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Special Theme Topic: Japanese Surveillance of Neuroendovascular Therapy in JR-NET/JR-NET2—Part II

Current Status of Endovascular Treatment for Vasospasm following Subarachnoid Hemorrhage: Analysis of JR-NET2

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Abstract

Endovascular treatments are employed for cerebral vasospasm following subarachnoid hemorrhage, which is not responded to the medical treatments. However, the effect or complication of the treatments is not known well. Here, we analyzed the data of Japanese Registry of Neuroendovascular Therapy 2 (JR-NET2) and revealed current status of the endovascular treatment for the cerebral vasospasm. JR-NET2 is conducted from January 1, 2007 to December 31, 2009. Information on the clinical status, imaging studies, treatment methods, the results of treatment, and status 30 days later were recorded. Totally 645 treatments for 480 patients (mean age, 59.4 years; 72.7% woman) were included. Factors related to the neurological improvement and treatment related complications were statistically analyzed. Treatments for ruptured cerebral aneurysm were direct surgery for 366 cases and endovascular treatment for 253 cases. The timing of the endovascular treatment for the cerebral vasospasm was within 3 hours in 209 cases, 3–6 hours in 158 cases, and more than 6 hours in 158 cases. Intra-arterial vasodilator was employed for the 495 cases and percutaneous transluminal angioplasty for 140 cases. Neurological improvement was observed in 372 cases and radiological improvement was seen in 623 cases. The treatment related complication occurred in 20 cases (3.1%), including 6 cases of intracranial hemorrhage, 5 cases of cerebral ischemia, a case of puncture site trouble, and 8 cases of others. Statistical analysis showed early treatment was related to the neurological improvement. Current status of endovascular treatment for cerebral vasospasm was revealed. Endovascular treatment was effective for vasospasm especially was performed early.

Key words: vasospasm, endovascular treatment, prognosis, complication

Introduction

Angiographic vasospasm has been reported to occur in 30% to 70% of patient following aneurysmal subarachnoid hemorrhage (SAH) and delayed ischemic neurological deficits caused by vasospasm may develop in 20% to 30% of patients.[1,2] Hypervolemic hypertensive therapy has gained wide acceptance, and calcium channel blockers have been reported to improve outcome in patients with vasospasm.[2] Despite reported cases with these treatments, vasospasm continues to be a major cause of morbidity and mortality following SAH. In recent years, endovascular treatment such as intra-arterial (IA) vasodilators and percutaneous transluminal angioplasty (PTA) are developing widely with some significant effects.[3–5]

Nationwide retrospective registration study of neurointervention namely Japanese Registry of Neuroendovascular Therapy (JR-NET) was conducted from January 2005 to December 2006. The purpose

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of JR-NET is to make clear the current status of endovascular treatment in Japan and to evaluate factors, which influence the result of the treatment. Thus, based on these analysis, it is finally intended to publish guidelines for standard treatment and education of the operator. On the basis of JR-NET, JR-NET-2 was conducted from January 1, 2007 to December 31, 2009, and endovascular treatment for cerebral vasospasm due to the aneurysmal SAH was registered additionally. To determine the most appropriate treatment of individual patients, we need to have a better understanding of the cerebral vasospasm. Here, we analyzed the data of JR-NET2 and revealed current status of the endovascular treatment for the cerebral vasospasm.

Materials and Methods

From January 1, 2007 through December 31, 2009, patients with cerebral vasospasm treated by neuroendovascular treatment were enrolled. Information on the clinical characteristics, imaging studies, treatment methods, and the results of treatment were recorded. Each patient's clinical status was recorded with the use of the modified Rankin scale (mRS). The primary end point was the 30 days outcome (mRS) following endovascular treatment. The treatment strategy was chosen by the patients or was determined in each institute. Four hundred and eighty patients were included (mean age 59.4, year; range 16–87 year). There were 327 women (68%).

Data were collected through the coordinating office and the data center, which was located at the University Medical Information Network. Then, it was converted to the Microsoft Excel file. Finally, it was statistically analyzed with JMP10.0 (SAS Institute Inc, Cary, North Carolina, USA). Factors related to neurological improvement and complication were analyzed first with univariate manner and possible factors are calculated with logistic regression analysis. Statistical significance was accepted at $p < 0.05$.

