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Endovascular Treatment for Vasospasm after Aneurysmal Subarachnoid Hemorrhage Based on Data of JR-NET3

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Abstract

Endovascular treatments for vasospasm after subarachnoid hemorrhage are typically performed for patients who are refractory to recommended medical therapies. We analyzed the current status of endovascular treatments based on the data of Japanese Registry of Neuroendovascular Therapy (JR-NET)3, and evaluated factors related to improvement of imaging findings and neurological condition, and to mechanical hemorrhage complications. We collected data of 1211 treatments performed from 2010 to 2014. Target vessels for treatments were anterior circulation (*n* = 1079), posterior circulation (*n* = 91), and both (*n* = 32); the distribution of vasospasm was the proximal vessel (*n* = 754) to the Circle of Willis, distal vessel (*n* = 329), and both (*n* = 119). Of the treatments, 948 cases (78.3%) were intra-arterial administration of vasodilators and 259 (21.4%) were percutaneous transluminal angioplasty (PTA); 879 cases were the first intervention. The treatment time from onset was within 3 h in 378 (31.2%) cases, between 3 and 6 h in 349 (28.8%) cases, and over 6 h in 245 (20.2%) cases. The statistically significant factors associated with improvement on imaging findings was the first treatment, and treatment within 3 h from onset compared with that after 6 h. Additionally, the first and early treatments after the symptoms were associated with significantly improved neurological condition. All complications of mechanical hemorrhage occurred along with PTA. The findings show that endovascular treatment for vasospasm was effective, especially for cases who suffered from symptomatic vasospasm with a short interval after onset.

Key words: vasospasm, endovascular treatment, neurological improvement

Introduction

Delayed cerebral ischemia (DCI) occurs in 20–40% of patients who are presented with subarachnoid hemorrhage (SAH),[1–3] and is a significant cause of disability and mortality for these patients.[4,5] Vasospasm, which contributes to DCI, has been identified on angiogram in 30–70% of patients with SAH.[1,2] Although DCI is less common after coiling than clipping for ruptured aneurysms according to a meta-analysis,[6] therapy for vasospasm after SAH, including endovascular treatment, has not been established yet.

Japanese Guidelines for the Management of Strokes recommend cisternal drainage on clipping, intravenous administration of fasudil hydrochloride[7,8] or ozagrel sodium,[9] or oral administration of cilostrazol[10] for prevention of DCI. Triple-H therapy[11] and hyperdynamic therapy[12] are also treatment strategies after delayed vasospasm is identified. Endovascular treatment for vasospasm, such as intra-arterial (IA) vasodilators and percutaneous transluminal angioplasty (PTA), is usually recommended for patients who are refractory to these recommended medical therapies.[13] However, the effect, procedure and timing of endovascular treatment has not been clarified.

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Japanese Registry of Neuroendovascular Therapy (JR-NET) is a nationwide retrospective registration study. Previous studies[14,15] have reported on data from JR-NET and JR-NET2, which were conducted from 2005 to 2006, 2007 to 2009, respectively. We analyzed the data of JR-NET3, which was registered from 2010 to 2014, and evaluated the outcomes of endovascular treatment for vasospasm following aneurysmal SAH.

Materials and Methods

A total of 40,169 endovascular treatment cases were enrolled for the JR-NET3 study from 2010 to 2014, and 1354 cases (3.37%) of those were endovascular treatment for vasospasm after SAH. We analyzed 1211 (89.4%) treatments in which detailed data was available.

Detailed data for each case included: (1) Characteristics of the patient, including age, sex, previous treatment for ruptured aneurysm and location of vasospasm, (2) data of the procedure, including the responsible doctor, anesthesia, number of treatments, timing, and strategy, and (3) results of the treatment, including improvement on imaging findings, neurological improvement, and complications. The locations of the target vessel were defined as anterior circulation, posterior circulation and both, and as proximal vessel, which included internal carotid artery, M1 portion of middle cerebral artery, vertebral artery and basilar artery, distal vessel, and both. The responsible doctor was classified into a supervisory doctor, specialist, and non-specialist of Japanese Society for Neuroendovascular Therapy (JSNET). The number of treatments variable was divided into the first, second and more treatments, and the timing was categorized into <3, 3–6, and >6 h. The procedure strategy was classified into IA administration of vasodilators and PTA.

We analyzed factors related to improvement on imaging findings, neurological improvement, and mechanical hemorrhage after the treatment, using JMP 10 (SAS Institute Inc., Cary, NC, USA). We used a chi-square test and Fisher's exact test in a univariate analysis, and logistic regression in a multivariate analysis. A value of $P < 0.05$ was defined as significant.

