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Original Article

Coiling for Ruptured Aneurysms in the Vasospasm Period: Safety and Efficacy Based on a Propensity Score Analysis

Takao Koiso, Tetsu Satow, Eika Hamano, Masaki Nishimura, Jun C. Takahashi, and Hiroharu Kataoka

Objective: To evaluate the efficacy and safety of interventional radiology (IVR) for aneurysmal subarachnoid hemorrhage (SAH) later than 3 days after onset.

Methods: A total of 71 patients between 2012 and 2017 who underwent endovascular coiling were divided into two groups according to the timing of treatment: Group E (treated within 3 days after onset) and group D (treated between 4 and 14 days after onset), and the outcomes between two groups were compared. A case-matched study was conducted to minimize the selection bias lying in this cohort.

Results: There were 56 (78.9%) and 15 (21.1%) patients in groups E and D, respectively. In group D, all patients arrived at the hospital later than 3 days after onset. The rates of patients with WFNS grade 1, 2, 3 and the presence of vasospasm upon the access route to the targeted aneurysm at the time of IVR were significantly higher in group D than in group E (93.3% vs 60.7%; p = 0.027, 33.3% vs 3.6%; p = 0.0037, respectively). There were no significant differences in the rate of intraprocedural complications, symptomatic vasospasm, delayed cerebral infarction due to vasospasm, retreatment, or modified Rankin Scale (mRS) at discharge. After propensity score matching, there were no significant differences in the outcomes between two groups.

Conclusion: Prompt coiling for patients with ruptured aneurysms who arrived later than 3 days after onset can be safely performed, even if they had vasospasm upon the access route.

Keywords ▶ aneurysmal subarachnoid hemorrhage, delayed treatment, coil embolization

Introduction

In the Japanese Guidelines for the Management of Stroke 2015, early operation within 3 days after onset is recommended for the surgical treatment of ruptured cerebral aneurysms.[1] However, if 3 days have passed, elective surgery is recommended because the outcome of treatment performed in the vasospasm period (4–14 days after the onset) is poor.[2] On the other hand, there were no consensus for interventional radiology (IVR) of ruptured cerebral aneurysms in the vasospasm period. The treatment outcome in the vasospasm period was reportedly comparable with that of early treatment.[3,4] Conversely, it was also reported that the patients performed IVR during 5–10 days after onset had poorer outcome than that the patients treated in the early phases.[5] In this study, we investigated whether there was a difference in the treatment outcome of IVR between that performed in the early phase and that performed in the vasospasm period at our facility.

Materials and Methods

This retrospective study was approved by the ethics committee of our institution (approved No. M30-013). Of 355 patients with ruptured saccular cerebral aneurysm treated at our hospital between January 2012 and December 2017, direct surgery was performed in 258, identification of the ruptured site was difficult due to the presence of multiple lesions in 8, the cerebral aneurysm was previously treated in 13, treatment with parent artery occlusion was performed in 3, the onset time was unclear in 1, and treatment

Department of Neurosurgery, National Cerebral and Cardiovascular Center, Suita, Osaka, Japan

Received: March 9, 2021; Accepted: June 19, 2021
Corresponding author: Takao Koiso. Department of Neurosurgery, Hitachi General Hospital, 2-1-1, Jonancho, Hitachi, Ibaraki 317-077, Japan
Email: s0201534@hotmail.co.jp

was performed later than 14 days after onset in 1. After excluding these patients, there were 71 subjects.

Perioperative management: After being diagnosed with subarachnoid hemorrhage (SAH) by CT, orotracheal intubation was applied under general anesthesia to all patients. Cerebral angiography was then performed and IVR was prioritized for aneurysms of posterior circulation, but for aneurysms of anterior circulation, the therapeutic modality was decided in consideration of its location and shape. When hydrocephalus was noted on CT at arrival, ventricular drainage was performed before IVR. During the procedure, heparin was administered to control the activated clotting time (ACT) at 200–250 seconds before catheterization of a guiding catheter. To prepare for intraprocedural rupture, a balloon catheter was set on standby on a table. After the procedure, lumbar spinal drain was placed to wash out SAH and control intracranial pressure. To prevent vasospasm after treatment, fasudil hydrochloride was administered, and antiplatelet therapy in combination with ozagrel sodium and cilostazol was performed. In 70 patients excluding 1 in whom evaluation of vasospasm was difficult due to a serious postprocedural condition, the presence of vasospasm was evaluated using CTA or MRA at 4–16 days after onset. When vasospasm was observed without extensive cerebral infarction, intra-arterial infusion of fasudil hydrochloride was performed.