This study was a project of The Japanese Society for Neuroendovascular Therapy. Investigators at each institution obtained the approval of the local institutional review board before joining the study.

Results

Of the 645 cases, 480 (74.4%) underwent a single treatment session, 109 (16.9%) underwent two treatment sessions, 56 patients (8.7%) underwent more than two treatment sessions. Surgical clip ligation was performed in 366 cases (58.7%), and endovascular coil occlusion was performed in 253 cases (40.5%). Cerebral aneurysm was not treated in 5 cases (0.8%). Responsible person was instructor in 222 cases (34.4%), board certified specialist in 320 cases (49.6%), and non-specialist in 103 cases (16.0%). The place where treatment performed was 620 cases (96.1%) in their institutes and 25 cases (3.9%) in the other institutes. IA vasodilator was performed for 495 cases (78.0%) and PTA was for 140 cases (22.0%). In 209 cases (39.8%), endovascular treatment was performed within 3 hours of the onset of neurological deterioration. One hundred fifty-eight cases (30.1%) were treated between 3 hours and 6 hours and 158 cases (30.1%) were more than 6 hours. General anesthesia was given for 87 cases (13.5%) and local anesthesia with/without sedation (86.5%) was given for 557 cases.

The distribution of the vasospasm is shown in Fig. 1. Internal carotid artery, M1 middle cerebral artery, vertebral artery, and basilar artery, were considered "proximal" vessels. Those beyond the above classification (e.g., M2 middle cerebral artery and posterior cerebral artery) were considered "distal" vessels. Eighty-four percent of ruptured aneurysms were in the anterior circulation. Technical success rate was 99.5% and the result of imaging study was improvement in 623 cases (96.7%).

Three hundred and seventy-two cases (64.7%) showed improvement in neurological function.

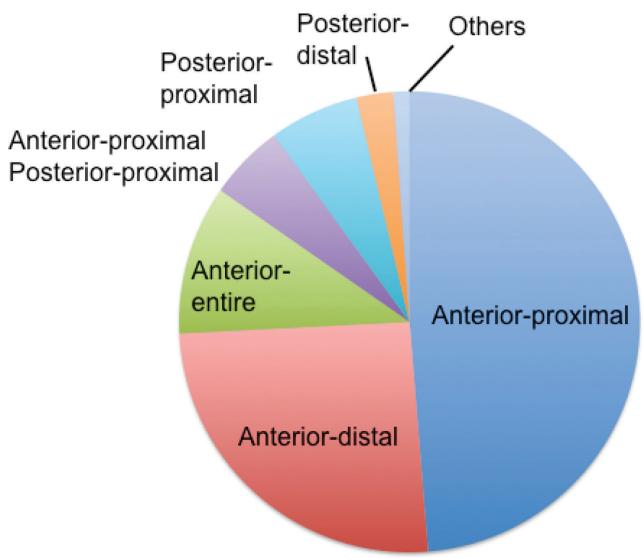

Fig. 1 Distribution of cerebral vasospasm. Anterior indicates anterior circulation. Posterior indicates posterior circulation. Internal carotid artery, M1 middle cerebral artery, vertebral artery, and basilar artery were considered "proximal" vessels. Those beyond the above classification were considered "distal" vessels.

One hundred and ninety-seven cases (34.3%) were unchanged neurologically and six cases (1.0%) deteriorated. Fig. 2 illustrates mRS of pre-treatment and 30 days following treatment. The multivariate logistic regression analysis revealed that an early treatment, local anesthesia, and better preoperative status (mRS) were significant factors affecting the neurological improvement (Table 1). The complication of the endovascular treatment occurred in 20 cases (3.1%), including 6 cases of intracranial hemorrhage, 5 cases of cerebral ischemia, a case of puncture site trouble, and 8 cases of others. The prognosis of the complication was 2 deaths, 1 severe disabilities, 2 minor disabilities, 8 transients, 5 asymptoms, and 2 others. Table 2 illustrates the results of statistical analysis of factors for complication. On multivariate analyses, treatment methods i.e., IA vasodilator and PTA, did not affect prognosis or complication. Thus, preoperative mRS status was not influenced with the complication of the treatment.