Results

The characteristics of patients and treatments were shown in Table 1. Rates of treatment for the ruptured aneurysm were as follows. Surgical clipping and endovascular coil embolization were performed in 703 (58.1%) cases and 469 (38.7%) cases, respectively.

Table 1 Characteristics of patients and treatments, and results after procedure

	JR-NET3 (n = 1211)	
	Mean ± SD or n (%)	
Age	59.5 ± 14.4	
Sex		
Female	803	66.3%
Male	408	33.7%
Treatment for ruptured aneurysm		
Direct surgery	703	58.1%
Endovascular embolization	469	38.7%
Target vessel		
Anterior circulation	1079	89.1%
Posterior circulation	91	7.5%
Both circulation	32	2.6%
Distribution		
Proximal vessel	754	62.3%
Distal vessel	329	27.2%
Diffuse type	119	9.8%
Responsible doctor		
Supervisory doctor	368	30.4%
Specialist	666	55.0%
Non-specialist	177	14.6%
Anesthesia		
General	118	9.8%
Local	1092	90.2%
Number of times		
The first time	879	72.6%
Over and second times	331	27.3%
Timing (h)		
<3	378	31.2%
3–6	349	28.8%
>6	245	20.2%
Strategy		
IA-vasodilators	948	78.3%
PTA	259	21.4%
Improvement on imaging study	1171	96.7%
Neurological improvement	670	55.3%
Complication		
Mechanical hemorrhage	4	0.3%
Non-mechanical hemorrhage	11	0.9%
Ischemia	19	1.6%
Dissection	2	0.2%

IA: intra-arterial, PTA: percutaneous transluminal angioplasty, SD: standard deviation.

Of target vessels, 1079 (89.1%) were located in anterior and 91 (7.5%) in posterior circulation, and the treatment was performed for both circulation vessels in 32 (2.6%) cases. About 754 (62.3%) vasospastic lesions were in the proximal vessel, and 329 (27.2%) were in the distal vessel. Additionally, 119 (9.8%) cases suffered from diffuse vasospasm of both proximal and distal lesions. For the number of treatments, 879 (72.6%) and 331 (27.3%) cases were the first, second and more treatments, respectively. The endovascular treatments were started within 3 h from the onset in 378 (31.2%) cases, between 3 and 6 h in 349 (28.8%) cases, and over 6 h from onset in 245 (20.2%) cases.

Vasodilators were intra-arterially administrated in 948 (78.3%) cases, and PTA was performed in 259 (21.4%) cases. The treatment strategies were shown in Table 2. Administration of IA vasodilators in approximately 75% of cases and PTA in approximately 25% of cases were performed for both circulations. Vasodilators were used in approximately 75% of cases for each target vessel, and approximately 25% of cases were treated by PTA.

Imaging revealed dilation in 1171 (96.7%) cases, and the neurological status improved in 670 (55.3%) cases by endovascular treatment (Table 3). Univariate and multivariate analysis demonstrated that the first treatment was the significant factor of imaging improvement, and treatment within 3 h from onset significantly improved the vasospasm compared with that at 6 h or later (Table 3). As for the neurological symptoms, local anesthesia, the first treatment and shorter time after the onset were significant factors by univariate analysis. Multivariate analysis showed that the first treatment was a statistically significant factor related to neurological improvement. Additionally, treatment with a shorter interval from onset was more effective for the improvement of neurological outcomes (Table 4).

In all of the procedures, 36 (3.0%) cases experienced complications, including four (0.3%) mechanical hemorrhage, 11 (0.9%) non-mechanical hemorrhage, 19 (1.6%) ischemia, and two (0.2%) dissection complications (Table 1). Target vessel in anterior circulation, vasospasm in proximal lesion, and PTA were the statistically significant factors associated with mechanical hemorrhage in the univariate analysis (Table 5).

Table 2 Treatment strategy for each circulation and distribution

	IA-vasodilators	PTA
Target vessel		
Anterior circulation	872 (78.5%)	236 (21.2%)
Posterior circulation	90 (73.2%)	32 (26.0%)
Distribution		
Proximal vessel	659 (75.5%)	211 (24.2%)
Distal vessel	357 (79.7%)	90 (20.1%)

IA: intra-arterial, PTA: percutaneous transluminal angioplasty.