Evaluation method: The patients were classified into those treated within 3 days after onset as the early group (Group E) and 4–14 days after the onset as the delayed group (Group D), and the following items were retrospectively compared using medical records and imaging data: Patients' background (age, sex, World Federation of Neurological Surgeons (WFNS) grade, re-rupture rate before IVR, aneurysm location, maximum diameter of the aneurysm, aneurysm neck size, aspect ratio, presence of vasospasm upon the access during treatment, and use of adjunctive technique), intraprocedural complications (symptomatic cerebral infarction, vascular dissection, vessel perforation, and cerebral hemorrhage), incidence of treatment procedure-induced vasospasm, incidence of symptomatic cerebral vasospasm, incidence of vasospasm-induced cerebral infarction, retreatment rate, and modified Rankin Scale (mRS) at discharge. Regarding the day of initial hemorrhagic event as day 0, days 4–14 were defined as the vasospasm period. The access route during the procedure was defined as a parent artery of the aneurysm in which the catheter was passed through. Aneurysm perforation was included in vessel perforation. Vasospasm was defined as 25% or greater stenosis by the warfarin–aspirin symptomatic intracranial disease (WASID) method.[6] Vasospasm-induced cerebral infarction was judged when vasospasm was observed on CTA/MRA and cerebral infarction was present in its blood supply region.

Statistical Analysis

For statistical analysis, JMP ver. 12.0 (JMP, Cary, NC, USA) was used. Qualitative variables were analyzed using Fisher's exact test. Quantitative variables are presented as the median and interquartile range (IQR), and were analyzed using the Wilcoxon rank sum test. In addition, to reduce the bias of patient background on the outcome, propensity score matching was performed.

Results

The patient background is shown in **Table 1**. Group E included 56 patients (median age: 67.0 years old, IQR: 50.0–78.8) and Group D included 15 patients (median age: 61.0 years old, IQR: 52.0–71.0). In Group D, all patients visited our hospital at 4 days or later after onset; 13 patients stayed at home and two patients had no definite diagnosis by a previous physician. The median duration of follow-up after admission was 588 days (IQR: 280–1160 days). The median time from onset to treatment was 1 day (IQR: 0–1) in Group E and 6 days (IQR: 5–8) in Group D. No significant difference was noted in the age or sex ratio between two groups ($p = 0.5634$, $p = 1.0000$). Re-rupture occurred before treatment in eight patients (14.3%) in Group E and in five patients (33.3%) in Group D, demonstrating an slight increase in Group D, but the difference was not significant ($p = 0.1300$). After admission, re-rupture occurred in three patients in Group E, but not in Group D. The number of WFNS grade 1, 2, or 3 patients were 34 (60.7%) in Group E and 14 (93.3%) in Group D, exhibiting a significantly higher rate in Group D ($p = 0.0267$). In addition, the rate of aneurysms of the anterior circulation was 69.6% (39 patients) in Group E and 53.3% (8 patients) in Group D, being not significantly different ($p = 0.7247$). There was no significant difference in the maximum diameter or neck size of the aneurysm between two groups ($p = 0.1925$, $p = 0.6725$). On the other hand, vasospasm was present upon the access route in two (3.6%) in Group E and in five (33.3%) in Group D, resulting in a significant difference ($p = 0.0037$). For one of the five patients in group D who had severe vasospasm at the time of arrival, the treatment was performed 2 days later when the improvement of vasospasm was confirmed. Regarding the adjunctive technique,

Table 1 Summary of clinical characteristics of 71 patients of aneurysmal SAH treated by IVR