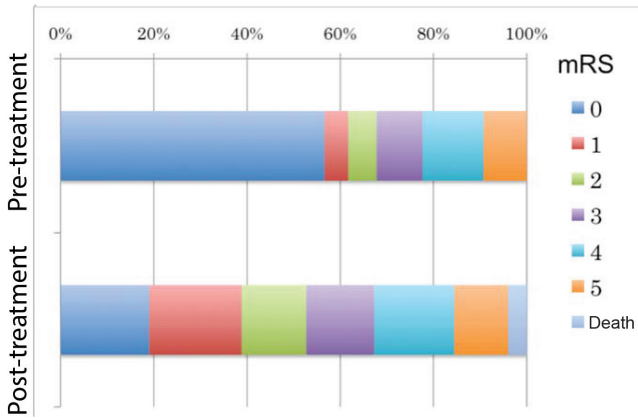

Fig. 2 Modified Rankin scale (mRS) at pre-treatment and 30 days after treatment.

Discussion

Vasospasm contributes to delayed ischemic neurological deficits and that may results in ischemic infarction.[2] In addition to hypervolemic therapy, intravenous ozagrel sodium and fasudil hydrochloride are frequently employed to prevent vasospasm in Japan.[6] Despite these treatments, some vasospasm would be symptomatic and be an indication for the endovascular treatment. The usefulness of endovascular treatment is widely accepted, however, current status is not known well. We analyzed the data of 645 cases, which were enrolled during 3 years in JR-NET2. To our knowledge, this constitutes the largest series of patients having undergone endovascular treatment for cerebra vasospasm to date. The majority of the patients were aged women, and cerebral aneurysms and the rupture were dominant in that population. In Japan, direct surgery is predominantly selected for treating cerebral aneurysm, therefore more than half of vasospasm cases were treated by direct surgery. The effect of endovascular treatment may be temporary, and one-fourth of cases were repeated. More than 80% of the vasospasm lesion was anterior circulation. These characteristics were not so different with previous reports.[7]

Table 1 Factors for neurological improvement

Factors	Contents	P value
Age		0.958
Sex	Man, woman	0.551
Treatment for aneurysm	Direct surgery, endovascular	0.910
Pre-treatment mRS		< 0.001*
Responsible operator	Instructor, specialist, non-specialist	0.173
Institute	Belongs, others	0.014*
Treatment times	1st, 2nd, 3rd	0.325
Anesthesia	General, local	0.007*
Timing of treatment	Within 6 hours, more than 6 hours	0.006*
Treatment methods	IA-vasodilator, PTA	0.084

IA: intra-arterial, mRS: modified Rankin scale, PTA: percutaneous transluminal angioplasty, *statistically significant.

Table 2 Factors for complications

Factors	Contents	P value
Age		0.562
Sex	Male, female	0.307
Treatment for aneurysm	Direct surgery, endovascular	0.390
Pre-treatment mRS		0.648
Responsible operator	Instructor, specialist, non-specialist	0.856
Institute	Belongs, others	0.152
Treatment times	1st, 2nd, 3rd	0.441
Anesthesia	General, local	0.098
Timing of treatment	Within 6 hours, more than 6 hours	0.702
Treatment methods	IA-vasodilator, PTA	0.711

IA: intra-arterial, mRS: modified Rankin scale, PTA: percutaneous transluminal angioplasty.