Discussion

Despite the development of endovascular devices and the progression of surgical techniques, management for vasospasm has not improved much. DCI continues to be a major cause of disability and mortality. For the prevention of vasospasm, oral administration of nimodipine, maintenance of euvolemia, and normal circulating blood volume are recommended in the American Heart Association (AHA)/American Stroke Association (ASA) guidelines (Class 1 evidence).[16] Also, intravenous administration of fasudil hydrochloride or ozagrel sodium, and cisternal drainage are recommended in the Japanese Guidelines for the Management of Stroke 2015.[17] Once DCI is diagnosed, induction of hypertension, not triple-H therapy, is recommended in the AHA/ASA guidelines (Class 1 evidence).[18] Both guidelines state that endovascular treatment is reasonable in patients with DCI that is refractory to other recommended medical therapies. However, IA-vasodilators and PTA do not have adequate information about their efficacy. In this registry study, 1121 cases of vasospasm treatment were enrolled, which, to the best of our knowledge, is the largest number of cases reported to date.

Of the treatments for ruptured aneurysm, 58% were surgical clipping and 39% were coil embolization. During the registration period for the study, Japanese physicians may have preferred direct surgery to endovascular treatment. The distribution of treated vasospasm vessels, with 90% located in anterior circulation and 70% distributed in proximal vessels, was similar to that of previous studies.[13,15] Although 30% of cases were handled by a supervisory doctor and 55% by a specialist, 15% of treatments were performed by non-specialists. Additionally, 90% were performed under local anesthesia. This tendency may reflect that endovascular treatment for vasospasm is an emergent intervention, and that the procedure is relatively simple and easy.

Intra-arterial-vasodilators composed 80% of all treatments in this study, and the remaining 20% were PTA. The AHA/ASA guidelines suggest that PTA should be considered for accessible lesions and IA-vasodilators for more distal vessels.[16] In our data, PTA was performed in 25% of proximal lesions and 20% of distal lesions, and IV-vasodilators were

Table 3 Factors related to improvement observed on imaging

	Improvement on imaging study	Univariate analysis	Multivariate analysis	
	Mean ± SD or *n* (%)	*P*-value	Hazard ratio (95% CI)	*P*-value
Age	59.4 ± 14.4	0.571		
Sex				
Female	775 (97.0%)	0.592		
Male	396 (97.5%)			
Treatment for ruptured aneurysm				
Direct surgery	684 (97.3%)	0.906		
Endovascular embolization	449 (97.0%)			
Target vessel				
Anterior circulation	1043 (97.0%)	0.600		
Posterior circulation	87 (96.7%)			
Both circulation	32 (100.0%)			
Distribution				
Proximal vessel	727 (96.9%)	0.573		
Distal vessel	319 (97.3%)			
Diffuse type	116 (98.3%)			
Responsible doctor				
Supervisory doctor	353 (96.4%)	0.573		
Specialist	647 (97.6%)			
Non-specialist	171 (97.2%)			
Anesthesia				
General	113 (98.3%)			
Local	1057 (97.1%)			
Number of times				
The first time	855 (97.8%)	0.027*	2.72 (1.28–5.68)	0.010*
Over and second times	315 (95.5%)		–	
Timing (h)				
<3	369 (97.9%)	0.158	2.88 (1.16–7.59)	0.023*
3–6	337 (96.8%)		1.63 (0.70–3.83)	0.254
>6	233 (95.1%)		–	
Strategy				
IA-vasodilators	919 (97.0%)			
PTA	252 (97.7%)			

CI: confidence interval, IA: intra-arterial, PTA: percutaneous transluminal angioplasty, SD: standard deviation, *Statistically significant.

Table 4 Factors related to neurological improvement by the treatment

	Neurological improvement	Univariate analysis	Multivariate analysis	
	Mean ± SD or *n* (%)	*P*-value	Hazard ratio (95% CI)	*P*-value
Age	59.5 ± 14.4	0.895		
Sex				
Female	454 (57.6%)	0.273		
Male	216 (54.3%)			
Treatment for ruptured aneurysm				
Direct surgery	394 (56.8%)	0.443		
Endovascular embolization	258 (56.8%)			
Target vessel				
Anterior circulation	603 (56.9%)	0.221		
Posterior circulation	42 (48.3%)			
Both circulation	19 (63.3%)			
Distribution				
Proximal vessel	414 (55.6%)	0.761		
Distal vessel	187 (58.1%)			
Diffuse type	63 (56.8%)			
Responsible doctor				
Supervisory doctor	205 (57.1%)	0.605		
Specialist	361 (55.4%)			
Non-specialist	104 (59.4%)			
Anesthesia				
General	48 (46.6%)	0.033*	0.82 (0.51–1.36)	0.443
Local	622 (57.5%)		–	
Number of times				
The first time	509 (58.9%)	0.005*	1.66 (1.22–2.26)	0.001*
Over and second times	160 (49.8%)		–	
Timing				
<3	273 (72.2%)	<0.001*	2.62 (1.85–3.73)	<0.001*
3–6	231 (66.8%)		1.87 (1.33–2.65)	<0.001*
>6	124 (51.5%)		–	
Strategy				
IA-vasodilators	529 (56.8%)			
PTA	141 (55.5%)			

CI: confidence interval, IA: intra-arterial, PTA: percutaneous transluminal angioplasty, SD: standard deviation, *Statistically significant.

