936	0.902-0.967	<0.001*
Timing (Hyperacute/ Subacute)	0.527	0.122-1.932	0.355
less WFNS grade (0-2)	0.147	0.0439-0.414	0.001*
Aneurysm size	0.885	0.770-1.009	0.073
ICH or ASH	0.566	0.208-1.501	0.256
Treatment (Clipping/Coiling)	2.055	0.708-6.465	0.198
Delayed vasospasm	1.654	0.650-4.389	0.297
Hydrocephalus	0.537	0.222-1.284	0.162
Occurrence of delayed vasospasm			
Gender (Femal /Male)	0.436	0.219-0.855	0.017*
less WFNS grade (0-2)	0.664	0.325-1.358	0.260
ICH or ASH	0.491	0.209-1.116	0.094
Treatment (Clipping /Coiling)	1.442	0.727-2.873	0.296
Hydrocephalus	0.388	0.184-0.794	0.011*
favorable clinical outcome (mRS0-2)	0.8591	0.393-1.891	0.703


A
Clues to Diagnosis
Syncope (n=1)
Abnormal behavior(n=3)
Consciousness disturbance (n=11)
Headache (n=16)
B
Duration to Diagnosis
endovascular
direct surgery
(Patients, n)
12
8
4
0
4
3
7
6
1
6
2
2
1
2-3
4-6
7-10
(Days)
pre-vasospastic
spastic
C
Reason of delayed treatment
aneursym not detected at initial examination (n=2)
overlookd SAH in another hospital (n=2)
transfer from another hospital (n=4)
delayed presentation (n=23)