	Total	Group E	Group D	p value
No. of patients	71	56	15	
Age, yrs				
Median	66.0	67.0	61.0	0.5634
IQR	50.0–77.0	50.0–78.8	52.0–71.0	
Sex, Female	55 (77.5%)	43 (76.8%)	12 (80.0%)	1.0000
WFNS grade 1–3	48 (67.6%)	34 (60.7%)	14 (93.3%)	0.0267
Re-rupture before Tx	13 (18.3%)	8 (14.3%)	5 (33.3%)	0.1300
Location of ruptured AN, anterior	47 (66.2%)	39 (69.6%)	8 (53.3%)	0.3566
AN maximum size, mm				
Median	5.8	5.9	4.5	0.7247
IQR	4.0–8.7	4.2–8.7	4.0–6.9	
AN neck size, mm				
Median	2.9	2.9	2.8	0.6725
IQR	2.1–3.7	2.0–3.9	2.4–3.5	
Aspect ratio				
Median	1.53	1.54	1.41	0.1925
IQR	1.20–1.79	1.26–1.94	1.07–1.68	
Vasospasm at access route, Yes	7 (9.9%)	2 (3.6%)	5 (33.3%)	0.0037
Adjunctive technique, Yes	32 (45.1%)	23 (41.1%)	9 (60.0%)	0.2469
Balloon	25 (35.2%)	18 (32.1%)	7 (46.7%)	
Double catheter	2 (2.8%)	1 (1.8%)	1 (6.7%)	
Stent	6 (8.5%)	4 (7.1%)	2 (13.3%)	

AN: aneurysm; IQR: interquartile range; IVR: interventional radiology; SAH: subarachnoid hemorrhage; WFNS: World Federation of Neurological Surgeons

Table 2 Intraprocedural and postprocedural adverse event of 71 patients of aneurysmal SAH treated by IVR

	Total	Group E	Group D	p value
Procedure-related complications				
Symptomatic CI	9 (12.7%)	7 (12.5%)	2 (13.3%)	
Arterial dissection	3 (4.2%)	2 (3.6%)	1 (6.7%)	
Vessel perforation	4 (5.6%)	3 (5.4%)	1 (6.7%)	
ICH	1 (1.4%)	1 (1.9%)	0	
Total	16 (22.5%)	12 (21.4%)	4 (26.7%)	0.7314
Postprocedural course				
Symptomatic vasospasm	15 (21.1%)	13 (24.1%)	2 (13.3%)	0.4942
CI due to vasospasm	12 (17.1%)	10/55 (18.2%)	2 (13.3%)	1.0000
Retreatment	7 (9.9%)	6 (10.7%)	1 (6.7%)	1.0000

CI: cerebral infarction; ICH: intracerebral hemorrhage; IVR: interventional radiology; SAH: subarachnoid hemorrhage

balloon assist was employed in 18 patients (32.1%) in Group E and in 7 patients (46.7%) in Group D, which was most frequently used in both groups, followed by stent assist in 4 (7.1%) in Group E and in 2 (13.3%) in Group D. Double catheters were used in one patient in each group (7.1%, 6.7%). No significant difference was noted in the use of adjunctive technique (41.1% vs 60.0%, p = 0.2469).

Intraprocedural complications and postprocedural course are shown in **Table 2**. Symptomatic cerebral infarction, vascular dissection, vessel perforation, and cerebral hemorrhage occurred in 7, 2, 3, and 1 patient, respectively (12 cases, 21.4% in total) in Group E, and in 2, 1, 1, and 0, respectively, in Group D (4 cases, 26.7% in total). No significant difference was noted in the incidence of complications between the groups (p = 0.7314). No patient developed vasospasm due to the therapeutic procedure in either group. Regarding postprocedural course, the incidence of symptomatic vasospasm was 24.1% (13 patients) in Group E and 13.3% (2 patients) in Group D, the incidence of vasospasm-induced cerebral infarction was 18.2% (10 patients) in Group E and 13.3% (2 patients) in Group D, and the retreatment rate was 10.7% (6 patients) in Group E and 6.7% (1 patient) in Group D, with no significant differences although slightly higher in Group E (p = 0.4942, p = 1.0000,