I. IA vasodilator or PTA

IA vasodilator infusion and PTA are the current modes of treatment. Generally, severe proximal vasospasm was treated with PTA, and distal vasospasm was treated with IA vasodilator. PTA is effective in expanding the luminal caliber, increasing cerebral blood flow, and improving neurologic function.[4,5] However, PTA is limited to vasospasm of the proximal large arteries at the base of the brain and has a reported 2–5% risk of stroke or death.[8,9] The data sounding vasodilator infusion are less established. Most experience is with papaverine, which has questionable clinical benefits and has significant side effect.[10,11] As a result, a shift toward calcium channel antagonists has emerged, with early reports showing angiographic response and clinical improvement with a better safety profile than either PTA or papaverine.[7] Moreover, fasudil hydrochloride, which is a potent vasodilator that inhibits protein kinases such as myosin light-chain kinase and protein kinase C in manner relatively specific for cerebral arteries, are routinely employed intravenously and selectively in IA in Japan.[6,12] In this study, IA vasodilator was employed three times as much as PTA. The effect or complications of each treatment are comparable. Almost all procedures were technically successful and resulted in radiological improvement.

II. Neurological improvement

Small uncontrolled studies report a wide range of clinical improvement: 10–80%.[13] In this study, 64.7% of treated cases are neurologically improved. And lots of clinical factors were analyzed using both univariate and multivariate analyses, which confirmed that the timing of the treatment, local anesthesia, and better pre-treatment mRS were important predictor of neurological recovery. It is reported that endovascular treatment is effective in improving the patient's neurological status if the procedure is performed as early as possible.[14] Trasnscranial Doppler ultrasound is the most useful tool to detect early stage of vasospasm and should be performed every day during vasospasm sensitive period. Usually, endovascular treatment for cerebral vasospasm is performed under local anesthesia. General anesthesia was employed for 13.5% of cases, perhaps for poor condition including consciousness disturbance. Thus, general anesthesia may affect blood pressure and cerebral ischemia. Finally, treatment appears to be less effective for severe disable cases.

III. Prognosis

There were 20 treatment-related complications in 645 cases (3.1%). Intracranial hemorrhage and cerebral ischemia are major complication. Although the detail is not known, vessel perforation with guide wire or vessel rupture may be a cause of intracranial hemorrhage.[5] And cerebral ischemia may be due to thromboembolism. The complication resulted in 2 deaths, 1 severe disable, and 2 minor disable. Morbi-morality rate was considered as acceptable. At 30 days mRS, 53% of cases had a good outcome, 43% had a poor outcome, and 4% died in our series (Fig. 2). Historically, mortality rates after SAH have been reported to be as high as 67% with up to a third requiring lifelong care[15] The prognosis may be affected by cerebral injury by SAH, vasospasm, hydrocephalus and so on.

IV. Limitation

The limitation of this study includes retrospective nature of the data analysis. Generally, indication of endovascular intervention is the medically refractory and angiographically proved vasospasm in patients with ischemic symptoms.[16] However, the treatment strategies depend on each institutes' policy. We do not have data of technique in detail. As IA vasodilator, it is speculated that most of them are fasudil hydrochloride, but papaverine or calcium (Ca) antagonist might be employed. In case of PTA, the type of balloon catheter is not known. Although JR-NET2 is a nationwide study, it does not cover all these topics. It is well known that cerebral vasospasm tends to occur in patient with higher SAH grade or diffuse thick SAH distribution i.e., Fisher grade III.[17] However, the information of the SAH grade and Fisher grade of SAH distribution are not available in JR-NET2. Regarding preoperative mRS, better mRS was related to improvement of the neurological status following endovascular treatment. On the other hand, preoperative mRS was not influence with treatment complication. The incidence of vasospasm in open surgery and endovascular coiling is interesting. However, only treated cases were registered in JR-NET. Therefore, the background or incidence of the vasospasm is not known in this study. Finally, this study is not designed to provide recommendations to determine which procedure is appropriate for treatment of cerebral vasospasm. Rather, it is meant to provide a framework for understanding the current status of endovascular treatment.

Conclusion

Current status of endovascular treatment for cerebral vasospasm following SAH was revealed. Endovascular treatment was effective for vasospasm especially which was performed early.

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Conflicts of Interest Disclosure

All authors hove no conflicts of interest. In addition, authors who are members of The Japan Neurosurgical Society state that all authors have registered online self-reported conflicts of interest disclosure statement forms through the website for The Japan Neurosurgical Society members.

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