Table 5 Factors associated with mechanical hemorrhage by the procedure

	Mechanical hemorrhage		*P*-value
Target vessel			
Anterior circulation	3/1078	0.3%	0.019*
Posterior circulation	0/91	0.0%	
Both circulation	1/32	3/1%	
Distribution			
Proximal vessel	2/753	0.3%	0.021*
Distal vessel	0/329	0.0%	
Diffuse type	2/119	1.7%	
Strategy			
IA-vasodilators	0/947	0.0%	<0.001*
PTA	4/259	1.5%	

IA: intra-arterial, PTA: percutaneous transluminal angioplasty, *Statistically significant.

used in small vessels slightly more often than in large vessels. It is possible that the difference of technical difficulty was small because of improvements in the trackability of balloon catheters and microguidewire. Papaverine was used as a vasodilator in the 1990's; however, its use declined because it was shown to have only transient effects[19] and to have a possibility of neurotoxicity.[20] The current common vasodilator for IA therapy is a calcium channel antagonist, milrinone,[21] and fasudil hydrochloride, which is a potent Rho-kinase inhibitor and vasodilator.[22] Considering that the registry period of this study was from 2010 to 2014, a popular drug of IA-vasodilators may have been fasudil hydrochloride.

In addition to IA-vasodilators, PTA is a method used to expand the vessel lumen. There are compliant and non-compliant balloon types for balloon catheters, and it remains unclear which balloon is better for the treatment of vasospasm.[23] It has been reported that PTA may reverse DCI in patients for whom medical therapy has failed.[24] Additionally, comparison between PTA and IA-papaverine has shown that PTA is superior as a permanent treatment of vasospasm with less retreatment.[25,26] However, PTA caused mechanical damage of endothelial cells and myocytes in experimental vasospasm,[27] and has the possibility for risk of fatal rupture, which is not present with IA-vasodilators.[28] Consistent with these reports, in this study mechanical hemorrhage occurred only in cases treated by PTA.

The initial aim of endovascular treatment for vasospasm is to expand the vessel lumen, and this was achieved in 97% of all the cases in this registry. This is compatible with rates reported in previous studies, including JR-NET2.[15] However, the final goal is neurological improvement, and the rate of neurological success in the current study was 55.3%, which is similar to JR-NET2 and other small studies.[29] We analyzed the data of JR-NET3 to evaluate the factors related to neurological improvement. By multivariate analysis, the most important factors were the number of treatments and timing of the treatment. It has been reported that time to reperfusion is the most important factor in recanalization therapy for acute ischemic stroke.[30,31] In the current analysis, the time from symptom onset to treatment was a significant factor, where earlier treatment resulted in a better outcome, especially for neurological symptoms. The number of treatments was another significant factor, and this was different from the analysis based on data from JR-NET2.[15] Repeated DCI is a risk of unwitnessed stroke, as is prolongation time between the onset and treatment. It may become more difficult to identify DCI by complicated neurological symptoms from the repeated vasospasm.

There was no difference in the effect between IA-vasodilators and PTA. From these results, the first line of treatment for symptomatic vasospasm refractory to medical therapy may be IA-vasodilators due to their relative ease of use and high safety, and PTA may be considered for repeated vasospasm and DCI.

Limitations

It is important to note that this was a retrospective registry study. This means that all the data, such as indication and treatment strategy, depended on each institute, and could include bias. We did not know which drug was used as a vasodilator or which type of balloon catheter was chosen for PTA. Registered treatments consist of cases treated by any specialist of JSNET, and treatments in which no specialists were involved were not registered. Additionally, the detailed data lacked important pre-treatment information, such as SAH grade, Fisher group, and distribution of SAH, intracerebral and intraventricular hematoma, and treatment data, such as interval from SAH and performed medical therapy.

In future studies, it will be necessary to perform a randomized control trial to further clarify the difference between IA-vasodilators and PTA, and to compare between endovascular and non-endovascular treatments.

Conclusion

Endovascular treatment for vasospasm after SAH was effective and safe according to analysis of data from JR-NET3, although all complications of mechanical hemorrhage were related to PTA. The first and early stage treatments within 3 h from the onset was most influential for the improvement of neurological symptoms.

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Conflicts of Interest Disclosure

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