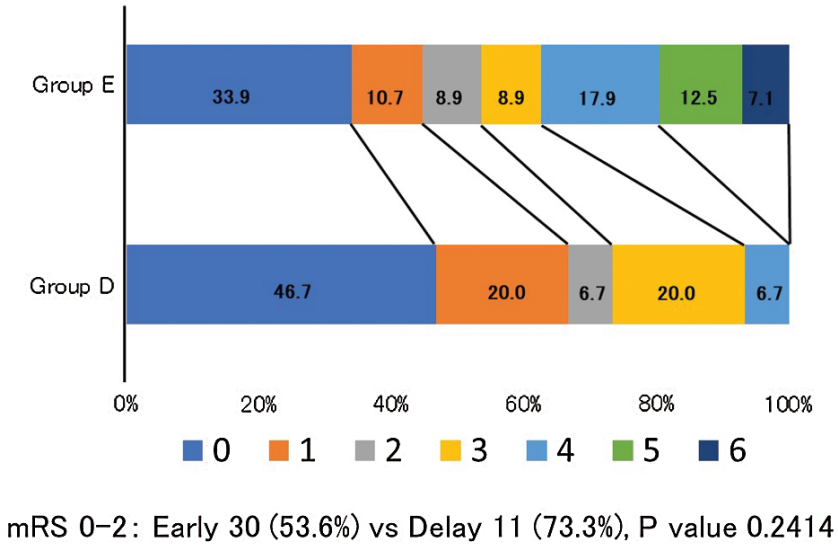

Fig. 1 Although the rate of patients with a mRS score 0-2 at discharge was not significantly different, it was slightly higher in the delayed group than in the early group. mRS: modified Rankin Scale

Table 3 Summary of clinical characteristics of 30 case-matched patients of aneurysmal SAH treated by IVR

	Total	Group E	Group D	p value
No. of patients	30	15	15	
Age, yrs				
Median	610	57.0	61.0	0.9834
IQR	50.0–76.8	50.0–81.0	52.0–71.0	
Sex, Female	24 (80.0%)	12 (80.0%)	12 (80.0%)	1.0000
WFNS grade 1–3	28 (93.3%)	14 (93.3%)	14 (93.3%)	1.0000
Re-rupture before Tx	6 (20.0%)	1 (6.7%)	5 (33.3%)	0.1686
Location of ruptured AN, anterior	18 (60.0%)	10 (66.7%)	8 (53.3%)	0.7104
AN maximum size, mm				
Median	4.9	5.2	4.5	1.0000
IQR	4.0–8.8	3.9–9.19	4.0–6.9	
AN neck size, mm				
Median	2.7	2.5	2.8	0.1912
IQR	2.2–3.3	1.9–3.2	2.4–3.5	
Aspect ratio				
Median	1.53	1.60	1.41	0.0850
IQR	1.27–1.75	1.44–1.96	1.07–1.68	
Vasospasm at access route, Yes	7 (23.3%)	2 (13.3%)	5 (33.3%)	0.3898
Adjunctive technique, Yes	14 (46.7%)	5 (33.3%)	9 (60.0%)	0.2723
Balloon	11 (36.7%)	4 (26.7%)	7 (46.7%)	
Double catheter	2 (6.7%)	1 (6.7%)	1 (6.7%)	
Stent	2 (6.7%)	0	2 (13.3%)	

AN: aneurysm; IQR: interquartile range; IVR: interventional radiology; SAH: subarachnoid hemorrhage

p = 1.0000). The mRS score at discharge between 0 and 2, representing independence in daily life and favorable outcomes, was noted in 30 patients (53.6%) in Group E and 11 patients (73.3%) in Group D. On the other hand, mRS 5–6, regarded as a poor outcome, was noted in 11 patients (19.6%) in Group E, but not in Group D. Although these differences were not significant, patients in Group D tended to be more favorable than patients in Group E (**Fig. 1**).

Propensity score matching was applied to the WFNS grade, which differed based on the patient background, and the two groups were similarly compared. In total, 30 patients (15 patients each) were selected. No significant difference was detected in the patient background, including WFNS grade (**Table 3**). No significant difference was noted in intraprocedural complications or postprocedural course between the groups after matching (**Table 4**).

Table 4 Intraprocedural and postprocedural adverse event of 30 case-matched patients of aneurysmal SAH treated by IVR

	Total	Group E	Group D	p value
Procedure-related complications				
Symptomatic CI	5 (16.7%)	3 (20.0%)	2 (13.3%)	
Arterial dissection	1 (3.3%)	0	1 (6.7%)	
Vessel perforation	3 (10.0%)	2 (13.3%)	1 (6.7%)	
ICH	1 (3.3%)	1 (6.7%)	0	
Total	10 (33.3%)	6 (40.0%)	4 (26.7%)	0.6999
Postprocedural course				
Symptomatic vasospasm	5 (16.7%)	3 (20.0%)	2 (13.3%)	1.0000
CI due to vasospasm	4 (13.3%)	2 (13.3%)	2 (13.3%)	1.0000
Retreatment	3 (10.0%)	2 (13.3%)	1 (6.7%)	1.0000
mRS 0–2 at discharge	20 (66.7%)	9 (60.0%)	11 (73.3%)	0.6999

CI: cerebral infarction; ICH: intracerebral hemorrhage; IVR: interventional radiology; mRS: modified Rankin Scale; SAH: subarachnoid hemorrhage

Discussion

In this study, patients with aneurysmal SAH were divided into two groups based on the timing of treatment: Group E was treated within 3 days after onset and Group D was treated 4–14 days after onset, and they were compared with the following factors: the patient background, aneurysm factors, presence of vasospasm upon the access route to the targeted aneurysm, intraprocedural complications, postprocedural course, and mRS score at discharge. The number of patients with lower WFNS grade and patients with vasospasm upon the access route during the procedure were both significantly higher in Group D than in Group E. On the other hand, no significant difference was noted in the treatment outcome, such as intraprocedural complications and postprocedural course.

Previous studies reported that the treatment outcome became poor with delayed treatment.[5,7] In the sub-analysis of international subarachnoid aneurysm trial (ISAT), which was the initial randomized controlled trial (RCT) demonstrating the efficacy of IVR for ruptured cerebral aneurysms, the risk of delayed cerebral infarction increased by 1.68 times in patients treated 5–10 days after onset compared with that in patients treated within 2 days after onset.[5] They also reported that the rate of patients with mRS score of 3 and higher at 1 year after treatment increased by 2.5 times in patients treated after 11 days or later compared with that in patients treated within 2 days. Re-rupture before treatment was considered as the main cause of poor outcome. In their study, the re-rupture rate was 0.7% in patients treated within 2 days, but it increased to 5.8% in patients treated at 11 days or later. Similarly, in a case-controlled study involving 459 patients, the rate of mRS 3–6 at 6 months after onset was 3.5% in patients treated within 24 hours after onset, 12.5% in patients treated at 1–3 days, and 50% at 4–10 days or later, demonstrating a poorer outcome with delayed treatment, and the cause was considered as delay of treatment for re-rupture and vasospasm.[8] In our study, the rate of re-rupture before treatment was higher in Group D, although the difference was not significant. Moreover, vasospasm was noted during the access to the targeted aneurysm at a higher rate in Group D. However, IVR was performed early after arrival except for one patient and the treatment outcome was not significantly different from that of Group E, suggesting that early therapeutic intervention is effective for patients who were in the vasospasm period.

In our study, no difference was noted in the incidence of complications between Groups D and E. In a retrospective study of the timing of IVR treatment involving 327 patients with ruptured cerebral aneurysm also reported that the rate of vasospasm upon the access route during treatment was significantly higher in the group treated at 3 days or later than in the group treated 0–2 days after onset, but no difference was noted in procedural complications.[8] Similarly, in a retrospective study involving 510 patients with ruptured cerebral aneurysm, no difference was noted in intraprocedural complications among patients treated in the hyper-early phase within 12 hours, within 48 hours, or 48 hours or later.[9] In addition, in coil embolization for the patients with vasospasm, the access was reportedly successful in 88–91%.[4,10] Kurata et al. reported cerebral infarction accompanying IVR in 1 (9.1%) of 11 patients with vasospasm during the access.[10] A study on the timing of treatment involving 119 patients also revealed that IVR did not influence the development of vasospasm.[11] Based on the above, IVR can be performed safely in vasospasm period because there was no difference in the incidence of intraprocedural complications due to the timing of

treatment and the outcome was relatively favorable, although vasospasm was present during the access.

This was a retrospective observational study and differences in the patient background were noted between two groups. In particular, the rate of patients with WFNS grade 1–3 on admission was significantly higher in Group D. As this likely influenced the treatment outcome, propensity score matching was performed to reduce the bias. No difference was noted in the treatment outcome after propensity score matching between the groups and the outcome was comparable between early-phase IVR and vasospasm-period IVR in this study. However, the number of patients was small; therefore, more patients must be investigated in the future. In addition, bias during the evaluation of vasospasm due to differences in the modality was unable to be excluded. Differences in the timing of examination among the patients may also have influenced the outcome. To demonstrate the efficacy and safety of early intervention by IVR for patients in vasospasm period, a prospective study comparing patients with elective treatment at 3 days or later and those treated within 3 days may be warranted.

Conclusion

The outcome of aneurysmal SAH treated later than 3 days after the onset was comparable with those treated within 3 days, although vasospasm on the access route was more frequently observed. For patients with ruptured aneurysm whose arrival was 3 days or later after the ictus prompt coiling is worth considering despite the presence of vasospasm.

Disclosure Statement

The authors declare no conflicts of interest.

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